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PHARMACOGENETIC BASES OF INDIVIDUAL SENSITIVITY AND PERSONALIZED ADMINISTRATION OF ANTIPLATELET THERAPY IN DIFFERENT ETHNIC GROUPS

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Cardiovascular diseases (CVDs) are the leading cause of disability and mortality worldwide. Increased thrombosis is the trigger point for the development of various CVDs and their complications, and therefore, therapy with P2Y12-receptor inhibitors is always pathogenetically justified and vital. However, according to the various data, 10-25% of patients treated with clopidogrel have "resistance" to antiplatelet therapy. The causes for the formation of resistance are still not clear. There is no generally accepted, standard methodology for determining resistance to antiplatelet agents. In addition, there are no methodological approaches to identify the patients with resistance to antiplatelet drugs, and standardized schemes for correcting a low sensitivity to these drugs.

The aim of this review was to summarize the available results of foreign and domestic studies devoted to the investigation of the effectiveness and safety problems of antiplatelet drugs administration from the point of view of the genetic predisposition to changes in their metabolism.

Materials and methods. For the review, the following information from scientific literature represented in open and accessible sources for the period of 1996-2020, was used: pharmgkb.org, PubMed, Scopus, Web of Science Core Collection, Elibrary. Search queries – "Genetic features+antiplatelet therapy+ethnic groups", "CYP2C19+clopidogrel+antiplatelet therapy effectiveness"; "Stent retrombosis+CYP2C19 polymorphism+ residual platelet reactivity" and "CYP2C19 polymorphism+ethnic groups+clopidogrel resistance" in both Russian and English equivalents. All these data are placed in electronic databases.

Results. Currently, the problem of the resistance formation to antiplatelet drugs is studied insufficiently. The best thought-out issue is the research of the effect of the polymorphic alleles carriage of the CYP2C19 gene on the residual platelet reactivity in the patients administrated with dual antiplatelet treatment, including clopidogrel. In general, the analysis of open literature sources indicates the presence of a statistically significant association between the carrier of slow alleles of the CYP2C19 gene and the residual platelet reactivity, clinically manifested by thrombosis and adverse cardiovascular events. The occurrence frequency of polymorphic carriage of the CYP2C19 gene varies in different ethnic groups, so it cannot be extrapolated to individual subjects, peculiar in the ethnic diversity.

Conclusion. To develop preventive and predictive measures aimed at overcoming resistance to antiplatelet agents, as well as working out methodological approaches to personalized prescribtion of this group drugs, a further investigation with the expansion of the search for causes and the study of the other genes participation of the cytochrome P450 system, is required.

Keywords: antiplatelet agents; clopidogrel; pharmacogenetics; ethnic groups; resistance to antiplatelet therapy

Abbreviations: CVD – cardiovascular diseases; CVC – cardiovascular pathology; PCI – percutaneous coronary intervention; ASA – acetylsalicylic acid; CVD – cardiovascular complication; MI – myocardial infarction; ACS – acute coronary syndrome; CHD – coronary heart disease.

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ФАРМАКОГЕНЕТИЧЕСКИЕ ОСНОВЫ ИНДИВИДУАЛЬНОЙ ЧУВСТВИТЕЛЬНОСТИ И ПЕРСОНАЛИЗИРОВАННОГО НАЗНАЧЕНИЯ АНТИАГРЕГАНТНОЙ ТЕРАПИИ В РАЗЛИЧНЫХ ЭТНИЧЕСКИХ ГРУППАХ

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Сердечно-сосудистые заболевания (ССЗ) являются ведущей причиной инвалидности и смертности населения во всем мире. Повышенное тромбообразование является пусковым моментом развития различных ССЗ и их осложнений, в связи с чем, терапия ингибиторами P2Y12-рецепторов всегда является патогенетически обоснованной и жизненно необходимой. Однако, по разным данным, у 10-25% пациентов, получающих клопидогрел, отмечается «резистентность» к антиагрегантной терапии. Причины формирования резистентности до сих пор не ясны. Общепризнанной, стандартной методики определения резистентности к антиагрегантам не существует. Кроме того, нет методологических подходов по выявлению пациентов с невосприимчивостью к антиагрегационным препаратам и стандартизированных схем коррекции низкой чувствительности к ним.

Цель. Целью написания данного обзора было резюмировать имеющиеся результаты зарубежных и отечественных исследований, посвященных изучению вопросов эффективности и безопасности назначения антитромбоцитарных препаратов с позиции генетической предрасположенности к изменению их метаболизма.

Материалы и методы. Для обзора использовали сведения научной литературы из открытых и доступных источников за период 1996–2020 гг., размещенных в электронных базах данных: pharmgkb.org; PubMed; Scopus; Web of Science Core Collection; Elibrary. Поисковые запросы – «генетические особенности+антиагрегационная терапия+этнические группы», «CYP2C19+клопидогрел+эффективность антитромбоцитарной терапии»; «ретромбоз стента+полиморфизм CYP2C19+ остаточная реактивность тромбоцитов» и «полиморфизм CYP2C19+этнические группы+резистентность к клопидогрелу» как в русском, так и английском эквиваленте.

