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საქართველოს სამედიცინო სიახლენი

პაციენტმა არტერიული ჰიპერტენზიით, რევმატოი-დული ართრიტის გარეშე (3 მამაკაცი, 17 ქალი, საშუალო ასაკი – 55,65±1,19 წ.).

კვლევის შედეგად დადგენილია:

- თერაპია ვალსარტანით და მისი კომბინაცია ინდაპამიდთან ყველა პაციენტში ჰიპერტონიული დაავადებით და რევმატოიდული ართრიტით იწვევს მარცხენა პარკუჭის ჰიპერტროფიის რეგრესს, მარცხენა პარკუჭის გეომეტრიის ნორმალიზებას პაციენტთა 33%-ში, მარცხენა პარკუჭის დიასტოლური ფუნქციის გაუმჯობესებას 88,2%-ში;

- თერაპიაში ინდაპამიდის ჩართვა იწვევს არტერიული წნევის საშუალო მაჩვენებლების შემდგომ დაქვეითებას ღამის სათებში, ნორმალიზებული არტერიული წნევის მქონე პაციენტების რაოდენობის ზრდას 50-დან 75%-მდე; თერაპია ამლოდიპინით და ინდაპამიდით არ ცვლის არტერიული წნევის დღეღამურ რიტმს და საშუალო არტერიული წნევის შემცირების ხარისხს და მთლიანად ჯგუფში არ არის საკმარისი;

- არტერიული წნევის დღეღამური პროფილის მაჩვენებლების ცვლილებები, დადგენილი ჰიპერტონიული დაავადების და რევმატოიდული ართრიტის მქონე პაციენტების უმრავლესობაში ხასიათდება სისტოლური არტერიული წნევის დღის და ღამის საშუალო მაჩვენებლების მატებით, დღის ვარიაბელობის ზრდით და ღამის საათებში დაქვეითების უფრო დაბალი ხარისხით, ვიდრე პაციენტებში რევმატოიდული ართრიტის გარეშე.

- როზუვასტატინის 20 მგ-ის გამოყენება ჰიპერტონიული დაავადების და რევმატოიდული ართრიტის მქონე პაციენტების კომპლექსურ მკურნალობაში პაციენტების უმრავლესობაში ხელს უწყობს სისხლის ლიპიდური სპექტრის სამიზნე მაჩვენებლების მიღწევას.

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## CLINICAL AND GENETIC FACTORS OF CARDIOVASCULAR EVENTS DEVELOPMENT AFTER PERCUTANEOUS CORONARY INTERVENTION

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The extensive introduction of interventional method for acute coronary syndrome (ACS) treatment and the use of dual antiplatelet therapy have made safety a topical issue. Bleeding develops in every 10th patient after ACS during the period of administration and within 2 years, up to 4% patients have bleeding during the first hospitalization [1-3]. According to foreign authors, the risk of in-hospital bleeding in such patients has grown in 1.8 times over the past 10 years. Moreover, it is known that people who have undergone the major bleeding in the hospital have a higher risk of ischemic episodes, including fatal ones, over the next year [4]. There are no data on the prevalence of bleeding after PCI in the Republic of Kazakhstan.In this regard, the search for new markers of early diagnosis of bleeding while taking dual antiplatelet therapy remains relevant.

Recommendations for the acetylsalicylic acid and adenosine phosphate (ADP) receptor antagonists' prescription as dual antiplatelet therapy are the standard treatment for patients with ACS.

Clopidogrel is a highly effective antithrombotic drug with a high safety profile. However, as shown by numerous studies [5, 6, 7], the effectiveness of antiplatelet therapy depends on many factors. It was registered in a study of platelet aggregation in two and a half thousand patients in the framework of the Framingham study that the main influence on platelet function is exerted by genetic characteristics. So, close relatives showed similar indicators of aggregation, and the insufficient antiplatelet effect and undesirable drug reactions of antiplatelet agents, in most cases, were of a family nature.

Pharmacodynamics effects have focused on platelet aggregation for clopidogrel activated by CYP2C19.

The following phenotypes are distinguished in the human population depending on the catalytic activity of the CYP2C19 isoenzyme: «extensive metabolizers» (EM); carriers ща genotype CYP2C19*1/*1, 50; «intermediate metabolizers» (IM); carriers of the genotypes CYP2C19*1/*2, *1/*3, *2/*17, *3/*17); «poor metabolizers» (PM); carriers of the genotypes CYP2C19*2/*2, *2/*3, *3/*3 and «ultra extensive metabolizers» (UM); carriers of the genotypes CYP2C19*1/*17, *17/*17 (http://www.pharmgkb.org/).

