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THE CLINICAL RESPONSE TO CLOPIDOGREL BASED ON CYP2C19 GENE POLYMORPHISMS IN CORONARY PATIENTS AFTER DRUG-ELUTING STENT IMPLANTATION

321.03 – CARDIOLOGY

Summary of doctoral thesis in medical sciences

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The thesis was elaborated at the Discipline of Clinical Synthesis, Department of Internal Medicine, the Genetics Laboratory, *Nicolae Testemitanu* State University of Medicine and Pharmacy of the Republic of Moldova and the Institute of Cardiology.

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1. INTRODUCTION

The actuality and importance of the researched problem. For decades, over half a billion people worldwide continue to be affected by cardiovascular diseases (CVD), constituting the leading cause of death globally. In 2021, 20.5 million people died due to cardiovascular conditions, representing approximately one-third of global deaths [1,2]. Cardiovascular disease is the most common cause of death in the member countries of the European Society of Cardiology, accounting for just under 2.2 million deaths in women and just over 1.9 million deaths in men, according to 2021 data. Among these, ischemic heart disease (IHD) is the primary cause of death due to cardiovascular diseases, representing 38% of total cardiovascular deaths in women and 44% in men [3].

Cardiovascular diseases consistently rank first among the causes of death in the Republic of Moldova, constituting 58.0% of total mortality [4]. The incidence of cardiovascular diseases in 2022 reached 1997.3 cases per 100,000 inhabitants, which is 1.2 times higher compared to 2021 (1 681.8 cases per 100,000 inhabitants). The prevalence was 29 793.2 cases per 100,000 inhabitants compared to 28 302.5 cases per 100.000 inhabitants in 2021 [5].

Ischemic heart disease is a pathological process characterized by obstructive or non-obstructive accumulation of atherosclerotic plaque in the epicardial arteries. It can have long, stable periods of progression but can become unstable at any time through plaque rupture or erosion, leading to the occurrence of an acute atherothrombotic event [6,7].

Myocardial revascularization plays a central role in the management of coronary syndromes alongside pharmacological treatment. The foundation of medical treatment for coronary patients after acute coronary syndrome (ACS) and/or percutaneous coronary intervention is dual antiplatelet therapy (DAPT) with aspirin and an oral $P2Y_{12}$ platelet receptor inhibitor for adenosine 5'-diphosphate (ADP) to prevent major adverse cardiovascular events (MACE), such as death, stent thrombosis, myocardial infarction (MI), and stroke [8,9].

Clopidogrel remains the most used and commonly prescribed $P2Y_{12}$ inhibitor. Despite this, the antiplatelet effects induced by clopidogrel are inadequate in nearly a quarter of patients and may present an increased risk of recurrent ischemic events [10]. Clinical practice guidelines recommend the use of more potent $P2Y_{12}$ inhibitors (prasugrel, ticagrelor) compared to clopidogrel to reduce ischemic events after ACS [11], but these may increase the risk of bleeding complications compared to clopidogrel [12,13]. Clopidogrel is a prodrug, and to result in the active metabolite that inhibits platelet aggregation, it must be metabolized via cytochrome P450 isoenzymes [14]. The main hepatic enzyme involved in converting clopidogrel to its active metabolite is CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19 of cytochrome P450). This enzyme is highly polymorphic, with more than 35 alleles [15]. Numerous retrospective studies have shown that loss-of-function alleles CYP2C19*2 and CYP2C19*3 are associated with high platelet reactivity during clopidogrel treatment and recurrent ischemic complications [16,17]. There is significant genetic variability among patients, and each patient may have a different response to commonly prescribed clopidogrel. Personalizing antiplatelet therapy by knowing a patient's CYP2C19 phenotype allows us to anticipate potential effectiveness, may help prescribe the optimal antiplatelet agent, and maximize benefits by reducing the risk of recurrent cardiovascular events and adverse effects such as bleeding [18].

In this context, it would be sensible to assess the existence of CYP2C19 enzyme polymorphisms in coronary patients from the Republic of Moldova who have undergone myocardial revascularization

with stent implantation, and to evaluate their effect on the incidence of major adverse cardiovascular events and bleeding after 6-12 months of dual antiplatelet therapy with aspirin and clopidogrel.

The aim of the study is to evaluate the clinical and paraclinical aspects, the ischemic and hemorrhagic risk of coronary patients who have undergone percutaneous coronary intervention with the implantation of a drug-eluting stent, and the impact of the clinical response to clopidogrel in the context of dual antiplatelet therapy based on the polymorphisms of the CYP2C19 gene.

To achieve the aim, the following objectives were outlined:

1. Determination of the frequency of CYP2C19 polymorphism, which influences the hepatic metabolism of clopidogrel, in coronary patients who underwent percutaneous coronary intervention with drug-eluting stent implantation based on the frequency of CYP2C19 polymorphism and in healthy subjects from the Republic of Moldova.
2. Study of clinical and paraclinical aspects, cardiovascular risk factors in coronary patients who underwent percutaneous coronary intervention with drug-eluting stent implantation based on the frequency of CYP2C19 polymorphism.
3. Assessment of bleeding risk (using the PRECISE-DAPT score) and ischemic risk (using the DAPT score) in coronary patients who underwent percutaneous coronary intervention with drug-eluting stent implantation.
4. Estimation of the impact of CYP2C19 polymorphism on the patient's clopidogrel metabolizer status: poor/intermediate, normal, and rapid/ultrarapid, in association with major bleeding and cardiovascular events (cardiovascular death, nonfatal myocardial infarction, stroke, severe recurrent angina, definite stent thrombosis, repeated revascularization) over the period of 6-12 months.
5. Analysis of the correlation of potential predictors for the occurrence of recurrent ischemic and bleeding events in patients with dual antiplatelet therapy comprising aspirin and clopidogrel after percutaneous coronary intervention, and the development of prognostic models to determine the likelihood of ischemic and hemorrhagic events.

General research methodology. A prospective observational analytical cohort study was conducted to assess the response to clopidogrel based on CYP2C19 polymorphisms in coronary patients after drug-eluting stent implantation. The study is the result of a scientific collaboration involving two medical centers in the Republic of Moldova (IMSP SCM "Sfânta Treime" and IMSP Institute of Cardiology) and the Genetics Laboratory of *Nicolae Testemitanu* State University of Medicine and Pharmacy. Initially, 211 patients requiring Dual Antiplatelet Therapy (DAPT) with aspirin and clopidogrel after myocardial revascularization through Percutaneous Coronary Intervention (PCI) with drug-eluting stent implantation for ACS were included in the research. Final evaluation was performed on 172 patients (39 excluded due to emerging exclusion criteria during the follow-up period). To determine the frequency of CYP2C19 polymorphisms in individuals without cardiovascular pathology, a cohort of 430 apparently healthy subjects enrolled in 2011 at the faculties of General Medicine, Pharmacy, and Dentistry at "Nicolae Testemițanu" State University of Medicine and Pharmacy was included in the study. The research was approved by the Research Ethics Committee of "N. Testemițanu" State University of Medicine and Pharmacy, examined at the session on May 14, 2018, with the issuance of favorable opinion No. 61 on May 21, 2018. All patients were

uniformly monitored until the end of the study. Evaluation criteria remained unchanged throughout the research.

The scientific novelty and originality of the obtained results lie in the evidence-based adjustment of prediction criteria for acute major ischemic events and bleeding in post-PCI coronary patients receiving Dual Antiplatelet Therapy (DAPT) with aspirin and clopidogrel. The assessment results provide arguments in favor of genotype-personalized DAPT based on the genetic polymorphism of CYP2C19 in post-PCI coronary patients taking DAPT (aspirin-clopidogrel). The following groundbreaking achievements were made: 1) identification of allelic frequencies of CYP2C12 and phenotypes in healthy subjects; 2) estimation of allelic frequencies of CYP2C12 and phenotypes in post-PCI coronary patients on DAPT; 3) evaluation of cardiovascular risk factors and management influencing parameters; 4) addressing major acute ischemic and bleeding events over 6-12 months in post-PCI patients on DAPT (aspirin-clopidogrel) depending on CYP2C19 polymorphism; 5) creation of a *Prediction Model for Acute Major Ischemic Events in post-PCI coronary patients undergoing dual antiplatelet therapy (aspirin + clopidogrel),* and 6) development of a *Predictive Model for Bleeding Events over a 6-12 month period in post-PCI coronary patients undergoing dual antiplatelet therapy (aspirin + clopidogrel).*

The scientific problem solved

The frequencies of the CYP2C19 polymorphism have been determined in coronary patients undergoing PCI with drug-eluting stent implantation and in healthy subjects from the Republic of Moldova. The impact of the CYP2C19 polymorphism on the clopidogrel metabolizer status of patients was assessed: slow/intermediate, normal, and rapid/ultra-rapid, in association with major hemorrhagic and cardiovascular events (cardiovascular death, nonfatal MI, stroke, severe recurrent angina, definite stent thrombosis, revascularization) over a period of 6-12 months. The evaluation results allowed the development of personalized genomic prediction strategies for acute major ischemic and hemorrhagic events in the context of CYP2C19 polymorphism: the development of the *Acute Major Ischemic Event Prediction Model in post-PCI coronary patients receiving DAPT (aspirin-clopidogrel),* which predicts these events based on the poor-intermediate metabolizer phenotype, the presence of a history of old myocardial infarction, abdominal circumference, and stent length on the lesion, and the development of *the Predictive Model for Bleeding Events* occurring within 6-12 months in post-PCI coronary patients receiving DAPT (aspirin-clopidogrel) based on the rapid-ultra-rapid metabolizer phenotype and hemoglobin level.

Theoretical Significance of the Research.

The present research once again highlights the literature data regarding the presence of interindividual variability in the response to clopidogrel and recurrent thrombotic events after PCI, with genetic variation in CYP2C19 being one of the factors responsible for the hyporesponse to this antiplatelet agent. The obtained results reinforce the theoretical concept data. It has been demonstrated once again that personalized medicine has the advantage, serving as the key to preventing the failure of antiplatelet treatment in patients who have undergone PCI with drug-eluting stent implantation.

The applicative value lies in the development of the *Prediction Model for Acute Major Ischemic Events in post-PCI coronary patients receiving DAPT (aspirin+clopidogrel).* Using multivariate regression, the model considers the slow-intermediate metabolizer phenotype, the

presence of a history of old myocardial infarction, abdominal circumference, and stent length on the lesion. Additionally, the *Predictive Model for Bleeding Events* over a period of 6-12 months in post-PCI coronary patients receiving DAPT (aspirin+clopidogrel) was established based on the rapid-ultrarapid metabolizer phenotype and hemoglobin levels at different stages of medical care provision. The study results formed the basis for the development of the concept of enhancing the prediction of recurrent ischemic and bleeding events, contributing to: 1) recommending CYP2C12 genotyping with the inclusion of the individual's phenotype in the electronic medical record. This would enable clinicians to make informed decisions, particularly when the individual is undergoing revascularization through PCI with drug-eluting stent implantation; 2) recommending CYP2C19 genotyping for patients with high-risk ACS in terms of both ischemic and bleeding events. This is particularly relevant for those requiring personalized dual antiplatelet therapy before initiating treatment with clopidogrel.

The scientific results have been implemented in the Department of Interventional Cardiology and Endovascular Surgery at the SCM "Sfanta Treime", in the Cardiovascular Surgery and Cardiac Rehabilitation Department of the Institute of Cardiology.

Approval of Scientific Results. The significant results have been communicated and discussed at various national and international scientific events, including the International Congress "Preparing the Future by Promoting Excellence" (Iasi, 2019), the Annual Scientific Conference dedicated to the days of *Nicolae Testemitanu* State University of Medicine and Pharmacy (Chisinău, October 15-18, 2018), the Annual Scientific Conference dedicated to the days of *Nicolae Testemitanu* State University of Medicine and Pharmacy (Chisinău, October 15-18, 2019), the 7th International Medical Congress for Students and Young Doctors "MedEspera" (Chisinău, 2018), the 58th Congress of the Romanian Society of Cardiology (Sinaia, Romania, 2019), and the 6th International Conference on Nanotechnologies and Biomedical Engineering - Proceedings of ICNBME-2023 (Chisinău, Moldova, September 20–23, 2023).