Результаты. Проблема формирования резистентности к антиагрегационным препаратам в настоящее время изучена недостаточно. Наиболее проработанным вопросом является изучение влияния носительства полиморфных аллелей гена CYP2C19 на остаточную реактивность тромбоцитов, у пациентов получающих двойную антиагрегационную терапию, включающую клопидогрел. Анализ открытых литературных источников, в целом, свидетельствует о наличии статистически значимой ассоциативной связи между носительством медленных аллелей гена CYP2C19 и остаточной реактивностью тромбоцитов, клинически проявляющуюся тромбозом и неблагоприятными сердечно-сосудистыми событиями. Частота встречаемости полиморфного носительства гена CYP2C19 варьирует в разных этнических группах, поэтому не может быть экстраполирована на отдельные субъекты, отличающиеся этническим разнообразием.

Заключение. Для разработки превентивных и предиктивных мер по преодолению резистентности к антиагрегантам, а также методологических подходов к персонализированному назначению препаратов этой группы, требуются дальнейшие исследования, с расширением поиска причин и изучением участия других генов системы цитохрома P450.

Ключевые слова: антиагреганты; клопидогрел; фармакогенетика; этнические группы; резистентность к антиагрегантной терапии

Список сокращений: ССЗ – сердечно-сосудистые заболевания; ССП – сердечно-сосудистая патология; ЧКВ – чрезкожное коронарное вмешательство; АСК – ацетилсалициловая кислота; ССО – сердечно-сосудистые осложнения; ИМ – инфаркт миокарда; ОКС – острый коронарный синдром; ИБС – ишемическая болезнь сердца.

INTRODUCTION

The modern world is in the midst of a global epidemy of infectious and non-infectious diseases [1]. The leading cause of mortality and disability of the population is currently cardiovascular diseases (CVDs). In the Russian Federation, the pathology of the circulatory system has been diagnosed in 27355.3 people per 100 thousand of the adult population; the diseases of the cardiovascular system are 56.8% as the cause of death [2].

Cardiovascular pathology (CVP) significantly disrupts patients' habitual lifestyles, contributes to disability and medical and social dysadaptation. The role of

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excessive platelet functioning in the pathogenesis of cardiovascular complications is, to a great extent, decisive since the systemic nature of microcirculatory disorders entails further, more irreversible consequences. In this connection, pathogenetic, antiplatelet therapy of CVDs is carried out for a long time, while the prerequisites for its implementation are efficiency and safety.

In clinical practice, it is quite common to observe patients with a lack of susceptibility even to double antiaggregatory therapy. Such patients develop serious cardiovascular events: sudden deaths, myocardial infarctions (MIs), ischemic strokes, unstable angina pectoris, and stent thrombosis, which can be repeated after percutaneous coronary intervention (PCI) [3].

The lack of the effect on therapy with acetylsalicylic acid (ASA) occurs, on average, in 54.8% of patients, and with clopidogrel – in 10–25% of patients [4–6]. As shown by numerous domestic and foreign studies, the risk of developing myocardial infarctions (MIs), episodes of unstable angina pectoris, ischemic strokes in the patients with resistance to antiplatelet therapy is 2.5–3.5 times higher than in the patients sensitive to it. The studies carried out demonstrate different ethnic sensitivity to clopidogrel, due to the variability in the frequency of occurrence of the slow alleles of the CYP2C19 gene.

In the authors' opinions, in this connection, the study of the genetic causes of the resistance development in various ethnic grops, has a promising scientific and practical value.

THE AIM of this review was to summarize the available results of foreign and domestic studies devoted to the investigation of the effectiveness and safety problems of antiplatelet drugs administration from the point of view of the genetic predisposition to changes in their metabolism.

MATERIALS AND METHODS

For the review, the following information from scientific literature represented in open and accessible sources for the period of 1996–2020, was used: pharmgkb.org, PubMed, Scopus, Web of Science Core Collection, eLIBRARY. Search queries – "Genetic features+antiplatelet therapy+ethnic groups", "CYP2C19+clopidogrel+antiplatelet therapy effectiveness"; "Stent retrombosis+CYP2C19 polymorphism+ residual platelet reactivity" and "CYP2C19 polymorphism+ethnic groups+clopidogrel resistance" in both Russian and English equivalents. All these data are placed in electronic databases.

RESULTS AND DISCUSSION

Clopidogrel metabolism

Most often, clopidogrel in combination with acetylsalicylic acid is prescribed as antiplatelet therapy. Clopidogrel is a prodrug, which requires its transformation in the liver to an active metabolite that can have a disaggregation effect. The absorption of the drug in the intestine occurs with the participation of P-glycoprotein, the synthesis of which is regulated by the MDR1 (ABCB1) gene. In the case of carriage of polymorphic alleles of the ABCB1 gene (alleles CC, CT, TT), the activity of clopidogrel during its absorption can change [7]. Approximately 85% of the absorbed drug is deactivated under the action of liver enzymes, while 15%, with the participation of cytochrome P450 isoenzymes CYP1A2, CYP2B6 and CYP2C19, are converted into an intermediate metabolite 2-oxo-clopidogrel (thiolactone). Further, from the intermediate inactive metabolite, mainly with the participation of CYP2C19, the active compound R130964 is formed. It inhibits platelet aggregation through irreversible blockade of ADP P2Y12 on the platelet surface. The best known is the carriage of polymorphic alleles CYP2C19, associated with a complete loss or decrease in the function of the enzyme, in which the formation of an active metabolite of clopidogrel does not occur [8–10]. The involvement of other cytochrome P450 enzymes requires a further in-depth study and systematization.