The individuals with UM phenotype have the production of CYP2C19 with increased enzymatic activity and, as a consequence, a decrease in the pharmacological effect of drugs taken in a standard dose (the risk of undesirable drug reactions increases, on the contrary, in the case of prodrugs).

Numerous studies have made it clear that CYP2C19*17 variant is responsible for the accelerated exchange of enzyme substrates, including clopidogrel. This can contribute to an increase in the formation of the drug active metabolite and, accordingly, to an increase in the effect of the drug dose [8]. An increase in the risk of bleeding is possible in patients in this case, especially in homozygotes for this allele. ADP-induced aggregation in homozygous patients is the smallest, and the risk of bleeding is maximal. At the same time, there was no significant effect of CYP2C19*17 on the incidence of stent thrombosis [9].

So, the carriage of the allelic variant of CYP2C19 * 17 leads to an increase in biotransformation and an increase in the antiplatelet effect of clopidogrel, which can potentially lead to the development of bleeding. Reduced risk of ischemic complications and increased risk of bleeding are supported by the results of two independent meta-analyzes - Li Y, et al [10] and Zabalza M, et al [11].

According to Li Y, Tang HL. it can be seen that, compared with non-carriers of the CYP2C19 * 17 variant, carriers have a 16% decrease in recurrence of ACS in 9428 patients receiving clopidogrel during 1 year of follow-up, but have an increased risk of bleeding. As expected, carriers of CYP2C19 * 17 also have lower residual platelet reactivity than carriers.

Nevertheless, the clinical significance of CYP2C19 * 17, to date, remains controversial, and a number of studies confirm the absence of an independent effect of this polymorphism on the metabolism of clopidogrel [10]. And the increase in the antiplatelet effect of clopidogrel at a high frequency of CYP2C19 * 17 carriage, the authors associate with the often concomitant, absence or decrease in the frequency of CYP2C19 * 2 carriage [10].

In their main work, Sim et al. [12] reported a low frequency of the CYP2C19 * 17 allele in Chinese subjects (4%) compared to Ethiopians and Swedes, who had the same distribution (18% in both). The prevalence of the variant allele was generally less than 5% in Asians and over 20% in white and African populations.

The frequency of CYP2C19 * 17 alleles in the Iranian population is 21.6% and is similar to the countries of the Middle East or Europe. The high frequency of the CYP2C19 * 17 allele in the Iranian population emphasizes the importance of this new allele variant in the metabolism of CYP2C19 substrates [13].

Considering the prevalence of cardiovascular diseases and the medical-social significance of their therapy and secondary prevention, the issues of individual sensitivity to clopidogrel comes first in the number of pharmacogenetic studies. The results of this study can be applied in cardiological practice in predicting complications after stenting. In turn, this will help to increase not only clinical efficacy, but also prevent the risk of bleeding in patients receiving clopidogrel accordingly. Therefore, genotyping CYP2C19 * 17 before taking clopidogrel will be of invaluable benefit to patients with coronary artery disease.

Objective: to evaluate the effect of clinical and genetic factors on the development of complication after percutaneous coronary intervention against a background of double antiplatelet therapy.

**Material and methods.** This study is a clinical and genetic, study design: case-control. The study was carried out as part of targeted funding research (Ministry of Education and Science of the Republic of Kazakhstan) for 2018-2020 on the theme: «A personalized approach for significant diseases solving» in accordance with the task: «Revealing and assessment of the main genetic markers of resistance to antiplatelet therapy in patients with coronary heart disease among representatives of the main ethnic group of Kazakhstan», registration №0118PKO1034. The study was approved by the Ethics committee; the written informed consent was obtained from the each participant. The patients included in the study were selected according to inclusion and exclusion criteria.

Inclusion criteria: patients with bleeding on the background of dual antiplatelet therapy (acetylsalicylic acid and clopidogrel). Patients after percutaneous coronary intervention, receiving dual antiplatelet therapy (acetylsalicylic acid and clopidogrel), without bleeding.

Exclusion criteria: patients with severe comorbidities were excluded from the clinical study, such as: chronic heart failure IIB, III degree; chronic rheumatic heart disease; acute violation of cerebral circulation; decompensated liver cirrhosis; severe renal dysfunction; malignant neoplasms; refusal to participate in the study.