The thesis was discussed, approved, and recommended for defense at the meeting of the Department of Internal Medicine, Clinical Synthesis Discipline, *Nicolae Testemitanu* State University of Medicine and Pharmacy of the Republic of Moldova (minutes no. 3 dated October 9, 2023), and the Scientific Seminar of profile 321.03. Cardiology (minutes no. 4 dated November 22, 2023).

Publications on the Thesis Topic. The study materials have been reflected in 29 scientific publications, including: 10 articles, including 3 articles in ISI, SCOPUS, and other international databases, 6 articles in B category, 1 article in C category; abstracts – 6 in the proceedings of national and international scientific conferences. Out of the total publications, 2 articles are without co-authors.

Volume and Structure of the Thesis. The thesis spans 107 pages and includes introduction, 4 chapters, 23 tables, 32 figures, synthesis of the obtained results, general conclusions and practical recommendations, bibliography from 165 sources, three innovation certificates, 6 implementation documents, information on the valorization of research results, and a statement of responsibility. The study materials have been reflected in 16 scientific publications.

Keywords: dual antiplatelet therapy (DAPT) with clopidogrel, CYP2C19 gene polymorphisms.

2. RESEARCH MATERIAL AND METODS

To achieve the proposed objective, an analytical observational prospective cohort study was conducted during the period of 2018-2021 at the IMSP "Institute of Cardiology", SCM "Sfanta Treime" in Chisinău municipality, and the Genetics Laboratory of the *Nicolae Testemitanu* State University of Medicine and Pharmacy. Ethical approval for the study was obtained from the Committee for Research Ethics at *Nicolae Testemitanu* State University of Medicine and Pharmacy on May 14, 2018, and informed consent was obtained from all participating patients.

2.1 Clinical Material Characteristics

In the research, initially, 211 patients who required dual antiplatelet therapy with aspirin and clopidogrel after myocardial revascularization through PCI with the implantation of an active drug-eluting stent for ACS were included. In the end, 172 patients were evaluated (39 patients were excluded from the study due to exclusion criteria that emerged during the follow-up period). The majority of the patients in the study had a diagnosis of acute myocardial infarction, accounting for 88.4% of cases, while 11.5% of cases were diagnosed with unstable angina.

The need for myocardial revascularization through PCI and dual antiplatelet therapy was indicated according to current guidelines from the European Society of Cardiology and national clinical protocols. Patients received a loading dose of 600 mg clopidogrel and 300 mg aspirin, followed by a maintenance dose of aspirin 75-100 mg and 75 mg clopidogrel daily.

Inclusion criteria:

1. Patients requiring antiplatelet therapy (aspirin + P2Y12 inhibitor – clopidogrel) after myocardial revascularization through PCI for ACS.
2. Informed consent obtained.

Exclusion criteria:

1. Patients on anticoagulant treatment;
2. Coronary patients with metal stent implantation (BMS, bare metal stent) or those not revascularized through PCI;
3. Patients who underwent coronary revascularization by aortocoronary bypass;
4. Patients with a history of gastrointestinal disease or surgery (except for simple appendectomy or hernia repair) that could influence drug absorption in the gastrointestinal tract;
5. Malignancy;
6. History of clinically significant or persistent thrombocytopenia;
7. Patients with active bleeding or significantly increased risk of bleeding, such as severe liver failure, present peptic ulcer, proliferative diabetic retinopathy, history of severe systemic bleeding, gastrointestinal bleeding, macrohematuria, intraocular bleeding, hemorrhagic stroke, or intracranial bleeding) or coagulopathy;
8. Renal failure requiring dialysis;
9. Advanced heart failure, LVEF <30%;

10. Medical, geographical, or social factors that would make participation in the study impossible, such as the inability to provide written informed consent and understand the full meaning of informed consent, or patient refusal to participate in the study;
11. Current use of antidepressants (fluoxetine, fluvoxamine, or moclobemide), use of medications for certain forms of epilepsy (carbamazepine or oxcarbazepine), use of proton pump inhibitors (omeprazole).

Out of the 172 patients included in the study, the majority were male – 140 cases, constituting 81.4% (95% CI 75.1, 86.7). The youngest patient who underwent PCI revascularization was 31 years old, while the oldest was 85 years old. The average age was 61±10 years, with a median of 61 (IQR=11), and the data had a normal distribution. Based on origin, 108 (62.8%) (95% CI 55.4, 69.8) were from urban areas, while 64 (37.2%) (95% CI 30.2, 44.6) were from rural areas.

Initially, **in phase I**, patient interviews were conducted, along with clinical examinations, collection of paraclinical data, calculation of the PRECISE-DAPT score to individualize the duration of DAPT, and collection of a blood sample (approximately 5 ml) from each subject for genotyping.

After obtaining the genotype and phenotype, all patients were divided into three research groups:

Subgroup I consisted of patients with the following genotypes: CYP2C19*1/*2, *2/*2, *2/*17; *3/17, including patients with an intermediate and slow metabolizer phenotype;

Subgroup II was composed of patients with the CYP2C191/1 genotype, the normal (extensive) metabolizers;

Subgroup III included patients with the genotype CYP2C191/17, CYP2C1917/*17, i.e., the rapid and ultrarapid metabolizers.

In phase II, the end points in the study subgroups were assessed after 6-12 months of DAPT administration: cardiovascular events (cardiovascular death, non-fatal myocardial infarction, stent thrombosis, aggravated angina with rehospitalization, repeated revascularization) and major or minor bleedings in coronary patients who underwent PCI, in correlation with the CYP2C19 gene polymorphisms over a follow-up period of 6-12 months. This included the statistical processing of data, obtaining results, and drawing conclusions.

To determine the frequency of CYP2C19 polymorphisms in individuals without cardiovascular pathology, a cohort of 430 apparently healthy subjects, enrolled in the year 2011 at the faculties of General Medicine, Pharmacy, and Dentistry at *Nicolae Testemitanu* State University of Medicine and Pharmacy, aged between 18 and 29, was recruited for the study. Exclusion criteria from the study included individuals who do not hold the citizenship of the Republic of Moldova, individual refusal to participate in the study, and pregnant women.

2.2 The study design is schematically represented in figure 2.1.

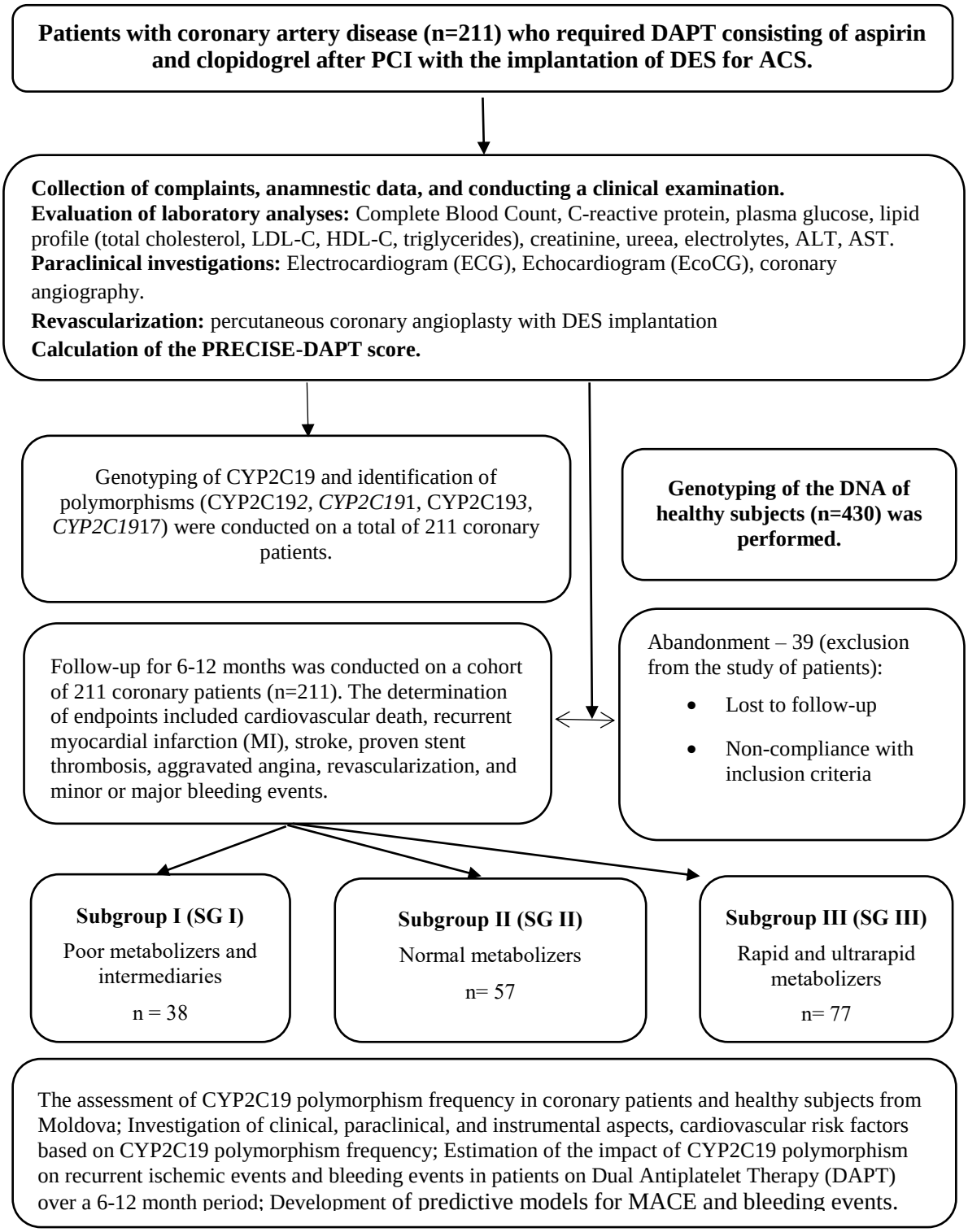

Figure 2.1**. Research design**

The monitoring of patients over the course of 6-12 months of DAPT administration was primarily conducted through telephone interviews with the patient, their relatives, or the family doctor. Additionally, visits to the cardiology clinic were carried out for 6-12 months, involving the determination of recurrent ischemic events (cardiovascular death, nonfatal myocardial infarction, stent thrombosis, worsened angina with hospitalization, repeated revascularization) and major or minor bleeding events

2.3 Research methods employed in the study

Initially, the survey was conducted through patient interviews, with the results included in a specially designed questionnaire. This questionnaire covered demographic information (age, gender, living environment), the patient's complaints characterizing anginal pains, medical history, the presence of risk factors, smoking status, comorbidities, and overall health. The clinical examination included the classic assessment of the patient with an evaluation of organ system data and the determination of hemodynamic indices (systolic blood pressure, diastolic blood pressure, heart rate). Anthropometric indices analyzed included height, body weight, body mass index (BMI), and waist circumference. Laboratory analyses comprised a complete blood count, plasma glucose, lipid profile, C-reactive protein (CRP), ALT, AST, creatinine, urea, electrolyte levels, quantitative troponin, CK-MB, and NT-proBNP. Non-invasive instrumental evaluations used in the study included ECG and 2D transthoracic echocardiography, while invasive instrumental investigations involved angiographic examination.

2.4 Characteristics of the Biological Material

From each patient, a blood sample (5 ml) was collected in an EDTA-containing vacutainer as an anticoagulant. The sample processing and molecular genetic analyses were conducted at the Genetics Laboratory of the *Nicolae Testemitanu* State University of Medicine and Pharmacy. Genomic DNA was extracted using the Thermo Scientific GeneJET Genomic DNA Purification Kit #0722; DNA purity and concentration were assessed using the NanoDrop 2000c Spectrophotometer (Thermo Fisher Scientific). Tests for CYP2C19 polymorphisms were conducted using the TaqMan® SNP Genotyping Assays method.