A number of alleles associated with changes in the activity of the CYP2C19 enzyme, were revealed by methods of genetic identification: a complete loss, for example, CYP2C19*2, CYP2C19*3, CYP2C19*4, CYP2C19*5, CYP2C19*6, CYP2C19*7, CYP2C19*8; a decrease in activity, for example, CYP2C19*9, CYP2C19*11, CYP2C19*13; or an increased activity – CYP2C19*17. In the case of deprivation or a function loss of the CYP2C19 enzyme, the formation of active metabolites of clopidogrel does not occur. Clinically, it can manifest itself by the activation of the thrombus formation process. In the case of carriage of a polymorphic allele responsible for the rapid rate of metabolic reactions, some individuals may experience undesirable side effects associated with an excessive disaggregation activity, for example, varying degrees of severity of hemorrhage [11].

Experience of researchers from other countries

Foreign pharmacokinetic and pharmacodynamic studies have demonstrated a wide variability in the concentration of the active metabolite of clopidogrel and the variability in suppression of the platelet function after taking clopidogrel at a standard dose. There are significant differences in the distribution of CYP2C19 polymorphic alleles. Moreover, the differences concern both separate individuals and ethnic populations living in designated areas [12–14].

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Table 1 – Summary information on the analysis of literary sources

COUNTRY	TYPE OF RESEARCH	SUMMARY / CONCLUSIONS	reference to the literature source
USA	Randomized, double-blind, active control study (reactivity assessment using Verify Now analysis – impact on thrombosis and safety [GRAVITAS]). 2,214 patients with high reactivity to treatment in 12-24 hours after PCI, with stents, in 83 centers in North America between July 2008 and April 2010.	It has been established that the problem of clopidogrel resistance is not solved by increasing the dose of the drug. Genetic testing is required for the carriage of polymorphic alleles of the CYP2C19 gene 2 *; 3 * with a loss of the enzyme functional activity.	[15]
USA	Genome-wide, associative study of platelet reactivity and cardiovascular events in patients receiving clopidogrel (GWAS). The study involved 2,750 people of European ancestry whose DNA had been genotyped.	The response to clopidogrel is highly variable. The GWAS study did not identify any other SNP, except CYP2C19 * 2, the value of which would have reached a genome-wide significance.	[21]
USA	A prospective, randomized, controlled study of antiplatelet therapy, taking into account the association of the CYP2C19 genotype and clinical evidence.	The developed document is an update of the Consortium guidelines on the clinical use of the results of testing the CYP2C19 genotype for patients requiring antiplatelet therapy. The document indicates the presence of interindividual, interethnic variability in the frequency distribution of polymorphic CYP2C19 alleles.	[32]
GREAT BRITAIN	Associated clinical study from April 1, 1996 to April 1, 2008, 259 young patients (aged <45 years).	The genetic variant of CYP2C19 * 2 is the main factor determining the prognosis in young patients receiving clopidogrel treatment after myocardial infarction.	[22]
GREAT BRITAIN	Genome-wide, associative clinical observation in patients with myocardial infarction (MI) with ST-segment elevation and without ST-segment elevation, n = 2,208 people who received clopidogrel.	Patients – carriers of two alleles of the CYP2C19 gene * 2; * 3 – were more at risk of developing an "endpoint" than in the group of patients without polymorphic carriage.	[23]
POLAND	Position paper of the working group on antiplatelet drug resistance, appointed by the section of cardiovascular interventions of the Polish cardiological society, approved by the working group on thrombosis of the European Society of Cardiology (including 91 sources).	Studies have shown significant interindividual, ethnic sensitivity to clopidogrel. In addition, the polymorphisms in the genes of P-glycoprotein and the purinergic receptor P2Y12 (a receptor for the action of clopidogrel) and their role in the reactivity of clopidogrel were studied. It was concluded that considering the ABCB1 genotype in addition to CYP2C19, makes it possible to better predict the development of clopidogrel resistance.	[16]
GERMANY	In Germany, 2C19 681G> cytochrome P450 polymorphism and the phenomenon of high platelet reactivity against the background of clopidogrel, were studied in 797 patients in 2008.	It has been established that carriers of polymorphic, non-functional CYP2C19 alleles are associated with increased residual platelet activity and an unfavorable clinical outcome of planned PCIs during the first year.	[37]
CHINA	Genome-wide, associative clinical study investigating the effect of the carriage of polymorphic alleles CYP2C19 * 2, ABCB1 and PON1 on the pharmacodynamics of clopidogrel and clinical outcomes in 670 Chinese patients after PCI.	The results indicate the ethnic specificity of the prevalence of the CYP2C19 * 2 allele. The incidence of CYP2C19 * 2 in the Chinese is higher than in the Caucasians, therefore, the cases of ineffectiveness of antiplatelet therapy and the use of PCI in the Chinese ethnic group are comparable.	[34]
CHINA	Comparative analysis of the frequency of polymorphic carriage of CYP2C19 in comparison with Caucasian and Eastern ethnic groups.	The analysis of the CYP2C19 genotypes in 107 Thais showed that the allele frequencies for CYP2C19 * 1, CYP2C19 * 2 and CYP2C19 * 3 have ethnic specificity in the distribution. The frequencies of defective CYP2C19 alleles in the Thais, especially CYP2C19 * 3, were lower than in other eastern populations.	[36]

