Genetic predisposition for the development of complications in patients after coronary artery stenting

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Abstract
In the review the authors analyzed the literature data on the state of knowledge of the problems of genetic polymorphisms CYP2C19 gene response to clopidogrel in patients with acute coronary syndrome. Despite on the technological advances and the widespread use of coronary stenting, restenosis at the site of angioplasty remains the main factor limiting its long-term effectiveness.

We made the literature review of the state of the study of the genetic polymorphism of the CYP2C19 gene for a response to clopidogrel in patients with acute coronary syndrome and percutaneous coronary intervention. To achieve this goal, a systematic search and subsequent analysis of publications and online resources were carried out. All publications are indexed in the PubMed, Medline, e-Library, CoogleScholar.

Key words: coronary heart disease, percutaneous coronary angioplasty, stenting, restenosis, clopidogrel, CYP2C19, acute coronary syndrome, gene polymorphism
Introduction

The problem of treatment of coronary heart disease (CHD) is one of the top priorities of the world and national healthcare, as it is on the first place among the causes of cardiovascular mortality [1].

Endovascular interventions have opened a new stage in cardiology, significantly expanding the possibilities of CHD treating. According to the intensity of development, coronary stenting outstripped all previous technologies of coronary angioplasty [2]. Despite significant initial success, the widespread introduction of coronary stenting into clinical practice led to not so optimistic long-term results obtained in the first randomized trials. Long-term results forced cardiologists to change their attitude to coronary stenting and approach to endovascular treatment more differentially [3].

This method has revealed a number of factors limiting its effectiveness and application, the main one of which remains restenosis of the coronary arteries, which occurs in 6-12 months after stent implantation [2].

In general, cardiovascular diseases in Kazakhstan are responsible for almost one-third of all deaths. In the structure of mortality from diseases of the circulatory system, 34% are the patients with coronary heart disease (CHD), of whom more than 30% are active working age persons (18-65 years) [4]. The prognosis and outcome of the disease is directly influenced by timely diagnosis, prevention of complications and early conduction of myocardial revascularization [5].

In large-scale clinical trials [6], it was found that asymptomatic restenosis occurs in approximately 48-58% of patients with Percutaneous Coronary Intervention (PCI). P. Ruygrok et al. (2001) evaluated clinical and angiographic factors associated with asymptomatic restenosis. Restenosis developed in 16% from 1 469 stented patients, while in 58% of them it was asymptomatic. Multivariate analysis of this group showed that male sex prevails among restenotic patients, and predictors of asymptomatic restenosis may have a minor degree of lesion during the first 6 months [6].

Genetic factors associated with complications while taking clopidogrel

Clopidogrel is a prodrug derived from thienopyridine, which requires biotransformation in the liver to the active metabolite. Clopidogrel selectively and irreversibly inhibits the purinergic receptor P2RY12 and, thus, leads to the loss of platelet function (*2/*2) or complex heterozygotes (*2/*3) [16]. The frequency of occurrence of these variants, as a rule, is less than 1% [15, 16] and their definition is of no clinical significance.

According to other sources [14], the prevalence of the allele with CYP2C19*2 genotype is about 25-30% in Europeans and 50-60% in Asians. Alleles with reduced or absent enzyme activity (for example, *3 – *8) were also detected. The frequency of CYP2C19*3 allele in most populations is below 1%; this allele is most common among Asians (2-9%) [15]. The less common CYP2C19 alleles associated with the lack or decreased activity of the enzyme are CYP2C19*4 (rs28399504), *5 (rs5637013), *6 (rs72552267), *7 (rs72558186), and *8. Frequency of occurrence of these variants, as a rule, is less than 1% [15, 16] and their definition is of no clinical significance.

CYP2C19 alleles with functions loss are inherited in an autosomal-dominant type. Thus, heterozygotes (for example, or *1/*2 and *1/*3) have a response to clopidogrel, which is intermediate, between the response of wild-type homozygotes (eg, *1/*1) and the homozygous response of alleles to loss of function (*2/*2) or complex heterozygotes (*2/*3) [16].

The first meta-analysis of Russian studies of clopidogrel pharmacogenetics in 2015 revealed that the presence of CYP2C19*2 polymorphism significantly increases the risk of complications such as cardiovascular mortality / myocardial infarction / stent thrombosis / ischemic stroke / transient ischemic attack (Chernov A.A., 2015). The data obtained are consistent with foreign meta-analyses on relevant topics (T. Bauer, 2011; Mao L., 2013).

Based on the ability of CYP2C19 substrates to metabolize people can be classified as enhanced metabolizers (UM), extensive metabolizers (EM), intermediate metabolizers (IM) and attenuated metabolizers (AM). Extensive metabolizers are homozygous for the CYP2C19*1 allele, which are associated with functional (physiological) metabolism mediated by CYP2C19. The genotype of the intermediate metabolizers have
Although studies show, that CYP2C19*17 carriers have lower residual platelet activity during clopidogrel treatment in comparison with non-carriers [15, 16], a 22% reduction in recurrent ACS and a 37% reduction of need in revascularization (PCI or CAPIB) in patients with acute myocardial infarction [17], as well as a significantly lower risk of recurrent ischemic cardiovascular events [18], other studies do not support such increased efficiency [10, 12, 19]. Moreover, a correlation between CYP2C19*17 presence and fatal cardiovascular events [12] or stent thrombosis was not observed [3]. Some of the inconsistencies in CYP2C19*17 data may be associated with small sample size of studies, a difference in study design, the studied population heterogeneity, different methodologies for genotyping and testing platelet functions, and partial conjunction CYP2C19*17 with CYP2C19*2 [12, 18, 20-22].

In his basic study, Sim et al. [9] reported a low frequency of the CYP2C19*17 allele in Chinese population (4%) in comparison to the Ethiopians and Swedes, who had the same distribution (18% in both). This broad interethnic variation in the allele frequency has now been confirmed in several studies [8, 13-14, 16-17, 21, 23-27]. The allele prevalence was usually <5% in Asians and about four times higher in the white and African populations. The frequency of CYP2C19*17 alleles in the Iranian population is 21.6% and is similar to the Middle East countries or Europe. The high frequency of the CYP2C19*17 allele in the Iranian population underlines this new allele variant importance in the metabolism of CYP2C19 substrates [29].

**Conclusion**

Thus, a review of literature data has shown the need for a genetic study (CYP2C19 genotyping) responsible for the metabolism of clopidogrel in patients with ACS/PCA to improve their clinical outcome.

Despite a large number of studies showing a decrease in the effectiveness of clopidogrel in patients with ACS/PCA from different ethnic groups with CYP2C19 genetic polymorphism, the role of genetic factors in individuals of the Kazakh population remains unclear. The studies on identification of the status of metabolizers in individuals with risk of stents thrombosis early developing are few and contradictory in accessible national literature.

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