The following loci related to clopidogrel were examined: rs4244285 (CYP2C19**2)*, *rs4986893 (CYP2C19*3), rs12248560 (CYP2C19*17) (Table 2.1)

Table 2.1**. Information about the CYP2C19 SNPs used in the current study**

Locus (dbSNP)	Variation	Assay ID	Context Sequence [VIC/FAM]
rs4244285	681G>A, *Transition Substitution*	C__25986767_70	TTCCCACTATCATTGATTATTTCCC[**A/G**] GGAACCCATAACAAATTACTTAAAA
rs4986893	636G>A, *Transition Substitution*	C__27861809_10	ACATCAGGATTGTAAGCACCCCCTG**[A/G]** ATCCAGGTAAGGCCAAGTTTTTTGC
rs12248560	-806C>T, *Transition Substitution*	C____469857_10	AAATTTGTGTCTTCTGTTCTCAAAG[**C/T**] ATCTCTGATGTAAGAGATAATGCGC

Genotyping results interpretation

TaqMan Genotyper Software (v.1.3.1., Applied Biosystems, Thermo Fisher Scientific) was used to verify the accuracy and reading of the genotype data, as well as the quality of genotyping for the whole set of patients and healthy subjects' profiles. The genotypes were checked for Hardy-Weinberg Equilibrium (HWE) using the Pearson Chi-square criterion. The conditions of compliance with HWE were $\chi 2 \leq 3.84$ and its $P \geq 0.05$.

2.5 Mathematical and Statistical Processing of the Data

The statistical processing of the results was carried out using the IBM SPSS Statistics software, version 26.

3. REZULTS

3.1 Exploring genetic and clinical-paraclinical aspects in coronary patients requiring dual antiplatelet therapy (aspirin + clopidogrel)

3.1.1 The genotypic frequency of the CYP2C19 polymorphism in coronary patients from the Republic of Moldova

The most common polymorphisms of the CYP2C19 gene were analyzed in the patients included in this study: CYP2C19*2, CYP2C19*3, and CYP2C19*17 [19]. The CYP2C192 allele was present in 47 subjects, of which 41 (19.4%) were CYP2C191/2 heterozygotes, and 6 (2.8%) were CYP2C192/2 homozygotes. Meanwhile, CYP2C19*3 was not detected in any subject in a homozygous state, and in one subject, i.e., in 0.5% of cases, it was found in a heterozygous state. The allele frequency for CYP2C192 was 12.6%, and for CYP2C193, it was 0.2%. The distribution of genotypes and allele frequencies for CYP2C192 and *3 is presented in table 3.1.

Table 3.1. **Allelic and genotypic frequency of the 681G>A polymorphism, rs4244285, and 636G>A polymorphism, rs4986893 in coronary patients from the Republic of Moldova**

Polymorphism	Allele frequency, %		Genotypes frequency, n %			χ^2	HWE p-value
	A	G	Homozigots AA	Heterozigots AG	Homozigots GG		
CYP2C19*2, 681G>A, rs4244285	12.6%	87.4%	n=6 (2.8%)	n=41 (19.4%)	n= 164 (77.7%)	2.805	0.094
CYP2C19*3, 636G>A, rs4986893	0.2%	99.8%	0.0%	n=1 (0.5%)	n=210 (99.5%)	0.001	0.975

Note: *HWE – Hardy-Weinberg Equilibrium; n – number of subjects.*

The -806C>T polymorphism, rs12248560, located at position 94761900 on chromosome 10, was analyzed in 210 patients, revealing the following frequency: 16 patients (7.6%) were homozygous TT for the abnormal allele, 92 (43.8%) were heterozygous (CT), and 102 (48.6%) were homozygous for the normal allele. The allele frequencies of C and T for the CYP2C19 gene in the study patients were 70.5% and 29.5%, respectively (table 3.2).

Table 3.2. **Allelic and genotypic frequency of the -806C>T polymorphism, rs12248560, in coronary patients from the Republic of Moldova**

Polymorphism	**Allele frequency, %**		**Genotypes frequency, n %**			**χ 2**	**HWE p-value**
	T	**C**	**Homozigots TT**	**Heterozigots CT**	**Homozigots CC**		
CYP2C19*17, -806C>T, rs12248560	29.5%	70.5%	n=16 (7.6%)	n=92 (43.8%)	n=102 (48.6%)	0.584	0.445

Note: HWE – Hardy-Weinberg Equilibrium; n –number of subjects.

According to the definition of the Clinical Pharmacogenetics Implementation Consortium (CPIC), the slow metabolizer phenotype was determined in 6 patients (2.8%, 95% CI 1.2, 5.8), the intermediate metabolizer phenotype in 42 patients (19.9%, 95% CI 14.9, 25.7), normal metabolizers were 68 (32.2%, 95% CI 26.2, 38.7), fast metabolizers - 79 (37.4%, 95% CI 31.1, 44.1), and ultrarapid metabolizers were 16 (7.6%, 95% CI 4.6, 11.7) out of the 211 coronary patients (table 3.3).

Table 3.3. **Frequency of the CYP2C19 genetic polymorphism in coronary patients from the Republic of Moldova**

		n	%	95.0% CI
Phenotype	Poor	6	2.8%	1.2, 5.8
	Intermediate	42	19.9%	14.9, 25.7
	Normal	68	32.2%	26.2, 38.7
	Rapid	79	37.4%	31.1, 44.1
	Ultrarapid	16	7.6%	4.6, 11.7
Genotype	*2/*2	6	2.8%	1.2, 5.8
	*1/*2	30	14.2%	10.0, 19.4
	*3/*17	1	0.5%	0.1, 2.2
	*2/*17	11	5.2%	2.8, 8.8
	*1/*1	68	32.2%	26.2, 38.7
	*1/*17	79	37.4%	31.1, 44.1
	*17/*17	16	7.6%	4.6, 11.7

Note: n – sample size; % – percentage, absolute frequency; % – relative frequency; CL – confidence level.

The CYP2C19 genotype frequencies in coronary patients from the Republic of Moldova do not deviate from Hardy-Weinberg equilibrium.

3.1.2 Genotypic Frequency of the CYP2C19 Polymorphism in Healthy Subjects from the Republic of Moldova

In the research, 430 apparently healthy students were included, comprising 302 female subjects (68.64%) and 128 male subjects (31.36%), aged between 18 and 29 years, with a median age of 19 years, observed in 231 individuals (52.5%). The 681G>A polymorphism, rs4244285, was

successfully analyzed in 428 healthy individuals. The CYP2C192 allele was present in 119 subjects, of which 112 (26.2%) were CYP2C191/2 heterozygotes, and 7 (1.6%) were CYP2C192/*2 homozygotes.

The 636G>A polymorphism, rs4986893, was successfully analyzed in 424 healthy individuals. The CYP2C193 allele was not detected in any subject in a homozygous state and in one subject, i.e., in 0.2% of cases, it was found in a heterozygous state. The allele frequency for CYP2C192 was 14.7%, and for CYP2C193, it was 0.1% [19]. The distribution of genotypes and allele frequencies for CYP2C192 and *3 is presented in table 3.4.

Tabelul 3.4. **Allelic and genotypic frequency of the 681G>A polymorphism, rs4244285, and 636G>A polymorphism, rs4986893 in healthy subjects from the Republic of Moldova**

Polymorphism	**Allele frequency, %**		**Genotypes frequency, n %**			**χ 2**	**HWE p-value**
	A	**G**	**Homozigots AA**	**Heterozigots AG**	**Homozigots GG**		
CYP2C19*2, 681G>A, rs4244285	14.7%	85.3%	n=7 (1.6%)	n=112 (26.2%)	n= 309 (72.2%)	0.766	0.381
CYP2C19*3, 636G>A, rs4986893	0.1%	99.9%	0.0%	n=1 (0.2%)	n=423 (99.8%)	0.001	0.975

Note: *HWE- Hardy-Weinberg Equilibrium; n – number of subjects.*

Comparing the observed genotype frequencies with those expected using the chi-square test, the Hardy-Weinberg equilibrium was assessed. For the CYP2C19**2* and CYP2C19*3 polymorphisms, no deviations from HWE were identified ($p>0.05$, $\chi2<3.84$). The distribution of genotype frequencies in the given sample had a p-value of 0.381, $\chi2=0.766$ for the CYP2C192 polymorphism, and for the CYP2C193 polymorphism, $p=0.001$, $\chi2=0.975$.

Polymorphism -806C>T, rs12248560, was successfully analyzed in 419 healthy individuals. 31 subjects (7.4%) were detected as homozygous TT for the abnormal allele, 119 (28.4%) were heterozygous (CT), and 269 (64.2%) were homozygous for the normal allele. The allele frequencies of C and T for the CYP2C19 gene in the study subjects were 70.5% and 29.5%, respectively (table 3.5).

Tabelul 3.5. **Allelic and genotypic frequency of the -806C>T polymorphism, rs12248560 in healthy subjects from the Republic of Moldova**

Polymorphism	**Allele frequency, %**		**Genotypes frequency, n %**			**χ 2**	**HWE p-value**
	T	**C**	**Homozigots TT**	**Heterozigots CT**	**Homozigots CC**		
CYP2C19*17, -806C>T, rs12248560	21.6%	78.4%	n=31 (7.4%)	n=119 (28.4%)	n=269 (64.2%)	10.917	0.001

Note: *HWE – Hardy-Weinberg Equilibrium, n – number of subjects.*

As homozygous TT for the abnormal allele 31 subjects (7.4%) were detected, 119 (28.4%) were heterozygous (CT), and 269 (64.2%) were homozygous for the normal allele. The allele frequencies

of C and T for the CYP2C19 gene in the study subjects were 70.5% and 29.5%, respectively (table 3.5).

3.1.3 Demographic and risk factor characteristics of patients in the total study cohort and subgroups SG I-III

Distribution of patients in subgroups I-III based on CYP2C19 phenotype, demographic data, and the presence of risk factors is presented in table 3.6.

Table 3.6. **Distribution of patients based on CYP2C19 phenotype, demographic data, and the presence of risk factors**