The study included 73 patients with coronary heart disease who underwent percutaneous coronary intervention receiving dual antiplatelet therapy (acetylsalicylic acid and clopidogrel) with bleeding and without bleeding. According to the results of the survey, the patients were divided into 2 groups: Group I (main) - patients with bleeding symptoms on the background of double antiplatelet therapy, Group II (control) - patients without bleeding on the background of double antiplatelet therapy.

The subjects belonged to the indigenous population and Kazakh nationality. All of patients of both sexes were at the age of 45-80. They were living in Karaganda region, were hospitalized in clinics at the municipal level. The study was carried out in the Shared Laboratory of the Scientific-research center based in Karaganda medical university (Karaganda, Republic of Kazakhstan).

Clinical examination of patients was carried out according to the generally accepted method with primary documentation filling using carefully collected medical history, objective examination of patients and laboratory and instrumental research methods.

Group I included 34 (46.57%) patients with verified coronary artery disease after percutaneous coronary intervention with bleeding, group II included 39 (53.43%) patients with verified coronary artery disease after percutaneous coronary intervention without bleeding signs. The fact of bleeding was ascertained when collecting anamnestic data. The average age of the subjects was 63.08 ± 8.86. Minimum 45 years, maximum 80 years.

Among the concomitant diseases, type 2 diabetes mellitus was common (29%); according to anamnestic data, 100% of patients have arterial hypertension. In total, 9% of cases of gastrointestinal bleeding were registered; in the same group, 9% of patients had a history of gastric ulcer and duodenal ulcer.

In patients with bleeding, the incidence of bleeding and severity were assessed according to the classification of the Bleeding Academic Research Consortium (BARC), approved by the Working Group on Thrombosis (2011). Based on the classification of the severity of bleeding BARC, the subjects were divided according to the severity of bleeding, where the most frequent sources were spontaneous subcutaneous hematomas (n=14), gingival and nasal bleeding were detected in the same number according to anamnestic data (n=8). According to the respondents, 9% had signs of GI that corresponded to FIIC according to Forrest classification based on FGDS data.

In the distribution of patients according to the BARC classifications, the most common was 1 severity, which included 46% of the subjects (n=16), 2 severity included 45% of the subjects (n=16), 3 severity was found in 9% (n=3) investigated.

An analysis of the polymorphism of the CYP2C19 gene allele 17 was revealed. Genotyping was carried out by a method based on the polymerase chain reaction. Whole blood obtained from the cubital vein of the subject was used as biological material. DNA was isolated from whole blood using the GeneJET Genomic DNA Purification Kit (Thermo Scientific). Samples preparation was performed using real-time PCR mix TaqMan® OpenArray® Genotyping Master Mix (Applied Biosystems). Gene polymorphism was determined using the QuantStudio TM 12K Flex Real-Time PCR system (Applied Biosystems) on TaqMan® OpenArray® Genotyping Plate, Custom Format 64 QuantStudio TM 12K Flex (Applied Biosystems) system. The tablets were filled with the reaction mixture using the QuantStudio TM 12K Flex Accufill System automated station (Applied Biosystems). Data analysis was performed using the TaqMan Genotyper Software v.1.3 software package.

Statistical processing of the obtained data was carried out using the software package Statistica 6.0. In order to determine the statistically normal distribution of the sample, the Shapiro – Wilk test was used, which is the criterion for checking whether the observed sample belongs to a normal population. In addition, it was determined the odds ratio index to evaluate the bleeding risk, depending on the contribution of a particular risk factor. The correspondence with the Hardy – Weinberg equilibrium of genotypes frequencies of the studied allelic variants in the control group and the study group was checked using the exact criterion. The Pearson $\chi 2$ criterion was used to check the statistical significance of the differences between the «case» and

*Table. Association of CYP2C19*17 gene polymorphism with a risk of bleeding*

| Genotype | The patients with bleeding (group I) n (%) | The patients without bleeding (group II) n (%) | OR | 95% CI | |
|---|---|---|---|---|---|
| | | | | Lower bound | Upper bound |
| CYP2C19*17 | n =34 | n=39 | | | |
| C/C | 31 (91%) | 34 (87%) | 0.658 | 0.145 | 2.984 |
| C/T | 3 (9%) | 5 (13%) | | | |

«control» groups, the odds ratio was calculated taking into account the 95% confidence interval.