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COUNTRY	TYPE OF RESEARCH	SUMMARY / CONCLUSIONS	reference to the literature source
JAPAN	Associative clinical and pharmacogenetic examination of 114 patients who underwent PCI.	The authors have concluded that not only the interindividual difference in the carriage of polymorphic CYP2C19 alleles in the Japanese population affects the sensitivity to clopidogrel, but also the level of hyperlipidemia. The authors have developed a multifactorial algorithm for predicting an individual response to clopidogrel therapy.	[29]
SOUTH KOREA	16 prospective cohort studies, including 7,035 patients carrying ≥ 1 CYP2C19 LOF allele (loss of function), and 13,750 patients with the wild-type genotype were included into meta-analysis.	Stratified analysis by ethnicity of the study population showed a higher chance of adverse clinical events in the Asian population with options LOFCYP2C19 (or 1.89, 95% CI 1.32-2.72) compared with the Western population (or 1.28, 95% CI 1.00–1.64).	[33]
SPAIN	Comparative study of the occurrence frequency of polymorphic genes CYP2C8, CYP2C9 and CYP2C19 in the ethnic groups of the Spaniards (n = 282) and Ecuadorian mestizos (n = 297).	Ethnic specificity in the distribution of occurrence frequencies of polymorphic alleles CYP2C19, has been established. The frequency of CYP2C19 * 17 alleles was higher in the Ecuadorians than in the Spaniards (P <0.001), and the frequency of CYP2C19 * 3 was the same in the studied groups. There was a higher activity of CYP2C8, CYP2C9 and CYP2C19 in the Ecuadorian mestizos, in contrast to the Spaniards.	[40]
CANADA	CYP2C19-associated polymorphism of mephenytoin in the Inuit population living in Canada (n = 152), has been investigated.	Ethnic specificity in the distribution of occurrence frequencies of polymorphic alleles CYP2C19 has been established. No CYP2C19 * 2 polymorphism has been found in this ethnic group. In terms of the frequency of phenotypes and the molecular basis of polymorphism, the Canadian Inuits are close to the Caucasians, and not to the Asian ethnic groups.	[41]
CROATIA	200 blood samples to study the prevalence of CYP2C9, CYP2C19 and CYP2D6 allelic variants in the Croatian ethnic group, have been genotyped.	For CYP2C19, the most frequent alleles were CYP2C19 * 1 and CYP2C19 * 2, with frequencies of 0.85 and 0.15. The occurrence frequency of polymorphic alleles CYP2C19 in the Croatian ethnic group was comparable to the Central European and Mediterranean populations.	[43]
SINGAPORE	The functional significance of SNP CYP2C19 * 2, * 3, * 17 and in Asian patients treated with clopidogrel and the prevalence of functionally significant polymorphisms among 300 Chinese, Malays and Asian Indians, have been investigated.	Interethnic differences in the frequency distribution of CYP2C19 genotypes have been established. To study the response to clopidogrel, it was proposed to study the CYP2C19 * 2 and * 3 polymorphisms, but not * 17 in the Chinese, and the CYP2C19 * 2 and * 17 polymorphisms, but not * 3 in the Indians. All three polymorphisms must be genotyped in the Malays.	[45]
RUSSIA	The occurrence frequency of polymorphic alleles CYP2C19 in patients of the central part of Russia and Siberia has been comparatively evaluated.	Interethnic variability in the distribution of polymorphic alleles of the CYP2C19 gene has been revealed.	[47]
RUSSIA	The occurrence frequency of polymorphic alleles of metabolism genes and transport proteins in three ethnic groups of Dagestan has been determined.	Interethnic variability in the distribution of polymorphic alleles of the CYP2C19 gene has been revealed.	[14]
RUSSIA	Work has been carried out to assess the effect of polymorphisms of the CYP2C19, ABCB1 genes and a low effect of the CYP3A4 isoenzyme on the development of complications after stent implantation in patients with ACS.	There was an increased laboratory resistance to clopidogrel (PRU> 208) in carriers of polymorphic alleles CYP2C19 * 2: 53.8% versus 16.2%, which, however, did not affect the frequency of stent thrombosis.	[49]

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COUNTRY	TYPE OF RESEARCH	SUMMARY / CONCLUSIONS	reference to the literature source
RUSSIA	Clinical observation and genetic testing of 399 patients with CVP have been carried out. for 18 months.	No statistically significant relationship has been found between the level of residual platelet reactivity and the carriage of polymorphic markers of the CYP2C19 gene.	[50]
RUSSIA	The prevalence of allelic variants of the CYP2C19 gene *1, *2, *3, *17 has been studied in patients receiving clopidogrel – representatives of the West Siberian and Far Eastern regions.	Depending on the degree of platelet aggregation, groups of patients with different sensitivity to clopidogrel have been identified.	[51]

The randomized, double-blind, multicenter, controlled study GRAVITAS made it possible to draw several significant conclusions necessary for the development of a targeted antiplatelet therapy strategy. First, it was found out that there is no benefit from the use of a double dose of clopidogrel in the patients whose platelet reactivity increases sharply after percutaneous coronary intervention (PCI) [15]. Second, the study made it possible to expand pharmacogenetic testing for the CYP2C19 enzyme. 1152 blood samples were examined, 40 polymorphisms including CYP2C19 *2, *3 *4, *5 *6, *7, *8, and *17; ABCB1 and PON1, were studied. The results showed that patients with one or two polymorphic alleles of the CYP2C19 gene, in which their functional activity is lost, do not react to a double dose of clopidogrel at all. An 11-fold increase in the risk of a sustained increase in platelet reactivity within 30 days was found out in the patients who were homozygous carriers of the CYP2C19 * 2 gene, compared with the patients who had a functionally active wild type of the gene. Heterozygotes also retained a high platelet reactivity – up to 62% compared to the carriers of the wild, fast allele [15].