		Phenotype						
		Poor-Intermediate (n=38)		**Normal (n=57)**		**Rapid-Ultrarapid (n=77)**		
		n, %	(95% IC)	n, %	(95% CI)	n, %	(95% CI)	p
Sex	Male	29 (76.3%)	(61.2, 87.6)	49 (86.0%)	(75.3, 93.1)	62 (80.5%)	(70.6, 88.2)	0.479
	Female	9 (23.7%)	(12.4, 38.8)	8 (14.0%)	(6.9, 24.7)	15 (19.5%)	(11.8, 29.4)	
Living environment	Urban	26 (68.4%)	(52.7, 81.4)	34 (59.6%)	(46.7, 71.6)	48 (62.3%)	(51.2, 72.5)	0.683
	Rural	12 (31.6%)	(18.6, 47.3)	23 (40.4%)	(28.4, 53.3)	29 (37.7%)	(27.5, 48.8)	
Obesity	No	24 (63.2%)	(47.3, 77.1)	32 (56.1%)	(43.2, 68.5)	53 (68.8%)	(57.9, 78.3)	0.321
	Yes	14 (36.8%)	(22.9, 52.7)	25 (43.9%)	(31.5, 56.8)	24 (31.2%)	(21.7, 42.1)	
Abdominal obesity	No	16 (42.1%)	(27.5, 57.9)	23 (40.4%)	(28.4, 53.3)	36 (46.8%)	(35.9, 57.8)	0.721
	Risk	4 (10.5%)	(3.7, 23.1)	8 (14.0%)	(6.9, 24.7)	13 (16.9%)	(9.8, 26.4)	
	Yes	18 (47.4%)	(32.2, 62.9)	26 (45.6%)	(33.2, 58.5)	28 (36.4%)	(26.3, 47.5)	
Smoking	No	21 (55.3%)	(39.6, 70.2)	26 (45.6%)	(33.2, 58.5)	37 (48.1%)	(37.1, 59.10)	0.914
	Yes	8 (21.1%)	(10.5, 35.8)	16 (28.1%)	(17.7, 40.6)	20 (26.0%)	(17.2, 36.5)	
	Ex-smoker	9 (23.7%)	(12.4, 38.8)	15 (26.3%)	(16.3, 38.7)	20 (26.0%)	(17.2, 36.5)	
Hypertension	No	5 (13.25%)	(5.2, 26.5)	13 (22.8%)	(13.4, 34.9)	15 (19.5%)	(11.8, 29.4)	0.658
	Stage I	0 (0.0%)	–	0 (0.0%)	–	2 (2.6%)	(0.5, 8.1)	
	Stage II	22 (57.9%)	(42.1, 72.5)	28 (49.1%)	(36.5, 61.9)	37 (48.1%)	(37.1, 59.1)	
	Stage III	11 (28.9%)	(16.5, 44.5)	16 (28.1%)	(17.7, 40.60	23 (29.9%)	(20.5, 40.7)	
Stroke	Cons.-	3 (7.9%)	(2.3, 19.6)	3 (5.3%)	(1.5, 13.4)	3 (3.9%)	(1.1, 10.00	0.083
	Cons.+	2 (5.3%)	(1.1, 15.8)	0 (0.0%)	.	0 (0.0%)	.	
DM	No	24 (63.2%)	(47.3, 77.1)	36 (63.2%)	(50.2, 74.8)	56 (72.7%)	(62.1, 81.7)	0.412
	Yes	14 (36.8%)	(22.9, 52.7)	21 (36.8%)	(25.2, 49.8)	21 (27.3%)	(18.3, 37.9)	
Chronic kidney disease	No	33 (86.8%)	(73.5, 94.8)	51 (89.5%)	(79.6, 95.5)	67 (87.0%)	(78.2, 93.1)	0.893
	Yes	5 (13.2%)	(5.2, 26.5)	6 (10.5%)	(4.5, 20.4)	10 (13.0%)	(6.9, 21.8)	
Previous MI	No	29 (76.3%)	(61.2, 87.6)	48 (86.0%)	(75.3, 93.1)	63 (81.8%)	(72.1, 89.2)	0.487
	Yes	9 (23.7%)	(12.4, 38.8)	8 (14.0%)	(6.9, 24.7)	14 (18.2%)	(10.8, 27.9)	
Previous PCI	No	33 (86.8%)	(73.5, 94.8)	48 (84.2%)	(73.2, 91.9)	71 (92.2%)	(84.6, 96.7)	0.341
	Yes	5 (13.2%)	(5.2, 26.5)	9 (15.8%)	(8.1, 26.8)	6 (7.8%)	(3.3, 15.4)	

Note: *n– sample size; % - percentage, MI – myocardial infarction; 95% CI – confidence interval; PCI –percutaneous coronary intervention; DM – diabetes mellitus; cons. - –without consequences; cons. + – with the presence of consequences.*

Thus, when distributing patients based on demographic characteristics, risk factors, and the presence of comorbidities, no statistically significant differences were recorded, resulting in a homogeneity of the study subgroups.

3.1.4 Results of instrumental and laboratory evaluations in coronary patients requiring dual antiplatelet therapy (aspirin + clopidogrel) after percutaneous coronary intervention

Distribution of patients in subgroups I-III based on CYP2C19 phenotype and **laboratory parameters** is presented in table 3.7.

Table 3.7. **Distribution of patients based on CYP2C19 phenotype and laboratory parameters**

Laboratory parameters	**Phenotype Poor-intermediate (n =38)**	**Phenotype Normal (n=57)**	**Phenotype Rapid-ultrarapid (n=77)**	**p**
Hemoglobin, g/l (median, IQR)	139 (19)	136 (24)	138 (20)	0.866
White blood cells, 10^9/L (median, IQR)	8.45 (4.2)	8.20 (2.6)	8.80 (2.9)	0.453
Eritrocte sedimentation rate, mm/h (median, IQR)	17.0 (19.0)	20.0 (26.0)	20.0 (24.0)	0.617
C-reactive protein, mg/ml (median, AIQ)	13.0 (18.90)	7.92 (12.77)	8.32 (7.98)	0.178
Glucose, mmol/l (median, IQR)	6.47 (2.3)	6.10 (2.5)	6.10 (1.5)	0.540
Creatinine, μmol/l (median, IQR)	88.7 (21.0)	91.3 (24.0)	89 (23.0)	0.780
RFG, ml/min/1.73m^2 (median, IQR)	89 (23.0)	89 (37.0)	88 (33.0)	0.686
TC, mmol/l (median, IQR)	4.80 (1.90)	5.44 (2.09)	5.40 (1.71)	0.191
LDL-C, mmol/l (median, IQR)	2.81 (1.55)	3.20 (1.78)	3.10 (1.33)	0.311
TG, mmol/l (median, IQR)	1.59 (1.08)	1.56 (1.08)	1.67 (0.99)	0.717
Creatine kinase-MB, U/L (median, IQR)	54.5 (85.23)	54.0 (67.18)	63.0 (104.44)	0.951
Quantitative troponin (median, IQR)	13.49 (34.79)	15.17 (23.28)	12.17 (26.06)	0.721
NT-proBNP, pg/ml (median, IQR)	1461 (2615)	1163 (1835)	1432 (1758)	0.257

Note: n – sample size; % –percentage; TG– triglycerides, LDL-C– low density lipoprotein cholesterol, TC– total cholesterol, GFR – Glomerular Filtration Rate, NT-proBNP – N-terminal pro-B-type natriuretic peptide,IQR – Interquartile Range.

Analyzing the laboratory investigation results, no statistically significant differences were observed in these research subgroups when comparing various laboratory parameters. The echocardiographic data of the patients in the study were found to be comparable in all three research subgroups. The distribution of patients based on CYP2C19 phenotype and angiographic characteristics is presented in table 3.8.

Table 3.8. **Distribution of patients based on CYP2C19 phenotype and angiographic characteristics**

Angiographic characteristics	**Phenotype Poor-intermediate (n =38)**	**Phenotype Normal (n=57)**	**Phenotype Rapid-ultrarapid (n=77)**	**p**
Radial access	37 (97.4%)	57 (100%)	77 (100%)	0.170
Femoral access	1 (2.6%)	–	–	
The nr. of affected coronary arteries:				
Monocoronary lesions	5 (13.2%)	6 (10.5%)	12 (15.6%)	
Bicoronary lesions	7 (18.4%)	9 (15.8%)	14 (18.2%)	
Tricoronary lesions	26 (68.4%)	42 (73.7%)	51 (66.2%)	0.905
The nr. of vessels with significant stenosis				
1				
2	12 (31.6%)	15 (26.3%)	35 (45.5%)	0.143
3	10 (26.3%)	20 (35.1%)	22 (28.6%)	
	16 (42.1%)	22 (38.6%)	20 (26.0%)	
Culprit lesion				
RCA	14 (36.8%)	24 (42.1%)	28 (26.3%)	
LAD	20 (52.6%)	24 (42.1%)	34 (44.2%)	0.751
aCX	3 (7.9%)	8 (14.03%)	14 (18.8%)	
LM	1 (2.6%)	1 (1.8%)	1 (1.3%)	
Complex PCI	3 (8.1%)	6 (10.6%)	7 (9.1%)	0.425
The number of treated vessels (mediana, min–max)	1 (1–2)	1 (1–3)	1 (1–1)	0.135
The number of treated lesions (mediana, min–max)	1 (1–2)	1 (1–5)	1 (1–3)	*0.015*
The total number of implanted stents (mediana, min–max)	1 (1–3)	1 (1–5)	1 (1–3)	0.536
The length of the stent per lesion (media)	28.6±15.4	29.1±13.8	26.1±10.4	0.775
The stent with the smallest diameter (media)	3.05±0.74	3.14±49	3.03±0.59	0.528
The type of drug-eluting stent:				
Generation I	10 (20.5%)	17 (22.7%)	22 (23.4%)	0.609
Generation II	39 (79.5%)	58 (77.3%)	72 (76.6%)	
TIMI score after PCI				
I	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.172
II	1 (2.6%)	4 (7.0%)	0 (0.0%)	
III	37 (97.4%)	53 (93.0%)	77 (100%)	

Note: *n – number; TIMI - Thrombolysis In Myocardial Infarction; RCA – right coronary artery; LAD – left anterior descending artery; aCX – Circumflex artery; LM – Left main.*

As observed in the above table, when distributing patients based on phenotype and angiographic data, no statistically significant differences were recorded, except for the number of treated lesions in the research subgroups, obtaining a p-value <0.05.

Analyzing the prescribed medication at discharge, in addition to dual antiplatelet therapy, all patients in the research subgroups were on statins. For the majority of patients, secondary prevention treatment predominantly included beta-blockers and ACE inhibitors/ARBs. Mineralocorticoid receptor antagonists were prescribed to more than half of the patients in the research subgroups. Prescription rates at discharge were lower for nitrates, loop diuretics, and hypoglycemic treatment.

Tabelul 3.9. **Medication prescribed at discharge for patients in subgroups I-III**

	Phenotype						
	Poor-Intermediar (n =38)		**Normal (n=57)**		**Rapid-Ultrarapid (n=77)**		
	n, %	95% IC	n, %	(95% CI)	n, %	(95% CI)	*p*
Beta-blockers	36 (94.7%)	(84.2, 98.9)	53 (93.0%)	(84.2, 97.6)	73 (94.8%)	(88.1, 98.2)	0.893
ACE-Is	27 (71.1%)	(55.5, 83.5)	48 (84.2%)	(73.2, 91.9)	67 (87.0%)	(78.2, 93.1)	0.093
ARBs	10 (26.3%)	(14.4, 41.7)	6 (10.5%)	(4.5, 20.4)	9 (11.7%)	(5.9, 20.2)	0.064
Mineralocorticoid receptor antagonists	28 (73.7%)	(58.3, 85.6)	37 (64.9%)	(52.0, 76.3)	48 (62.3%)	(51.2, 72.5)	0.478
Nitrates	11 (28.9%)	(16.5, 44.5)	7 (12.3%)	(5.7, 22.6)	12 (15.6%)	(8.8, 24.9)	0.094
Loop diuretics	14 (36.8%)	(22.9, 52.7)	17 (29.8%)	(19.2, 48.5)	15 (19.5%)	(11.8, 29.4)	0.115
Statins	38 (100%)	–	57 (100%)	–	77 (100%)	–	–
Hypoglycemic treatment	14 (36.8%)	(22.9, 52.7)	20 (35.1)	(23.7, 48.0)	21 (27.3%)	(8.3, 37.9)	0.484

Note: *n – sample size; % – percentage; 95% CI – confidence interval; ACE – angiotensin-converting enzyme inhibitors: ARBs – angiotensin receptor blockers.*

The prescribed medication at discharge did not statistically differ among the three research subgroups. Therefore, the research groups were homogeneous, taking this aspect into consideration.

3.2 Recurrent ischemic events and bleeding occurrences in coronary patients who received DAPT for a period of 6-12 months after percutaneous coronary intervention

3.2.1 Assessment of bleeding risk (using the PRECISE-DAPT score) in coronary patients who underwent percutaneous coronary intervention with drug-eluting stent implantation

When distributing patients according to the accumulated score in calculating the PRECISE-DAPT score, it was observed that the majority of patients in the study had a low to moderate PRECISE-DAPT score, indicating a low bleeding risk, and required standard DAPT for 12 months. However, according to the DAPT score, 67.7% of SG I, 66.0% of SG II, and 61.8% of patients in SG III had a high risk of ischemic events, indicating the need for prolonged DAPT.

Table 3.10. **Distribution of patients in SG I-III according to the accumulated score in calculating the PRECISE-DAPT score and DAPT**

PRECISE-DAPT score	**Phenotype Poor-intermediate (n =38)**	**Phenotype Normal (n=57)**	**Phenotype Rapid-ultrarapid (n=77)**	**p**
Low score	30 (78.9%) (95% CI, 64.2, 89.5)	48 (84.2%) (95%, CI 73.2, 91.9)	61 (79.2%) 95% CI, 69.2, 87.1)	
Moderate score	6 (15.8%) (95% CI, 6.9, 29.7)	6 (10.5%) (95% CI, 4.5, 20.4)	11 (14.3%) (95% CI, 7.8, 23.4)	0.940
High score	2 (5.3%) (95% CI, 1.1, 15.8)	3 (5.3%) (95% CI, 1.5, 13.4)	5 (6.5%) (95% CI, 2.5, 13.6)	
DAPT score ≥2 points	21 (67.7%) (95% CI, 50.3, 82.1)	35 (66.0%) (95% CI, 52.7, 77.7)	42 (61.8%) (95% CI, 49.9, 72.6)	0.811
<2 points	10 (32.3%) (95% CI, 17.9, 49.7)	18 (34.0%) (95% CI, 22.3, 47.3)	26 (38.2%) (95% CI, 27.4, 50.1)	

Note: *n- sample size; %-percentage; 95% CI - confidence interval.*

No statistically significant differences were determined in the three study subgroups.