**Results and discussion.** During the study all the patients (n=73) were divided into 2 groups: group I included 34 (46.57%) patients with verified ischemic heart disease after the stenting procedure with bleeding, group II included 39 (53.43%) patients with verified ischemic heart disease after a stenting procedure without bleeding signs. Patients in both groups received DAT. The fact of bleeding was ascertained during the survey and collection of anamnestic data. The average age of the subjects was 63.08±8.86 (min 45 years, max 80 years). The distribution of patients in groups corresponded to the normal distribution according to Shapiro – Wilk.

The subjects mainly were men (74%), the patients at the age of 45-65 years accounted 64%, and only 10% were over 65 years old. In contrast, fewer women were included in the study (16%), but women were older, mostly more than 65 years old (18%), the smallest number were between 55-65 years old.

The odds ratio (OR) was calculated to determine the risk of bleeding after PCI according to the anamnestic data of the respondents.

According to the analysis of anamnestic data, it was found that the predictors of bleeding in patients after PCI against a background of DAT were: female gender (OR=3.405, p=0.027), diabetes mellitus (OR=2.399, p=0.046), BMI (OR=1.200, p=0.038), stenting of the coronary arteries (OR=1.045, p=0.030).

Based on the analysis of laboratory and instrumental data, it was revealed that the bleeding predictors in patients after PCI against a background of DAT were: the level of red blood cells (OR=2.292, p=0.049), the platelets level (OR=3.964, p=0.048), hemoglobin (Hb) (OR=1.333, p=0.042), ESR (OR=1.008, p=0.009), ejection fraction (OR=1.248, p=0.043), glomerular filtration rate (OR=1.227, p=0.002).

In our study, genotyping on the allelic variant CYP2C19*17 (rs12248560) by polymerase-chain reaction was realized in 73 patients of both groups (main, control) receiving DAT after PCI.

According to a genetic study, CYP2C19*17 C/T gene polymorphism was detected in 9% of patients with bleeding during double antiplatelet therapy.

The odds ratio (OR) was calculated with 95% confidence interval taking into account the data obtained by polymerase-chain reaction to determine the association of CYP2C19*17 gene polymorphism with the risk of bleeding in patients after PCI against a background of DAT. Table presents the data on the impact of CYP2C19*17 gene polymorphism on the bleeding risk.

According to results of the analysis of genotypes in the first and second groups, there was no statistically significant difference in genotypes of the 17 allele CYP2C19 in the Kazakh population. The obtained values were Odds Ratio <1 (OR=0.658), 95% confidence interval [0.145-2.984] for all the studied polymorphisms which indicates the absence of polymorphism association of the CYP2C19*17 gene with a risk of bleeding.

It was found on the base of the clinical and laboratory characteristics of the bleeding risk in patients after percutaneous coronary intervention that the bleeding predictors after PCI against a background of DAT were: female gender (OR=3.405, p=0.027), the presence of diabetes mellitus (OR=2.399, p=0.046), body mass index (BMI) (OR=1.200, p=0.038), coronary artery stenting (OR=1.045, p=0.030), erythrocytes level (OR=2.292, p=0.049), platelets amount (OR=3.964, p=0.048), hemoglobin (Hb) (OR=1.333, p=0.042), erythrocyte sedimentation rate (ESR) (OR=1.008, p=0.009), ejection fraction (OR=1.248, p=0.043), glomerular filtration rate (OR=1.227, p=0.002). According to a genetic study, CYP2C19*17 C/T gene polymorphism was detected in 9% of patients with bleeding during double antiplatelet therapy. The analysis of genotypes in the first and second groups showed no statistically significant difference in genotypes of the 17 allele CYP2C19. The obtained values were Odds Ratio <1 (OR=0.658), 95% confidence interval [0.145-2.984] for all the studied polymorphisms which indicates the absence of polymorphism association of the CYP2C19*17 gene with a risk of bleeding.

Some studies show that CYP2C19*17 carriers associated with clopidogrel use in comparison with non-carriers have a lower residual platelet reactivity [10,11], a 22% reduction in repeated ACS and a 37% reduction in revascularization in patients with acute myocardial infarction [12], as well as a significantly lower risk of recurring ischemic cardiovascular events [13]. Other studies do not support such increased efficacy [8,14,15]. Moreover, there was no association between CYP2C19*17 and fatal cardiovascular events [8] or stent thrombosis [16].

Thus, the analysis of risk factors that have shown a high chance as bleeding predictors in the decision-making process about DAT prescribing in each specific clinical case will allow recommending a rational combination, significantly reducing the risk of possible bleeding and personifying therapy. The obtained values of the odds ratio (OR=0.658) with a confidence interval [0.145-2.984] for all the studied polymorphisms allows to state the absence of CYP2C19*17 gene polymorphism association with the bleeding risk in the examined patients.