In Poland, interindividual variability of response to the oral administration of antiplatelet drugs was studied by Kuliczkowski et al. A position document of the working group on the antiplatelet drug resistance was developed, administrated by the section of cardiovascular interventions of the Polish Cardiological Society and also approved by the working group on thrombosis of the European Society of Cardiology [16]. The position document united and summarized all the available research results in the field of atherothrombosis and also made it possible to state a high percentage of clinical failures in the patients receiving double antiaggregation therapy, which predetermined the search relevance for individual genetic causes of resistance to antiaggregatory drugs. The carried out studies have proven a significant interindividual, ethnic sensitivity to clopidogrel.

CYP2C19*2 was found most frequently in Caucasian, African American and Asian peoples [17]. The frequency of occurrence of CYP2C19*2 alleles in Asian populations (~ 30%) was significantly higher than in the Caucasians (~13%) and African Americans (18%) [18, 19]. In the study by Sorich Michael J. et al., an association between the carriage of the CYP2C19 loss of function allele and major cardiovascular events was established. Moreover, the PCI frequency was significantly different in the ethnic groups of Europeans and Asians [20].

In a genome-wide, associative study (GWAS) of the platelet reactivity and cardiovascular events in the patients treated with clopidogrel, conducted by the International Pharmacogenetic Consortium (IPGC), it was also shown that the response to clopidogrel has a significant variability. At the same time, according to the authors, alleles of the loss of CYP2C19 function make up only a certain part in the structure of the reasons for the low response to the drug. The study involved 2,750 people of the European ancestry, whose DNA was genotyped. The GWAS study did not reveal any other SNP, except CYP2C19 * 2, the value of which would have reached a general genome significance. At the same time, in the subgroups of ischemic heart disease, percutaneous coronary intervention and acute coronary syndrome, mutations in SCOS5P1, CDC42BPA and CTRAC1 showed a general genome significance associated with the occurrence of cardiovascular death, myocardial infarction or a stroke, which requires comprehension and a further research in this direction [21].

The CYP2C19 genotype was associated with the fact of the “end point” in the form of cardiovascular death, non-fatal myocardial infarction in young patients with myocardial infarction and receiving clopidogrel at the dose of 75 mg/daily. It turned out that in the patients – carriers of CYP2C19*2 (28%) – the risk of recurrence of an acute coronary event during the first year was several times higher than in the patients – carriers of the wild type. Moreover, the authors positioned the polymorphism of the CYP2C19 genotype as the only significant predictor of the primary outcome in this patient population [22].

In England, a study was conducted in patients with myocardial infarction (MI) with a ST-segment elevation and without it (n = 2208 people) who received clopidogrel [23]. All patients underwent genotyping for the following genes – CUR2C19; CYP3A5; ABCB1; P2Y12, P2RY12; ITGB3 (IIB-IIIA receptor). For CYP2C19, the frequencies of the CYP2C19 alleles *2, *3, *4 and *5 were studied. In this study, the criterion of the “endpoint”, or

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the primary outcome, was used. It included death from any cause (strokes, myocardial infarction, stent thrombosis, etc.) during the first year after the development of myocardial infarction. In the group of patients with the presence of cardiovascular events and complications, the frequency of single nucleotide polymorphisms in the CYP3A5, P2RY12 and ITGB3 genes was significantly higher than in the group without the "endpoint". The patients carrying two alleles of the CYP2C19 gene were more at risk of developing an "endpoint" than in the group of patients without a polymorphic carriage [23].

A research group under Sibbing D., Stegherr J., Latz W.'s direction examined 772 patients who had been stented and were receiving dual antiplatelet therapy (aspirin and clopidogrel). All patients received clopidogrel 600 mg/daily as a loading dose and 75 mg/daily as a maintenance dose. Alleles CYP2C19*1 and *2 were genotyped. The primary endpoint or probable stent thrombosis was determined within 6 months after stenting. It turned out that in the patients carrying at least one variant of the CYP2C19*2 allele, the risk of recurrent thrombosis was much higher than in the patients carrying functionally active alleles [24].

Other randomized, controlled trials have shown that the patients who had undergone PCIs and were receiving clopidogrel at the dose of 300 mg/daily followed by a maintenance dose of 75 mg/daily, had a higher incidence of adverse cardiovascular outcomes (death from cardiovascular causes) and re-thrombosis of the stent, in the case of carriage of polymorphic genes encoding CYP2C19, CYP2C9, CYP2B6, CYP3A5, CYP3A4 and CYP1A2. Moreover, it was found out that the most pronounced relationship was between the carriage of polymorphic alleles of the isoenzyme CYP2C19 and death [25, 26].

The problem of searching for the causes of the resistance development to clopidogrel was studied in Portugal. According to the above studies, the patients with carriage of CYP2C19*2 and *17 had a poorer medium-term prognosis of ischemic events compared to other diplotypes. This fact also reflects the specificity in establishing associations with clinical outcomes of ischemic events [27].

Separate studies were devoted to the investigation of the polymorphism of P-glycoprotein – the ABCB1 gene responsible for the adsorption of clopidogrel in the gastrointestinal tract after the oral administration. Thus, it was shown that a decrease in the concentration of clopidogrel after a single dose of 300 or 600 mg, was observed in the patients homozygous for the ABCB1 variant of the 3,435T allele [28].