3.2.2 Recurrent ischemic events and bleeding incidents recorded in the overall patient cohort during a follow-up period of 6-12 months after percutaneous coronary intervention with drug-eluting stent implantation

The recurrent ischemic events recorded in the overall patient cohort during a follow-up period of 6-12 months after PCI with drug-eluting stent implantation are presented in table 3.11 [20].

Table 3.11. **Recurrent ischemic events in the overall patient group**

		n	**%**	**(95% CI)**
Cardiovascular death		20	11.6	(7.5, 17.0)
Myocardial Infarction	non-fatal	12	7.0	(3.9, 11.5)
Stroke	No	168	97.7	(94.6, 99.2)
	Fatal stroke	2	1.2	(0.2, 3.7)
	Non-fatal stroke	2	1.2	(0.2, 3.7)
Stent thrombosis	No	168	97.7	(94.6, 99.2)
	Yes	4	2.3	(0.8, 5.4
Unstable angina	No	152	88.4	(83.0, 92.5)
	Yes	20	11.6	(7.5, 17.0)
Stent restenosis	Confirmed	3	1.7	(0.5, 4.6)
Repeat revascularization through PCI	No	155	90.1	(85.0, 93.9)
	Target vessel	8	4.7	(2.2, 8.6)

Note: *n –sample size; %- percentage; 95% CI – confidence interval; PCI – percutaneous coronary intervention.*

Clinical bleeding events were detected in 13 cases (7.6%, 95% CI 4.3, 12.2), all of which were classified as minor in severity. According to the BARC classification, 11 cases (6.4%, 95% CI 3.4, 10.8) were of type I, and 0.6% (95% CI 0.1, 2.7) were of type II.

3.2.3 Recurrent major ischemic events and bleeding events for patient subgroups

At the end of the follow-up period (6-12 months), the predominance of survivors was determined in SG II vs. SG III vs. SG I: 53 (93.0%, 95% CI 84.2, 97.6) vs. 71 (92.2%, 95% CI 84.6, 96.7) vs. 28 (73.7%, 95% CI 58.3, 85.6), respectively. Cardiac death prevailed in patients from SG I vs. SG III vs. SG II: 10 (26.3%, 95% CI 14.4, 41.7) vs. 6 (7.8%, 95% CI 3.3, 15.4) vs. 4 (7.0%, 95% CI 2.4, 15.8), respectively. Thus, a statistically significant value was recorded (Pearson Chi-Square 10.259, p=0.006).

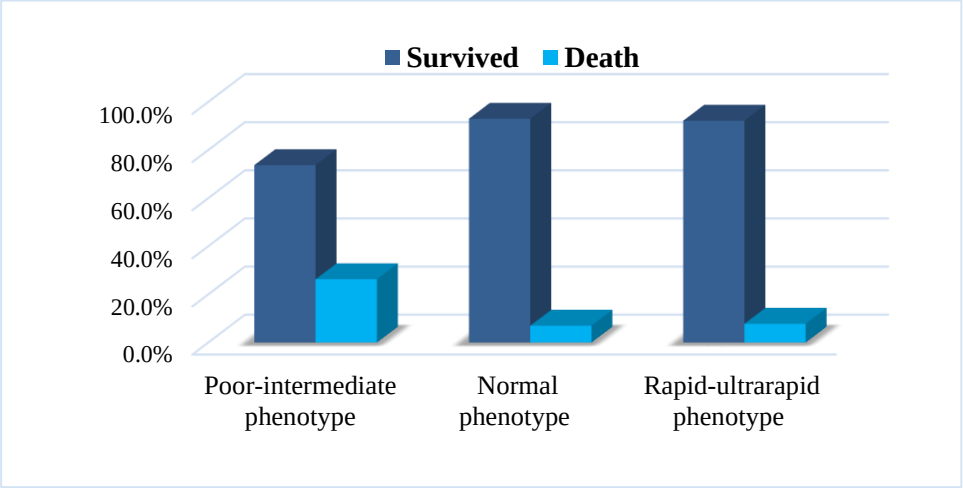

Figure 3.1. **Presence of the composite endpoint of cardiovascular death during the DAPT (aspirin + clopidogrel) administration period based on the CYP2C19 phenotype**

Non-fatal myocardial infarction was predominantly diagnosed in patients from SG I vs. SG III vs. SG II: 7 (18.4%, 95% CI 8.6, 32.8) vs. 3 (3.9%, 95% CI 1.1, 10.0) vs. 2 (3.5%, 95% CI 0.7, 10.8), respectively. A statistically significant value was determined (Pearson Chi-Square 20.006, p=0.000).

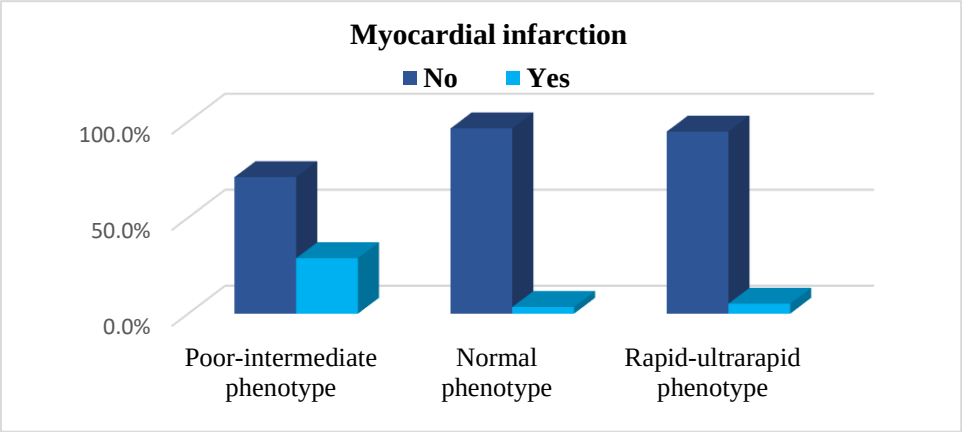

Figure 3.2. **Presence of the composite endpoint of myocardial infarction during the DAPT (aspirin + clopidogrel) administration period based on the CYP2C19 phenotype**

Defined stent thrombosis was most frequently observed in patients with slow and intermediate metabolism, in 3 cases (7.9%, 95% CI 2.3, 19.6), and one case in patients with rapid and ultrarapid metabolism (1.3%, 95% CI 0.1, 5.9), revealing a statistically significant value (Pearson Chi-Square 6.903, p= 0.032).

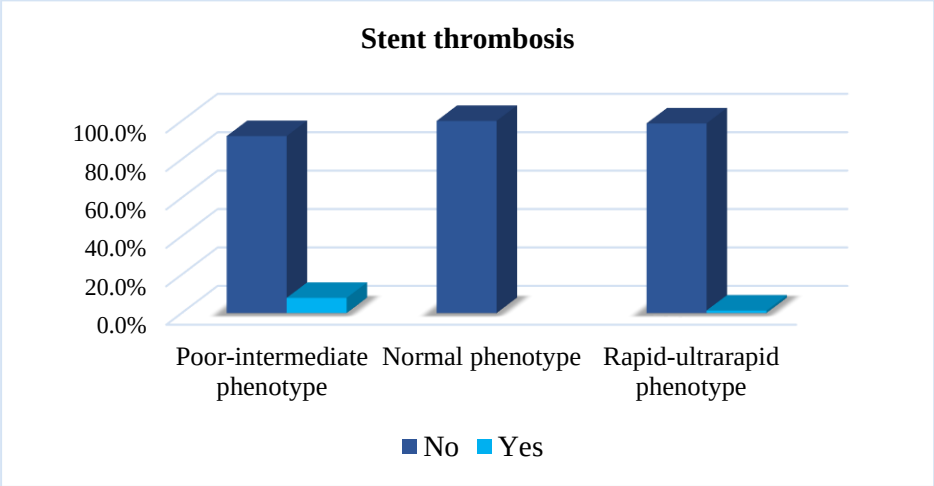

Figure 3.3. **Presence of the composite endpoint of stent thrombosis during the DAPT (aspirin + clopidogrel) administration period based on the CYP2C19 phenotype.**

Readmission with the clinical diagnosis of unstable angina was more frequently encountered in patients from SG I vs SG III vs SG II: 9 (23.7%, 95% CI 12.4, 38.8) vs 7 (9.1%, 95% CI 4.2, 17.0) vs 4 (7.0%, 95% CI 2.4, 15.8), respectively, registering once again a statistically significant value (Pearson Chi-Square 7.037, p=0.030).

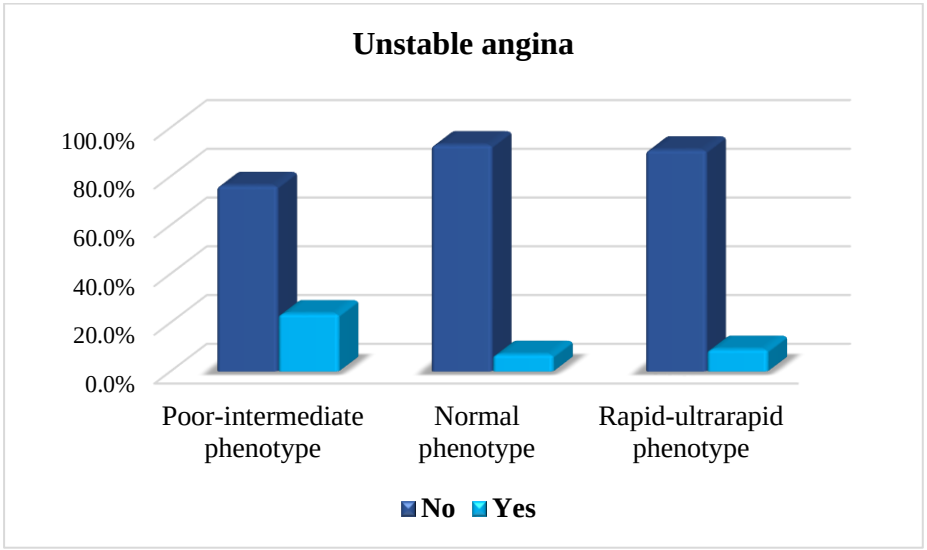

Figure 3.4. **Presence of the composite endpoint of unstable angina during the DAPT (aspirin + clopidogrel) administration period based on the CYP2C19 phenotype**

Repeated revascularization through PCI on the prevalent target vessel was observed in patients from SG I vs SG III vs SG I: 5 (13.2%, 95% CI 5.2, 26.5) vs 2 (2.6%, 95% CI 0.5, 8.1) vs 1 (1.8%, 95% CI 0.2, 7.9), respectively. Additionally, revascularization on another vessel was more frequent

in SG I patients as well - 5 (13.2%, 95% CI 5.2, 26.5), in SG II it occurred in 3 patients (5.3%, 95% CI 1.5, 13.4), and it was least common in SG III patients, yielding a statistically significant value (Pearson Chi-Square 15.975, p = 0.003).