Moreover, some of the inconsistencies in the data on CYP2C19*17 may be associated with a small range of sample, a different research design, a small effect size, heterogeneity of the studied population and various methodologies for genotyping and testing of platelets functions.

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## SUMMARY

## CLINICAL AND GENETIC FACTORS OF CARDIOVASCULAR EVENTS DEVELOPMENT AFTER PERCUTANEOUS CORONARY INTERVENTION

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The new cardiovascular events development remains the main factors limiting its long-term effectiveness despite technological progress and the widespread use of percutaneous coronary intervention (PCI).

Objective - to assess the effect of clinical and genetic factors on the development of complication after percutaneous coronary intervention with double antiplatelet therapy (DAT).

Case-control. The main group included 34 (46.57%) patients with ischemic heart disease after the procedure of percutaneous coronary intervention with bleeding, the control group included 39 (53.43%) patients with verified ischemic heart disease after the procedure of percutaneous coronary intervention without bleeding signs.

The average age of the patients in the main group was 63.25±8.7, this group included 65% men and 35% women. The average age of the patients in the control group was 63.82±8.9, this group included 87% men and 13% women, respectively. It was found on the base of the clinical and laboratory characteristics of the bleeding risk in patients after percutaneous coronary intervention that the bleeding predictors after PCI against a background of DAT were: female gender (OR=3.405, p=0.027), the presence of diabetes mellitus (OR=2.399, p=0.046), body mass index (BMI) (OR=1.200, p=0.038), coronary artery stenting (OR=1.045, p=0.030), erythrocytes level (OR=2.292, p=0.049), platelet count (OR=3.964, p=0.048), hemoglobin (Hb) (OR=1.333, p=0.042), erythrocyte sedimentation rate (ESR) (OR=1.008, p=0.009), ejection fraction (OR=1.248, p=0.043), glomerular filtration rate (OR=1.227, p=0.002). According to a genetic study, CYP2C19*17 C/T gene polymorphism was detected in 9% of patients with double antiplatelet therapy.

There was no statistically significant difference in genotypes of the 17th allele CYP2C19 in accordance with the results of the analysis of genotypes in the first and second groups. The Odds Ratio values (OR=0.658), 95% confidence interval [0.145-2.984] were obtained for all the studied polymorphisms, which indicates the absence of polymorphism association of CYP2C19*17 gene with a risk of bleeding.

**Keywords:** coronary heart disease, gene polymorphism, percutaneous coronary intervention, stenting, restenosis, bleeding, clopidogrel, CYP2C19, acute coronary syndrome.

## РЕЗЮМЕ

# КЛИНИКО-ГЕНЕТИЧЕСКИЕ ФАКТОРЫ РАЗВИТИЯ СЕРДЕЧНО-СОСУДИСТЫХ СОБЫТИЙ ПОСЛЕ ЧРЕСКОЖНОГО КОРОНАРНОГО ВМЕШАТЕЛЬСТВА

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Несмотря на широкое использование чрескожного коронарного вмешательства (ЧКВ), развитие новых сердечно-сосудистых событий остается основным фактором, ограничивающим его долговременную эффективность.

Целью исследования явилась оценка влияния клинических и генетических факторов на развитие осложнений после чрескожного коронарного вмешательства на фоне двойной антитромбоцитарной терапии.

Дизайн исследования - случай-контроль. Основная группа включала 34 (46,57%) больных ишемической болезнью сердца (ИБС) после процедуры чрескожного коронарного вмешательства с кровотечением, средний возраст составил 63,25±8,7 г., из них 22 (65%) мужчин, 12 (35%) женщин. Контрольную группу составли 39 (53,43%) больных верифицированной ИБС после процедуры чрескожного коронарного вмешательства без признаков кровотечения, средний возраст составил 63,82±8,9 г., из них 34 (87%) мужчин, 5 (13%) женщин.