In Japan, a study was conducted by Miura G. et al. The aim was to investigate the genetic and non-genetic factors responsible for the antiplatelet effects of clopidogrel in Japanese patients undergoing coronary stent implantation [29]. It was concluded that the frequency of CYP2C19 polymorphic carriage in Japanese patients is close to the frequency of the identical single nucleotide substitutions in Asians. The researchers have assotiated the antiplatelet effects of clopidogrel in the steady state not only with CYP2C19 genotypes, but also with several nongenetic, modifiable factors, including dyslipidemia. Based on their own research results, the authors proposed a multifactorial algorithm for predicting individual responses to clopidogrel therapy [29].

In the pharmacoeconomic study by Jiang Minghuan, You Joyce H.S. et al., lifelong health costs were modeled, taking into account the quality-adjusted life years (QALYs) of the three antiplatelet regimens, in hypothetical 60-year-old ACS patients after PCIs. The first model included the administration of clopidogrel at the dose of 75 mg daily, the second – clopidogrel at the dose of 225 mg daily, and the third model suggested a universal alternative antiplatelet therapy (prasugrel or ticagrelor). It has been proved by a mathematical method that clopidogrel therapy at the dose of 75 mg daily is more cost-efficient only when the prevalence among the population of CYP2C19 alleles with a loss of function is less than 2.6%. That explains the relevance and the need for further population genetic studies [30].

In the study by Hokimoto Seiji, Akasaka Tomonori et al. it was found out that the simultaneous use of esomeprazole with clopidogrel does not cause a decrease in the antithrombotic efficacy of clopidogrel or an increase in the risk of cardiovascular events, regardless of the CYP2C19 genotype. These results are interesting from a research and practice belief, since they indicate a less significant role of modifiable factors, such as drug interactions, on the effectiveness of antiaggregatory therapy [31].

In the United States, clinical guidelines on the implementation of pharmacogenetic studies of the CYP2C19 gene in the clopidogrel therapy process, were developed by a consortium of physicians [32]. The document was worked out on the basis of the fundamental research showing that alleles of CYP2C19 function loss, disrupt the formation of active metabolites of clopidogrel which leads to a significant decrease in platelet inhibition. Ineffective CYP2C19 alleles increase the risk of serious adverse cardiovascular events among the patients receiving clopidogrel with ACS undergoing PCIs. Appropriate indications for genotype-directed antiplatelet therapy of CYP2C19 have been developed and recommendations for specific CYP2C19 alleles have been refined.

A group of South Korean scientists conducted a comparative meta-analysis of CYP2C19 gene polymorphism and the risk of adverse clinical outcomes in the patients with an ischemic heart disease of various ethnic groups who were receiving clopidogrel [33]. The meta-analysis comprised 16 prospective cohort studies, including 7,035 patients carrying ≥ 1 CYP2C19 LOF allele (loss of function) and 13,750 patients with the wild-type genotype. The results of the studies from the central and eastern parts of Europe turned out to be identical, while the ones from the western countries were contradictory.

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A stratified analysis by ethnicity of the study population showed a higher chance of adverse clinical events in the Asian population with variants LOFCYP2C19 (or 1.89, 95% CI 1.32–2.72) compared with the Western population (or 1, 28, 95% CI 1.00–1.64). In addition, the carriers of ≥1 CYP2C19 LOF allele had twice as high mortality and stent thrombosis compared with the wild-type homozygotes.

According to the Chinese researchers Tang Xiao-Fang, Wang Jing, Zhang Jia-Hui et al., the prevalence of the CYP2C19 * 2 allele in the Chinese is higher than in the Caucasians, therefore, the cases of ineffectiveness of antiplatelet therapy and the use of PCIs in the Chinese ethnic group are comparably more. The authors studied the effect of carriage of polymorphic alleles CYP2C19 * 2, ABCB1 and PON1 on clopidogrel pharmacodynamics and clinical outcomes in 670 Chinese patients after PCIs. It turned out that only alleles of CYP2C19 function loss had a dose-dependent effect on the pharmacodynamics of clopidogrel. However, the role of the ABCB1 and PON1 genotypes in the antiplatelet effect of clopidogrel has not been established [34]. The studies have been carried out to research the activity of clopidogrel in 183 Chinese patients with a stroke. After loading with clopidogrel at the dose of 300 mg and seven maintenance doses of clopidogrel at the dose of 75 mg, the platelet function was assessed. According to the results of the study, it was established that both CYP2C19 alleles (*2 and *3) are significantly associated with a maximum platelet aggregation and a low response to clopidogrel [35]. A comparative analysis of the frequency of polymorphic CYP2C19 carriage was carried out in the Thai population and in the Caucasian and Eastern ethnic groups [36]. The analysis of the CYP2C19 genotypes in 107 Thais showed that the allele frequencies for CYP2C19*1, CYP2C19*2 and CYP2C19*3 were 0.71 (95% CI 0.65–0.77), 0.27 (95% CI 0.21–0.33) and 0.02 (95% CI 0.01–0.05), respectively. The frequencies of the defective CYP2C19 alleles in the Thais, especially of CYP2C19*3, were lower than in other eastern populations.