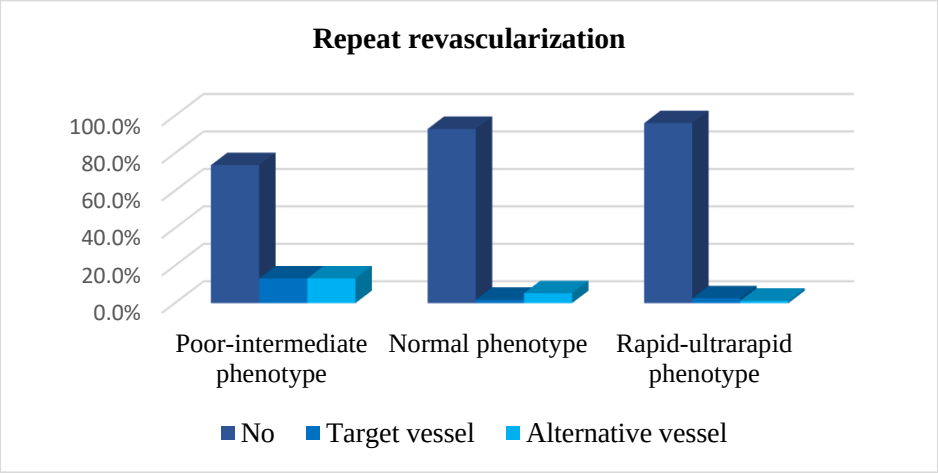

Figure 3.5. **Distribution of patients based on the need for repeated revascularization through PCI and CYP2C19 phenotype**

The assessment of patients monitored for clinical bleeding events at 6-12 months revealed a predominance in patients from SG III vs SG II vs SG I: 10 (13%, 95% CI 6.9, 21.8) vs 2 (3.5%, 95% CI 0.7, 10.8) vs 1 (2.6%, 95% CI 0.3, 11.6), respectively.

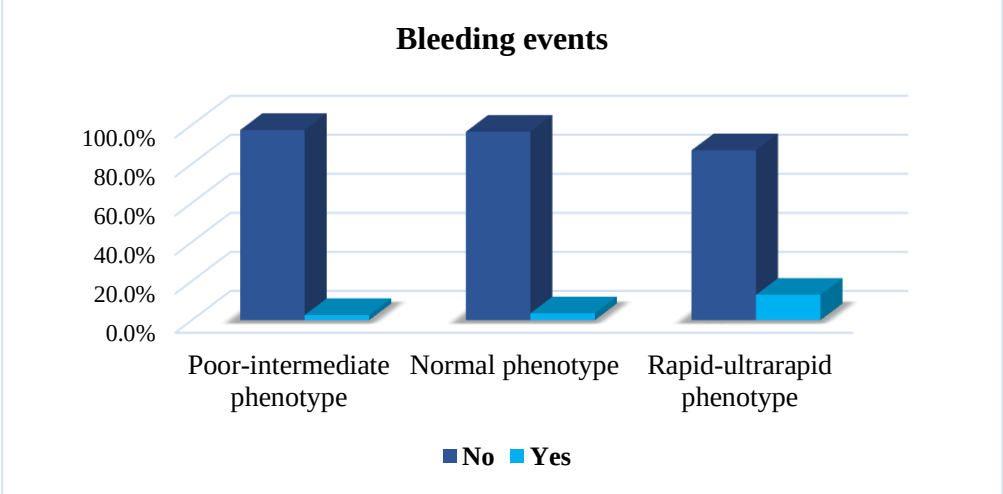

Figure 3.6. **Distribution of patients based on bleeding events during DAPT and the CYP2C19 phenotype**

The classification of bleeding by severity detected the presence of only minor bleedings, more frequently in patients from SG III vs SG II vs SG I: 14 (16.1%, 95% CI 9.5, 24.9) vs 2 (3.4%, 95% CI 0.7, 10.4) vs 1 (2.4%, 95% CI 0.3, 10.8), respectively. Bleedings according to BARC were of type I in 15 patients, predominantly in patients from SG III vs SG II vs SG I: 13 (14.9%, 95% CI 8.6, 23.5) vs 2 (3.4%, 95% CI 0.7, 10.4) vs 1 (2.4%, 95% CI 0.3, 10.8), respectively.

3.3 Predictive models based on the CYP2C19 phenotype

3.3.1 Predictive model for determining the probability of recurrent ischemic events in patients receiving dual antiplatelet therapy with aspirin + clopidogrel after percutaneous coronary intervention with drug-eluting stent implantation

Analysing the correlation to identify potential predictors for the occurrence of recurrent ischemic events in patients on DAPT with aspirin + clopidogrel after PCI revealed an association between CYP2C19*2 and *3 allele carriers (loss-of-function alleles) with poor/intermediate metabolism of clopidogrel, previous myocardial infarction, abdominal circumference and stent length per lesion in patients on DAPT (aspirin + clopidogrel) after PCI.

The development of a prognostic model to determine the probability of recurrent ischemic events was carried out through multivariate analysis (logistic regression). The following characteristics were processed for estimating predictive potential: the coefficient of determination (Nagelkerke R Square), calibration indicators (Hosmer–Lemeshow test and calibration plot), discrimination indicators (specificity, sensitivity, Area Under the Receiver Operating Characteristic Curve (AUC-ROC) with sensitivity optimization), and specificity/sensitivity relationship by modifying the critical point (cut-off). Model stability was assessed through resampling via bootstrapping.

The obtained results were described according to the recommended requirements in statistical literature. The development of the predictive model for determining the probability of recurrent ischemic events in patients on DAPT (aspirin + clopidogrel) post-PCI based on CYP2C19*2 and *3 allele carriers (loss-of-function alleles) and poor/intermediate metabolism, as well as the presence of a history of previous myocardial infarction, abdominal circumference and stent length per lesion.

Table 3.12. **Predictive model for recurrent ischemic events**

Variables		**B**	**S.E.**	**Wald**	**df**	**Sig.**	**Exp(B)**	**95% C.I.for EXP(B)**	
								Lower	**Upper**
1.	Poor-intermediate	2.029	0.601	11.389	1	0.001	7.609	2.341	24.725
2.	Previous myocardial infarction	1.777	0.633	7.873	1	0.005	5.909	1.708	20.439
3.	Circumference abdominal	0.048	0.023	4.141	1	0.042	1.049	1.002	1.098
4.	Length of the stent per lesion	0.051	0.021	5.641	1	0.018	1.052	1.009	1.097
	Constant	-9.839	2.807	12.284	1	0.000	0.000		

Note: *Constant – the constant value of the equation, B – coefficient values, S.E. – standard errors, Wald statistic – Wald, df – degrees of freedom, Sig. – statistical significance, Exp(B) – odds ratio (OR) values, 95% C.I. for EXP(B) – confidence interval for odds ratio.*

The null hypothesis (potential predictors are not able to predict the outcome better than a constant) was rejected (the omnibus test of the model coefficients ($\chi 2 = 32.437$, df = 5, $p<0.001$).

Further analysis showed the following characteristics of the developed model. The coefficient of determination, Nagelkerke R Square, showed a value of 0.189 (18.9%), meaning that 18.9% of the variance in the variable of interest (occurrence of myocardial infarction) was explained/covered by the proposed model. The calibration indicator (Hosmer–Lemeshow test) demonstrated a non-significant value, $\chi 2 = 7.984$, df = 8, p = 0.435, indicating fidelity in predicting results across the entire range of predicted scores.

The model included the constant (B = -9.839), the state of intermediate-poor metabolizer (B = 2.029), previous myocardial infarction (B = 1.777), abdominal circumference (B = 0.048), and stent length per lesion (B = 0.051), with appropriate signs, consistent with logical expectations (Table 3.12).

Considering the mentioned coefficients, the developed model has the following mathematical expression (Formula 3.1):

$$p = \frac{1}{1+e-(-2{,}816) +(2.029)* \text{Poor\_intermediate} +(1.777)* \text{PMI} +(0.048)* \text{CA} +(0.051)*\text{Lg.stent.les}}$$

Note: p – the probability of recurrent ischemic events; e (exponential) – a constant equal to 2.71828; PMI – previous myocardial infarction; CA – abdominal circumference; Lg. stent.les – the length of the stent per lesion.

The parameters in the developed model had the following effects. For patients with an intermediate-poor metabolism level, the risk of recurrent ischemic events was estimated to be 7.60 times higher (OR (odds ratio)=7.609 (95% CI 2.341, 24.725)) compared to a person without it. Additionally, the presence of a history of previous myocardial infarction increased the risk of recurrent ischemic events in post-PCI coronary patients receiving DAPT (aspirin + clopidogrel) by 5.90 times (OR (odds ratio)=5.909 (95% CI 1.708, 20.439)) compared to those without this diagnosis. Abdominal circumference is a predictive factor that increases the risk of recurrent ischemic events, with an OR = 1.049 (95% CI 1.002, 1.098), indicating that each centimeter increases the risk of recurrent ischemic events by 4.8%. Similarly, the length of the stent per lesion was determined as a potential predictor (OR=1.052, 95% CI 1.009, 1.097). As a discrimination indicator, the area under the ROC curve for the predictive model was 0.866, with a 95% confidence interval (0.782 to 0.950) and a significant difference from the value of 0.5 (p=0.000) (figure 3.7).

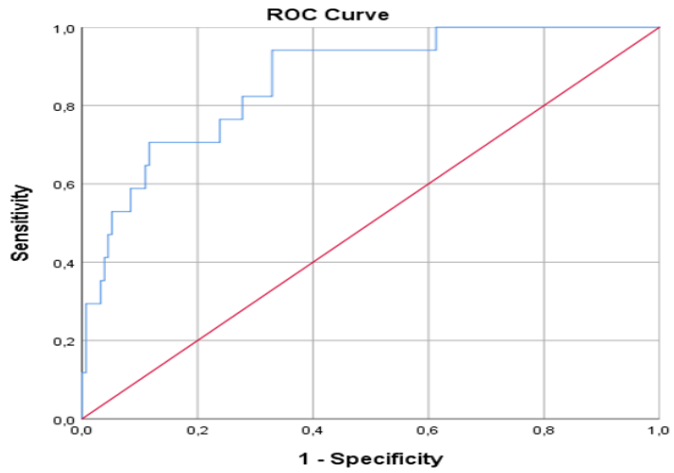

Figure 3.7. **ROC Curve of the predictive model for the occurrence of recurrent ischemic events in patients with DAPT after PCI based on the carriage of CYP2C19*2 and *3 Alleles**

This predictive model was proposed for the probability of myocardial infarction occurrence over a period of 6-12 months in post-PCI coronary patients receiving DAPT (aspirin + clopidogrel). The potential predictors include the phenotype of intermediate-poor metabolizer, the presence of a history of previous myocardial infarction, abdominal circumference, and the length of the stent per lesion.

3.3.2 Predictive model for determining the probability of bleeding events in patients undergoing dual antiplatelet therapy with aspirin + clopidogrel after percutaneous coronary intervention with drug-eluting stent implantation

The development of a predictive model for determining the probability of bleeding events in patients receiving dual antiplatelet therapy (DAPT) with aspirin + clopidogrel post-percutaneous coronary intervention (PCI), based on the carriage of CYP2C19*17 alleles (gain-of-function alleles) and rapid/ultrarapid metabolism, was conducted.

The null hypothesis (potential predictors are not capable of predicting the outcome better than a constant) was rejected (omnibus test of model coefficients $\chi2 = 11.291$, df = 2, $p<0.004$). Further analysis revealed the following characteristics of the developed model.

The determination indicator, Nagelkerke R Square, showed a value of 0.153 (15.3%), indicating that 15.3% of the variance in the variable of interest (occurrence of bleeding events) was explained/covered by the proposed model.

The calibration indicator (Hosmer–Lemeshow test) demonstrated a non-significant value, $\chi2 = 7.427$, df = 8, p=0.491, indicating that the results were faithful in predicting outcomes across the entire range of predicted scores.