На основании оценки клинико-лабораторных характеристик риска развития кровотечений у больных после чрескожного коронарного вмешательства выявлено, что предикторами развития кровотечений у больных после ЧКВ на фоне двойной антитромбоцитарной терапии являлись: женский пол (OR=3.405, p=0.027), наличие сахарного диабета (OR=2,399, p=0,046), ИМТ (OR=1.200, p=0,038), стентирование коронарных артерий (OR=1.045, p=0,030), уровень эритроцитов (OR=2.292, p=0.049), уровень тромбоцитов (OR=3.964, p=0,048), гемоглобин (Hb) (OR=1.333, p=0,042), СОЭ (OR=1.008, p=0,009), фракция выброса (OR=1.248, p=0.043), скорость клубочковой фильтрации (OR=1.227, p=0.002). По данным проведенного генетического исследования полиморфизм гена CYP2C19*17 C/T выявлен у 9% пациентов на фоне двойной антитромбоцитарной терапии. Анализ генотипов в первой и второй группе статистически значимой разницы по генотипам 17 аллеля CYP2C19 не выявил. Для всех исследованных полиморфизмов получены значения Odds Ratio (OR=0.658), 95% доверительный интервал 0,145-2,984, что позволяет судить об отсутствии ассоциации полиморфизма гена CYP2C19*17 с риском развития кровотечений.

## რეზიუმე

# გულ-სისხლძარღვოვანი მოვლენების განვითარების კლინიკურ-გენეტიკური ფაქტორები კანგავლითი კორონარული ჩარევის შემდგომ

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ყარაგანდის სახელმწიფო სამედიცინო უნივერსიტეტი, ყაზახეთი

ტექნიკური პროგრესის და კანგავლითი კორონარული ჩარევის გამოყენების ფართო გავრცელების მიუხედავად, ახალი გულ-სისხლძარღვოვანი მოვლენების განვითარება რჩება ამ ჩარევის გრძელვადიანი ეფექტურობის შემზღუდავ ძირითად ფაქტორად.

კვლევის მიზანს წარმოადგენდა კლინიკური და გენეტიკური ფაქტორების გავლენის შეფასება გართულებების განვითარებაზე კანგავლითი კორონარული ჩარევის შემდგომ ორმაგი ანტითრომბოციტული თერაპიის ფონზე.

კვლევის დიზაინი – შემთხვევა-კონტროლი. ძირითადი ჯგუფი მოიცავდა 34 (46,57%) პაციენტს გულის იშემიური დაავადებით და სისხლდენით კანგავლითი კორონარული ჩარევის პროცედურის შემდეგ, საშუალო ასაკი - 63,25±8,7 წელი,მათგან 22 (65%) - მამაკაცი, 12 (35%) - ქალი. საკონტროლო ჯგუფი შეადგინა 39 (53,43%) პაციენტმა ვერიფიცირებული გულის იშემიური დაავადებით და სისხლდენის ნიშნების გარეშე კანგავლითი კორონარული ჩარევის პროცედურის შემდეგ, საშუალო ასაკი - 63,82±8,9 წელი, მათგან 34 (87%) მამაკაცი, 5 (13%) ქალი.

კანგავლითი კორონარული ჩარევის შემდეგ სისხლდენის განვითარების რისკის კლინიკურ-ლაბორატორიული მახასიათებლების შეფასების საფუძველზე დადგენილია,რომ სისხლდენის განვითარების პრედიქტორებს ორმაგი ანტითრომბოციტული თერაპიის ფონზე წარმოადგენს: მდედრობითი სქესი OR=3.405, p=0.027), შაქრიანი დიბეტის არსებობა (OR=2,399, p=0,046), სხეულის მასის ინდექსი (OR=1.200, p=0,038), კორონარული არტერიების სტენტირება (OR=1.045, p=0,030), ერითროციტების დონე (OR=2.292, p=0.049), თრომბოციტების დონე (OR=3.964, p=0,048), ჰემოგლობინი (OR=1.333, p=0,042), ედს (OR=1.008, p=0,009), განდევნის ფრაქცია (OR=1.248, p=0.043), გორგლოვანი ფილტრაციის სიჩქარე (OR=1.227, p=0.002). ჩატარებული გენეტიკური კვლევის მონაცემების მიხედვით, გენი CYP2C19*17 C/T-ის პოლიმორფიზმი გამოვლინდა პაციენტების 9%-ში ორმაგი ანტითრომბოციტული თერაპიის ფონზე. გენოტიპების ანალიზით პირველ და მეორე ჯგუფებში CYP2C19-ის 17 ალელის სტატისტიკურად სარწმუნო განსხვავება არ აღინიშნა. ყველა გამოკვლეული პოლიმორფიზმისათვის მონაცემები მიღებულია Odds Ratio (OR=0.658), სარწმუნობის 95%-იანი ინტერვალი - 0,145-2,984, რაც მიუთითებს გენი CYP2C19*17 -ის პოლიმორფიზმის ასოციაციის არარსებობაზე სისხლდენის განვითარების რისკთან.