In 2008, 797 patients in Germany studied 2C19 681G> cytochrome P450 polymorphism and the phenomenon of high platelet reactivity in the presence of clopidogrel. It was found out that carriers of polymorphic, non-functional CYP2C19 alleles are associated with increased residual platelet activity and unfavorable clinical outcome of planned PCIs during the first year. Moreover, it was found out that the residual platelet aggregation in the initial state did not differ significantly between the genotypes [37].

In 2008, 2C19 681G> polymorphism of P450 cytochrome and a phenomenon of a high platelet reactivity against the background of clopidogrel, were studied in 797 patients in Germany. It was found out that carriers of polymorphic, non-functional CYP2C 19 alleles are associated with an increased residual platelet activity and unfavorable clinical outcome of the planned PCIs during the first year. Moreover, it was found out that the residual platelet aggregation did not differ significantly between genotypes in the initial state [37].

In Poland, a group of scientists studied a platelet function in 105 patients with ACS who had received PCIs. After ACS, the patients were followed up for 12 months. During the first year of follow-up, two out of 11 patients who were carriers of polymorphic alleles 2*CYP2C19, had a recurrent development of ACS [38].

Similar studies were carried out in Florence [39]. The role of the CYP2C19*2 polymorphism in the occurrence of stent thrombosis (ST), or adverse cardiovascular events during a 6-month follow-up after PCIs with stent implantation, against the background of dual antiplatelet therapy, was assessed. In the patients with stent thrombosis or a combination of thrombosis and sudden death, a higher prevalence of carriers of the slow CYP2C19 alleles was noted.

A comparative study of the occurrence frequency of polymorphic genes CYP2C8, CYP2C9 and CYP2C19 in the ethnic groups of the Spaniards (n=282) and Ecuadorian mestizos (n = 297) has been conducted by foreign researchers. Blood samples were genotyped for alleles CY2C8*3, CYP2C9*2, CYP2C9*3, CYP2C19*2 and CYP2C19*3, CYP2C19*17 [40]. It turned out that the frequency of CYP2C19*17 alleles was higher in the Ecuadorians than in the Spaniards (P <0.001), and the frequency of CYP2C19*3 was the same in these two populations (P>0.05). Other allelic variants were found out at significantly lower frequencies in the Ecuadorians than in the Spaniards (P<0.05). There was a higher activity of CYP2C8, CYP2C9 and CYP2C19 in Metis-Ecuadorians, in contrast to the Spaniards, which, according to the authors, may mean differences in the dosage requirements for the drugs metabolized by these cytochromes, and should be also considered in the studies associated with the alleles and diseases. [40].

The CYP2C19-associated mephenytoin polymorphism was investigated in the Inuit population living in Canada (n = 152). The frequency of the polymorphic CYP2C19*1 allele, determined in unrelated subjects, was 0.12 (95% CI: 0.07–0.17). CYP2C19*2 was not detected in this ethnic group. It was concluded that Canadian Inuits resemble Caucasian rather than Asian populations, both in phenotype frequency and in the molecular basis of polymorphism [41].

A group of Iranian scientists studied the effect of polymorphism of the P2Y12, CYP3A5 and CYP2C19 genes on platelet reactivity in the postoperative period. All patients included in the study received aspirin at the dose of 80-325 mg one week before PCI. After taking 600 mg of clopidogrel at 2 hours, 24 hours and 30 days after PCIs, platelet aggregation was measured by a turbidimetric aggregation analysis with two different concentrations of ADP. The work showed that the maximum resistance to clopidogrel was observed 2 hours after taking the loading dose of the drug. At the same time, an asso-

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ciative relationship between the carriage of polymorphic CYP2C19, CYP3A5, and P2Y12 alleles and a clopidogrel reactivity in the Iranian population was not established. According to the authors, this indicates a greater influence of non-genetic, modifiable traits on the variability of the response to clopidogrel [42].

In 2003, 200 blood samples were genotyped in Croatia to study the prevalence of allelic variants CYP2C9, CYP2C19 and CYP2D6. The allele frequencies for CYP2C9*1 (wt), CYP2C9*2, and CYP2C9*3 were 0.74, 0.165, and 0.095, respectively. For CYP2C19, the most frequent alleles were CYP2C19*1 and CYP2C19*2, with frequencies of 0.85 and 0.15. For CYP2D6, the most common alleles were CYP2D6*1 (the frequency of 0.765), CYP2D6*2 (0.04), CYP2D6*3 (0.0275), CYP2D6*4 (0.14), CYP2D6*5 (0.01) and CYP2D6*6 (0.015). The study showed that in the Croatian ethnic group, the prevalence of allelic variants and predicted genotypes corresponds to other European populations and can be interpolated between the values for the Central European and Mediterranean populations [43].

In Mexico, the polymorphism of the ABCB1, CYP3A5, CYP2C19, and P2RY12 genes was studied [44]. Polymorphisms ABCB1 T3435C, CYP3A5 V3 A6986G, P2RY12 G52T, P2RY12 C34T, CYP2C19 V2 and V3 (positions g681a and G636A, respectively) were analyzed using 5' exonuclease genotyping. The CYP2C19 * 3 G636A allele was not identified in the Mexican mestizo population. However, in the study group, significant differences (P<0.05) were observed in the distribution of polymorphisms T3435C, A6986G, G681A, G52T, and C34T in comparison with the recorded frequencies in the populations of Indians of South America, the Caucasus, Asia and Africa [44]

The clinical significance of SNPS CYP2C19*2, *3, *17 and PON1 Q192R in the Chinese, Malays and Asian Indians was studied. The results were obtained indicating the presence of pronounced interethnic variability in the formation of the response to clopidogrel. The authors concluded that in the Chinese, the CYP2C19*2 and *3 polymorphisms but not *17 must be studied. While in the Indians, polymorphisms CYP2C19*2 and *17, but not *3 have a great clinical significance in the formation of resistance to clopidogrel. In the Malays, the authors propose to study all three polymorphisms for the individual selection of the dose of clopidogrel [45].