Table 3.12. **Predictive model for of bleeding events**

Variables		**B**	**S.E.**	**Wald**	**df**	**Sig.**	**Exp(B)**	**95% CI (B)**	
								Lower	**Upper**
	Phenotype Rapid-Ultrarapid	1.641	0.692	5.628	1	0.018	5.163	1.330	20.039
	Hemoglobin (g/l)	-0.047	0.021	4.812	1	0.028	0.954	0.915	0.995
	Constant	2.731	2.771	0.971	1	0.324	15.346		

Note: *Constant – the value of the equation constant, B – coefficients B, S.E. – standard errors, Wald statistic – Wald statistic, df – degrees of freedom, Sig. – statistical significance, Exp (B) – odds ratio (OR) values, 95% C.I. for EXP(B) – confidence interval for odds ratio.*

The model included the constant (B = 2.731), the intermediate-slow metabolizer status (B = 1.641), and the hemoglobin value (g/l) (B = -0.047), with appropriate and logically signed coefficients (Table 3.12). Considering the mentioned coefficients, the developed model has the following mathematical expression (Formula 3.2):

$$p = \frac{1}{1+e-(-2{,}816)+(1.200)*\text{Rapid}-\text{Ultrarapid phenotype}+(-0.047)*\text{Hb}}$$

Note: p – the probability of bleeding events,e – the mathematical constant approximately equal to 2.71828, Hb – the hemoglobin value in g/l.

The parameters in the developed model had the following effects. For patients with rapid-ultrarapid metabolism, the risk of bleeding events was estimated to be 5.16 times higher (OR (odds ratio) = 5.163 (95% CI 1.330, 20.039)) compared to individuals without it in post-PCI coronary patients receiving DAPT (aspirin + clopidogrel). Additionally, the hemoglobin level was associated with a decreased risk of bleeding events (OR = 0.954, 95% CI 0.915, 0.995), indicating that each unit (g/l) decrease in hemoglobin reduces the risk of bleeding events by 4.7%.

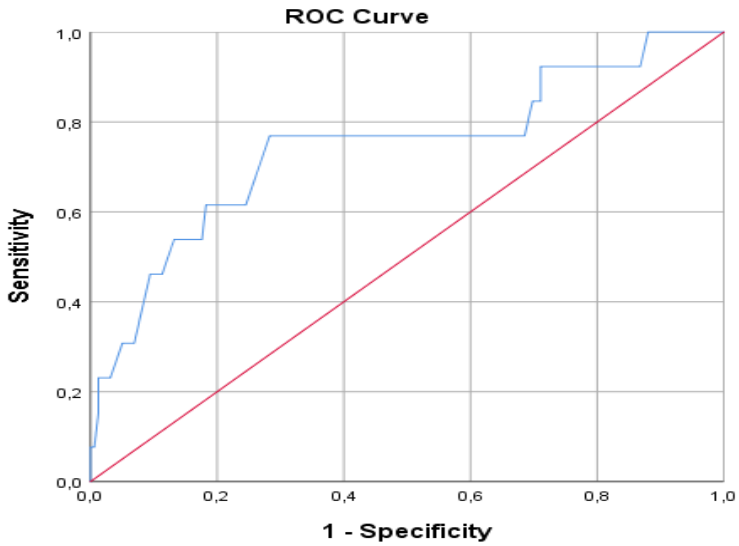

Figure 3.8. **ROC Curve of the Predictive Model for the Occurrence of Bleeding Events in Patients with DAPT after PCI based on the carriage of the CYP2C19*17 allele.**

As a discrimination indicator, the area under the ROC curve for the predictive model was 0.744, with a 95% confidence interval (0.582 to 0.905) and a significant difference from the value of 0.5 (p = 0.004) (Figure 3.8).

This predictive model was proposed for the probability of bleeding events over a period of 6-12 months in post-PCI coronary patients receiving DAPT (aspirin + clopidogrel). The potential predictors include the phenotype of rapid-ultrarapid metabolizer and the hemoglobin level.

CONCLUSIONS

1. The distribution of CYP2C19*2, 3, and 17 alleles in coronary patients (12.6% vs 0.2% vs 29.5%) is similar to that observed in the population cohort of apparently healthy subjects in the Republic of Moldova (14.7% vs 0.1% vs 21.6%), with a predominance of the CYP2C19*17 allele over the CYP2C192 allele. The data obtained are in agreement with previously reported findings regarding the frequencies of CYP2C19 alleles in other European populations.

2. In the conducted study, examining cardiovascular risk factors, anamnestic data, clinical presentation, and paraclinical aspects in coronary patients with different CYP2C19 phenotypes undergoing PCI with drug-eluting stent implantation associated with optimal drug therapy showed no significant variation.

3. The distribution of patients based on the PRECISE-DAPT score revealed that the majority had a low risk of bleeding, indicating the use of standard-duration dual antiplatelet therapy. Additionally, the DAPT score highlighted a significant proportion of patients at high risk of ischemic events, underscoring the potential need to extend the duration of DAPT. These findings emphasize the importance of careful assessment of bleeding and ischemic risks in the therapeutic approach of post-PCI patients.

4. The assessment of patients monitored for acute major ischemic events over 12 months found 20 deaths (11.6%), all of cardiovascular cause, predominantly in those with a poor/intermediate metabolizer phenotype (26.3%) versus normal metabolizer (7.8%) versus rapid/ultrarapid metabolizer (7.0%, p=0.006). The poor/intermediate metabolizer phenotype in patients was associated with: nonfatal myocardial infarction (18.4%, p=0.0001), definite stent thrombosis (2.3%, p=0.032), fatal/nonfatal stroke (1.2%), repeated hospitalization (11.6%, p=0.030), repeated revascularization via PCI on the target vessel (13.2%), and stent restenosis (1.7%). Clinical bleeding events were detected in 7.6% of cases, predominantly in patients with the rapid/ultrarapid metabolizer phenotype, mainly of minor type according to the BARC classification.
5. Based on the research results, two prediction models were developed: one for recurrent major ischemic events and another for the probability of bleeding events occurring within 6-12 months in post-PCI coronary patients who are on DAPT. These models included factors such as metabolizer phenotype, history of myocardial infarction, abdominal circumference, stent length, and hemoglobin value, demonstrating very good performance in predicting the respective events (AUROC=0.866 and 0.744, respectively).

PRACTICAL RECOMMENDATIONS

1. Recommendation for genotyping CYP2C19, including the individual's phenotype in the electronic medical record, to guide clinicians in selecting antiplatelet treatment when undergoing PCI with drug-eluting stent implantation.
2. Recommendation for genotyping CYP2C19 in high-risk ACS patients, requiring personalized dual antiplatelet therapy before starting clopidogrel treatment. This allows the identification of patients resistant to clopidogrel treatment (poor metabolizers) or, conversely, at high risk of bleeding (ultrarapid metabolizers).
3. Implementation of the *Predictive Model for Acute Major Ischemic Events in post-PCI coronary patients receiving DAPT (aspirin-clopidogrel).* The model includes the intermediate-slow metabolizer phenotype, a history of old myocardial infarction, abdominal circumference, and stent length per lesion.
4. Implementation of the *Predictive Model for of Bleeding Events over a 6-12 month period in post-PCI coronary patients receiving DAPT (aspirin-clopidogrel)* at different stages of healthcare provision. This allows the assessment of bleeding events during DAPT, considering the rapid-ultrarapid metabolizer phenotype and hemoglobin levels.

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✓ **articles in ISI, SCOPUS and other international databases**

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29. Caproș N., Caproș N., Popa A., **Dogot M.,** Matcovschi S. Boala Niemann-Pick, cap. 41. 422-429 pps. În: *MAZUR-NICORICI, L., DIACONU, C. C., ABABII, P. et al. Compendiu de boli rare=Compendium of Rare deseases.* Chișinău: S.n., 2020, (Tipogr. *Impressum*), 506 pps.

SUMMARY

Dogot Marta "**Clinical response to clopidogrel according to CYP2C19 gene polymorphisms in coronary patients after pharmacological stent implantation**".

PhD thesis in medical sciences, 321.03 – Cardiology, Chisinau, 2023.

The thesis is exposed on 107 pages and includes introduction, 4 chapters, 23 tables, 33 figures, synthesis of obtained results, general conclusions and practical recommendations, bibliography from 165 sources, three certificates of innovator, 6 implementing acts, information on capitalization of research results and declaration on assumption of responsibility. The study materials were reflected 16 scientific publications. **Keywords:** Double antiplatelet therapy (DAPT) with clopidogrel, gene polymorphisms CYP2C19. **Field of study:** cardiology. **The aim of the stady** is to evaluate the clinical-paraclinical and instrumental aspects, the ischemic and hemorrhagic risk of coronary patients, who have benefited from percutaneous coronary intervention with pharmacological stent implantation and the impact of the clinical response to clopidogrel within the DAPT. **Objectives:** To determine the frequency of CYP2C19 polymorphism in coronary patients, who have benefited from percutaneous coronary intervention (PCI) with pharmacological stent implantation (DES) and in healthy subjects in the Republic of Moldova; Study of clinical-paraclinical and instrumental aspects, cardiovascular risk factors in coronary patients who have benefited from PCI with DES implantation depending on the frequency of CYP2C19 polymorphism; Assessment of bleeding risk (PRECISE-DAPT score) and ischemic risk (DAPT score); Estimation of the impact of CYP2C19 polymorphism on patients' metaboliser status: slow/intermediate, normal and fast/ultrafast, in association with major bleeding and cardiovascular events during 6 -12 months; Analysis of correlation of potential predictors of myocardial infarction in patients with DAPT (aspirin + clopidogrel) after PCI and development of prognostic models to determine the probability of occurrence of ischemic and hemorrhagic events.**The importance and relevance of the theme**. The study allowed the evaluation of clinical-paraclinical and instrumental aspects, ischemic and hemorrhagic risk of coronary patients, who benefited from PCI with DES implantation within DAPT. It was established the role of genetic factors - CYP2C19 polymorphism, which determines ischemic and bleeding risk, serum and instrumental markers in predicting fatal and non-fatal complications in coronary patients, who benefited from PCI with DES implantation. **Scientific problem solved**. There were determined the frequencies of CYP2C19 polymorphism, which determines the hepatic metabolism of clopidogrel in coronary patients, who benefited from PCI with DES implantation and in healthy subjects from the Republic of Moldova. The impact of CYP2C19 polymorphism on patients' metaboliser status of clopidogrel was assessed: poor/intermediate, normal and rapid/ultrarapid, in association with major bleeding and cardiovascular events during 6-12 months. The results of the evaluation allowed the elaboration of strategies for prediction of acute ischemic and hemorrhagic major events of genome-personalized DAPT, based on genetic polymorphism of CYP2C19. **Scientific novelty and originality.** For the first time, the following were achieved: identification of allelic frequencies of CYP2C19 and phenotypes of healthy subjects according to CYP2C19 polymorphism; estimation of allelic frequencies of CYP2C19 and phenotypes of post-PCI coronary patients, administering DAPT (aspirin-clopidogrel) according to CYP2C19 polymorphism; evaluation of cardiovascular risk factors, clinical, paraclinical parameters, that can influence the management of DAPT (aspirin-clopidogrel) using DAPT and PRECISE-DAPT scores in a period of 6-12 months; addressing major acute ischemic and bleeding events over 6-12 months of post-PCI patients administering DAPT (aspirin-clopidogrel) depending on CYP2C19 polymorphism; development of the *Prediction model of acute ischemic major events in post-PCI coronary patients, administering DAPT (aspirin-clopidogrel),* elaboration of the *Predictive model for the probability of occurrence of bleeding events in a period of 6-12 months in post-PCI coronary patients, administering DAPT (aspirin-clopidogrel).* **Theoretical significance of research**. The conducted study once again highlighted the literature data regarding the presence of interindividual variability in the response to clopidogrel and recurrent thrombotic events after PCI. Genetic variation in CYP2C19 is identified as one of the factors responsible for hyporesponsiveness to this antiplatelet agent. The obtained results support the theoretical concept data. Once again, the advantage of personalized medicine has been demonstrated, emphasizing its key role in preventing antiplatelet treatment failure in patients who have undergone PCI with drug-eluting stent implantation. **The applicative value**. The applicative value lies in the development of predictive models for recurrent ischemic events and bleeding in coronary patients post-PCI who are on DAPT with aspirin-clopidogrel. The study results form the basis for the concept of strengthening the prediction of recurrent ischemic events and bleeding, contributing to: 1). recommending CYP2C12 genotyping with the inclusion of the individual's phenotype in the electronic medical record, this would enable clinicians to guide decision-making when the individual undergoes revascularization through PCI with DES. 2). recommending CYP2C19 genotyping for patients with a high risk of acute coronary syndrome, prone to ischemic and bleeding events, requiring personalized dual antiplatelet therapy before initiating clopidogrel treatment. **Implementation of results**. The scientific results were implemented in the Department of Interventional Cardiology and Endovascular Surgery IMSP SCM "Sf. Treime", cardiosurgery and cardiac rehabilitation department IMSP Institute of Cardiology.

ADNOTARE

Dogot Marta **„Răspunsul clinic la clopidogrel în funcție de polimorfismele genei CYP2C19 la pacienții coronarieni după implantare de stent farmacologic”.**
Teză de doctor în științe medicale, 321.03 – Cardiologie, Chișinău, 2023.

Teza este expusă pe 107 de pagini și include introducere, 4 capitole, 23 de tabele, 33 de figuri, sinteza rezultatelor obținute, concluzii generale și recomandări practice, bibliografie din 165 de surse, trei certificate de inovator, 6 acte de implementare, informație privind valorificarea rezultatelor cercetării și declarația privind asumarea răspunderii. Materialele studiului au fost reflectate 16 publicații științifice. **Cuvinte-cheie:** Dubla terapie antiplachetară (DAPT) cu clopidogrel, polimorfismele genei CYP2C19. **Domeniul de studiu:** cardiologie. **Scopul lucrării** constă în evaluarea aspectelor clinico-paraclinice, riscului ischemic și hemoragic al pacienților coronarieni care au beneficiat de intervenție coronariană percutană (PCI) cu implantare de stent farmacologic (DES) și impactului răspunsului clinic la clopidogrel în cadrul DAPT. **Obiective**: Determinarea frecvenței polimorfismului CYP2C19 la pacienții coronarieni care au beneficiat de PCI cu implantare de DES și la subiecții sănătoși din Republica Moldova; Studierea aspectelor clinico-paraclinice, a factorilor de risc cardiovasculari la pacienții coronarieni care au beneficiat de PCI cu implantare de DES în funcție de frecvența polimorfismului CYP2C19; Aprecierea riscului de hemoragie (cu ajutorul scorului PRECISE-DAPT) și riscul ischemic (prin scorul DAPT); Estimarea impactului polimorfismului CYP2C19 pe statutul pacienților de metabolizator al clopidogrelului: lent/intermediar, normal și rapid/ultrarapid, în asocierea cu evenimentele hemoragice și cardiovasculare majore în perioada de 6 -12 luni; Analiza corelației a potențialilor predictori de apariție a evenimentelor ischemice recurente la pacienții cu DAPT(aspirină + clopidogrel) după PCI și elaborarea modelelor de prognostic pentru determinarea probabilității de apariție a evenimentelor ischemice și hemoragice. **Importanța și relevanța temei.** Studiul a permis evaluarea aspectelor clinico-paraclinice, riscului ischemic și hemoragic al pacienților coronarieni care au beneficiat de PCI cu implantare de DES în cadrul DAPT. S-a stabilit rolul factorilor genetici - polimorfismului CYP2C19, ce determină riscul ischemic și de sângerare și a markerilor serici și instrumentali în predicția complicațiilor fatale și non-fatale la pacienții coronarieni, care au beneficiat de PCI cu implantare de DES. **Problema științifică rezolvată.** Au fost determinate frecvențele polimorfismului CYP2C19, ce determină metabolismul hepatic a clopidogrelului la pacienții coronarieni care au beneficiat de PCI cu implantare de DES și la subiecții sănătoși din Republica Moldova. A fost apreciat impactul polimorfismului CYP2C19 pe statutul pacienților de metabolizator al clopidogrelului: lent/intermediar, normal și rapid/ultrarapid, în asocierea cu evenimentele hemoragice și cardiovasculare majore în perioada de 6 -12 luni. Rezultatele evaluării au permis elaborarea strategiilor de predicție ale evenimentelor majore ischemice acute și hemoragice a DAPT genom-personalizate în baza polimorfismului genetic a CYP2C19. **Noutatea și originalitatea științifică.** În premieră au fost realizate: identificarea frecvențelor alelice ale CYP2C19 și fenotipurilor subiecților sănătoși în funcție de polimorfismul CYP2C19; estimarea frecvențelor alelice ale CYP2C19 și fenotipurilor pacienților coronarieni post-PCI care administrează DAPT în funcție de polimorfismul CYP2C19; evaluarea factorilor de risc cardiovasculari, parametrilor clinici, paraclinici, ce pot influența managementul DAPT cu ajutorul scorurilor DAPT și PRECISE-DAPT în perioadă de 6-12 luni; abordarea evenimentelor majore ischemice recurente și de sângerare în perioadă de 6-12 luni ale pacienților post-PCI care administrează DAPT în dependență de polimorfismul CYP2C19; crearea *Modelului de predicție a evenimentelor majore ischemice acute la pacienții coronarieni post-PCI care administrează DAPT(aspirină-clopidogrel),*elaborarea *Modelului predictiv pentru probabilitatea de apariție a evenimentelor de sângerare în perioadă de 6-12 luni la pacienții coronarieni post-PCI care administrează DAPT (aspirină-clopidogrel).* **Semnificația teoretică a cercetării.** Cercetarea dată a scos în evidență încă o dată datele din literatură privind prezența variabilității interindividuale a răspunsului la clopidogrel și a evenimentelor trombotice recurente după PCI, iar variația genetică CYP2C19 reprezintă unul din factorii responsabili pentru hiporăspunsul la acest agent antiplachetar. Rezultatele obținute vin în susținerea datelor conceptului teoretic. S-a arătat încă o dată avantajul medicinei personalizate care este cheia pentru prevenirea eșecului tratamentului antiplachetar la pacienții care au beneficiat de PCI cu implantare de DES. **Valoarea aplicativă** constă în elaborarea modelelor de predicție a evenimentelor ischemice recurente și de sângerare la la pacienții coronarieni după PCI care administrează DAPT (aspirină-clopidogrel) pe o perioadă de 6-12 luni. Rezultatele studiului au stat la baza elaborării conceptuluii de fortificare a predicției a evenimentelor ischemice recurente și de sângerare și contribuie la: 1) recomandarea genotipării CYP2C12 cu includerea fenotipului persoanei în fișa medicală electronica, astfel ar permite orientarea clinicianul în luarea deciziilor atunci când aceasta este supusă revascularizării prin PCI cu implantare de stent farmacologic; 2) recomandarea genotipării CYP2C19 pacienților cu SCA cu risc crescut de ischemie și de sângerare, necesitanți de terapie dubla antiplachetară personalizată înaintea începerii tratamentului cu clopidogrel. **Implementarea rezultatelor.** Rezultatele științifice au fost implimenate în Departamentul de Cardiologie Intervențională și Chirurgie Endovasculară IMSP SCM “Sf. Treime”, secția cardiochirurgie și reabilitare cardiacă IMSP Institutul de Cardiologie.

РЕЗЮМЕ

Догот Марта «**Клинический ответ на клопидогрель по CYP2C19 полиморфизмам генов у пациентов с коронарными заболеваниями после фармакологической имплантации стента**».
Докторская диссертация по медицинским наукам, 321.03 – Кардиология, Кишинев, 2023.

Диссертация состоит из 107 страниц и включает в себя введение, 4 главы, 23 таблицы, 33 рисунка, синтез полученных результатов, общие выводы и практические рекомендации, библиографию из 165 источников, три сертификата на изобретение, шесть актов внедрения, информацию о реализации результатов и заявление о принятии ответственности. Материалы исследования были отражены в 16 научных публикациях. **Ключевые слова:** Двойная антиагрегантная терапия (ДАТ) с клопидогрелем, полиморфизмы гена CYP2C19. **Область исследования:** кардиология. **Цель** работы заключается в оценке клинических, параклинических и инструментальных аспектов, ишемического и геморрагического риска у пациентов с коронарными заболеваниями, прошедших чрескожные коронарные вмешательства (ЧКВ) с стента, выделяющий лекарство (СВЛ) а также влияния клинического ответа на клопидогрель в рамках ДАТ. **Задачи:** Определить частоту CYP2C19 полиморфизма у пациентов которым было выполнено ЧКВ с СВЛ, и у здоровых пациентов в Республике Молдова; Изучение клинико-параклинических аспектов, факторов риска у пациентов с коронарными заболеваниями, перенесших ЧКВ с СВЛ, в зависимости от полиморфизма CYP2C19; Оценка риска кровотечений (с использованием шкалы PRECISE-DAPT) и ишемического риска (шкала DAPT); Оценка влияния полиморфизма CYP2C19 на метаболический статус пациентов: медленный/промежуточный, нормальный и быстрый/сверхбыстрый, в ассоциации с ишемических и геморрагических событиями в течение 6-12 месяцев; Анализ корреляции потенциальных предикторов инфаркта миокарда у пациентов с ДАТ (аспирин + клопидогрель) после ЧКВ и разработка прогностических моделей для определения вероятности возникновения ишемических и геморрагических событий. **Важность и актуальность темы.** Исследование позволило оценить клинико-параклинические аспекты, а также риски ишемии и геморрагии у пациентов с коронарными заболеваниями, прошедших ЧКВ с СВЛ и получающих ДАТ. Была установлена роль генетических факторов, таких как полиморфизм CYP2C19, в определении риска ишемии и кровотечения, а также роли сывороточных и инструментальных маркеров в прогнозировании фатальных и нефатальных осложнений у пациентов с коронарными заболеваниями, прошедшими ЧКВ с СВЛ. **Проблема, решенная в рамках исследования.** Были определены частоты полиморфизма CYP2C19 у пациентов с прошедших ЧКВ с СВЛ, а также у здоровых субъектов из Республики Молдова. Было оценено воздействие полиморфизма CYP2C19 на статус метаболизма клопидогреля у пациентов: медленного/промежуточного, нормального и быстрого/ультрабыстрого, в связи с крупными сердечно-сосудистыми и геморрагическими событиями в течение 6-12 месяцев. Результаты оценки позволили разработать стратегии персонализированного прогнозирования крупных ишемических и геморрагических событий при ДАТ на основе генетического полиморфизма CYP2C19. **Научная новизна и оригинальность.** Впервые были осуществлены: идентификация аллельных частот CYP2C19 и фенотипов здоровых субъектов в зависимости от полиморфизма CYP2C19; оценка аллельных частот CYP2C19 и фенотипов у пациентов с коронарными заболеваниями после ЧКВ принимающих ДАТ (включающую аспирин и клопидогрель), в зависимости от полиморфизма CYP2C19; оценка факторов сердечно-сосудистого риска, клинических, параклинических, лабораторных, которые могут влиять на управление ДАТ (с аспирином и клопидогрелем) с использованием балловых шкалы DAPT и PRECISE-DAPT в течение 6-12 месяцев; подход к острым ишемическим событиям и кровотечениям в течение 6-12 месяцев у пациентов после ЧКВ, принимающих ДАТ (с аспирином и клопидогрелем), в зависимости от полиморфизма CYP2C19; создание модели прогнозирования повторных ишемических событий и кровотечений у пациентов после ЧКВ принимающих ДАТ (включающую аспирин и клопидогрель) в течение 6-12 месяцев. **Смысл теоретического аспекта исследования.** Проведенное исследование еще раз подчеркнуло данные литературы относительно наличия межиндивидуальной вариабельности ответа на клопидогрель и повторных тромботических событий после коронарного стентирования. Генетическое изменение в CYP2C19 выявляется как один из факторов, ответственных за гипореактивность к данному антиагреганту. Полученные результаты поддерживают данные теоретического концепта. Опять же было продемонстрировано преимущество персонализированной медицины, подчеркивая ее ключевую роль в предотвращении неудачи антиагрегантной терапии у пациентов, прошедших ЧКВ. **Значение приложения** заключается в разработке прогностических моделей для повторяющихся ишемических событий и кровотечений у пациентов после PCI, принимающих ДАТ с аспирином и клопидогрелем в течение 6-12 месяцев. **Имплементация результатов.** Научные результаты были внедрены в Департамент Интервенционной Кардиологии и Эндоваскулярной Хирургии Муниципальная клиническая больница "Святая Троица", отделение кардиохирургии и реабилитации сердечных заболеваний ГМСУ "Институт Кардиологии".