In France, within the framework of the creation of the French myocardial infarction register (FAST-MI), the modification of the P2RY12 receptor and the effect of the carriage of polymorphic sequences of this gene on the clinical efficacy of clopidogrel were studied. Associative connections were not established [46]. Apparently, the carriage of this polymorphism cannot be considered as an independent cause of clinical failures of antiplatelet therapy. It seems promising and most important to study the frequency of carriage of polymorphic alleles P2RY12, ABCB1 (C3435T, G2677T, and C136T) in combination with the study of CYP2C19 gene polymorphism both in populations and in separate individuals.

Results of Russian studies

In the Russian Federation, the frequency of occurrence of CYP2C19 polymorphisms in the Russian and Nogai populations has been studied. The frequency of occurrence of polymorphic CYP2C19 alleles in patients from the central part of Russia and Siberia has been comparatively evaluated [47]. The occurrence frequency of polymorphic alleles of metabolism genes and transport proteins in three ethnic groups of Dagestan has been determined [14]. The studies have demonstrated a wide interethnic variability in the distribution of polymorphic alleles of the CYP2C19 gene.

The work to assess the influence of polymorphisms of the CYP2C19, ABCB1 genes and a low activity of the CYP3A4 isoenzyme on the development of complications after stent implantation in the patients with ACS, has been carried out [48]. There was an increased laboratory resistance to clopidogrel (PRU>208) in carriers of polymorphic alleles CYP2C19*2: 53.8% vs. 16.2%, which, however, did not affect the incidence of stent thrombosis. The same changes concerned the study of CYP2C19*17 gene polymorphism.

The effect of CYP2C19 gene polymorphism on platelet reactivity, pharmacokinetics and pharmacodynamics of clopidogrel, the incidence of cardiovascular events and complications, has been studied [49]. As a result of genotyping, 39 out of 55 people were identified with the genotype (CYP2C19*1 / *1), 14 were heterozygous carriers (CYP2C19*1 / *2) and 2 patients were with the CYP2C19*2 / *2 genotype. It was found out that patients with a clinical resistance to clopidogrel, confirmed by laboratory tests, had a higher risk of ischemic complications.

Clinical observation and genetic testing of 399 patients with CVPs [50] have been conducted by Komarov A.L. et al. for 18 months. The main inclusion criteria were: a stable manifestation of ischemic heart disease, myocardial revascularization, an ACS episode more than a month ago, clopidogrel monotherapy (n = 83), or clopidogrel + ASA (n = 316). In this case, the daily dose of clopidogrel and ASA was 75-150 mg of each drug. The following parameters were selected as primary endpoints: death from cardiovascular causes, ACS, ischemic strokes, transient ischemic attack (TIA), coronary artery revascularization, and cases of any bleeding according to TIMI (Thrombolysis In Myocardial Infarction). The residual platelet reactivity was determined by the Born turbodimetric method in 3 and 6 months. There was no statistically significant relationship between the level of residual platelet reactivity and the carriage of polymorphic markers of the CYP2C19 gene.

The prevalence of allelic variants of the CYP2C19 gene *1, *2, *3, *17 has been studied in the patients receiving clopidogrel – representatives of the West Sibe-

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rian and Far Eastern regions. Depending on the degree of the platelet aggregation, the groups of patients with different sensitivity to clopidogrel, were identified. In this study, a statistically significant relationship between the CYP2C19*2 polymorphic variant and the change in the aggregation after taking clopidogrel, was established [51].

CONCLUSION

The analysis of the literature sources devoted to the study of the carriage of polymorphic cytochrome P450 genes involved in the metabolism of antiplatelet drugs, indicates the multifactoriality of candidate genes and the heterogeneity of the polymorphic alleles distribution of the CYP2C19 genes in ethnic groups. This creates preconditions for the need for fundamental, populations studies of hereditary sensitivity to antiaggregatory drugs in various subjects of the Russian Federation. In many countries, based on the results of determining the genotypes of CYP2C19, appropriate indications for genotype-directed antiplatelet therapy have already been developed, and recommendations for specific alleles of CYP2C19 have been refined. At the same time, we consider it necessary to further study the influence of the carriage of other polymorphic alleles of the cytochrome P450 genes – CYP1A2 and CYP2B6, as well as the polymorphism of platelet receptors on the formation of resistance to antiaggregation therapy. Based on the results of the CYP2C19 genotypes determination, appropriate indications for genotype-directed antiplatelet therapy have already been developed, and recommendations for specific CYP2C19 alleles have been refined in many countries.

At the same time, the effect of carriage of other polymorphic alleles of the cytochrome P450 genes – CYP1A2 and CYP2B6, as well as platelet receptor polymorphism, on the formation of resistance to antiaggregation therapy, is necessary to be studied further.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

B.I. Kantemirova – planning and writing the review; E.A. Orlova – collecting the material and editing the review; O.S. Polunina – review editing; E.N. Chernysheva – collecting the material for the review; M.A. Abdullaev – collecting the material for the review; D.A. Sychev – planning, working out the concept of the article.

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