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АССОЦИАЦИИ ПОЛИМОРФИЗМОВ ГЕНОВ И ПРОГНОЗА У ВЫСОКО ПРИВЕРЖЕННЫХ МЕДИКАМЕНТОЗНОЙ ТЕРАПИИ ПАЦИЕНТОВ ПОСЛЕ ИНФАРКТА МИОКАРДА

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Associations of Gene Polymorphisms and Prognosis in Highly Adherent to Treatment Patients After Myocardial Infarction

Резюме

Цель. Оценить наличие ассоциаций генетических факторов с риском развития комбинированной конечной точки (ККТ), включающей смертельные исходы, нефатальные инфаркты миокарда (ИМ) и мозговые инсульты в течение однолетнего наблюдения пациентов, перенесших ИМ и высоко приверженных лекарственной терапии. **Материалы и методы.** В исследование включено 250 высоко приверженных медикаментозной терапии пациентов с ИМ (68,8% мужчин, медиана возраста — 62,8 (54,7; 71,4) года), у которых методом полимеразной цепной реакции определяли полиморфизмы Thr174Met и Met235Thr в гене *AGT, Arg389Gly* и Ser49Gly в гене *ADRB1*, Ser447Ter в гене *LPL* и Leu28Pro в гене *APOE*, Trp212Ter и G681A в гене *CYP2C19*, а в дальнейшем оценивали их связь с неблагоприятным исходом. Высоко приверженными медикаментозной терапии считали пациентов, принимавших все назначенные им при выписке лекарственные препараты в течение 12 месяцев наблюдения. **Результаты.** Значимая связь с риском развития ККТ была отмечена для полиморфизма гена *CYP2C19 (G681A)*, участвующего в метаболизме клопидогреля. У лиц с зарегистрированными событиями, объединенными в ККТ, генотип GA гена *CYP2C19 (G681A)* встречался чаще, чем в группе без событий (ОШ 1,97; ДИ 95% 1,05 — 3,69, p=0,03), а генотип GG — реже (ОШ 0,51; ДИ 95%, 0,28 — 0,95, p=0,03). Генотип AA статистической значимой связи с прогнозом не имел ввиду малой численности группы пациентов с данным генотипом (n=3). Для аллеля A гена *CYP2C19 (G681A)* показатель ОШ риска развития ККТ составил 1,96 (ДИ 95%, 1,06 — 3,64, p=0,03). **Заключение.** Полученные результаты свидетельствуют о необходимости индивидуального подхода при выборе препаратов из группы ингибиторов P2Y12-рецепторов для двойной антиагрегантной терапии и, в случае выбора клопидогреля, о необходимости решения вопроса о целесообразности проведения фармакогенетического тестирования по *CYP2C19*.

Ключевые слова: *инфаркт миокарда; неблагоприятный исход; Thr174Met; Met235Thr; Arg389Gly; Ser49Gly; Ser447Ter; Leu28Pro; Trp212Ter; G681A*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Aim. To evaluate the influence of genetic factors on the risk of developing a combined endpoint, during a one-year supervision of patients, who had myocardial infarction and highly adherent to drug therapy. **Material and methods.** The research included 250 patients with high adherence to treatment with myocardial infarction, using the method of polymerase chain reaction we determined the polymorphisms Thr174Met and Met235Thr in the *AGT* gene, Arg389Gly and Ser49Gly in the *ADRB1* gene, Ser447Ter in the *LPL* gene and Leu28Pro in the *APOE* gene, Trp212Ter and G681A in the *CYP2C19* gene, and then we evaluated their influence on the prognosis. **Results.** A significant influence on the risk of developing combined endpoint was noticed for the polymorphism of *CYP2C19 (G681A)* gene. For the GA genotype of the *CYP2C19* gene (G6881A), the OR of developing an unsuccessful outcome was 1.97 (95% CI 1.05 — 3.69) (P = 0.03). For carrier-state of A allele the OR was 1.46 (95% CI 1.06 — 3.64) (P = 0.03). **Conclusion.** The results received indicate the need for individual approach for the choice of drugs from the group of inhibitors P2Y12-receptors for dual antiplatelet therapy, and if clopidogrel is chosen it is necessary to resolve the issue of pharmacogenetic testing for *CYP2C19*.

Key words: *myocardial infarction; prognosis; Thr174Met; Met235Thr; Arg389Gly; Ser49Gly; Ser447Ter; Leu28Pro; Trp212Ter; G681A*

Conflict of interests

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ADRB1 — beta-1 adrenergic receptor gene, *AGT* — angiotensinogen gene, *APOE* — apolipoprotein E gene, *CYP2C19* — cytochrome P450 gene of family 2 of subfamily C number 19, *LPL* — lipoprotein lipase gene, BB — beta-blockers, DAPT — double antiplatelet therapy, CI — confidence interval, ACE inhibitors — angiotensin-converting enzyme inhibitors, MI — myocardial infarction, CEP — combined endpoint, QAQ-25 — quantitative adherence questionnaire, CS — cerebral stroke, ACS — acute coronary syndrome, OR — odds ratio

Introduction

Myocardial infarction (MI) is one of the most severe forms of coronary heart disease accompanied by high mortality rates, both in the acute phase and later stages of the disease [1]. While, of late, mortality in the acute period of myocardial infarction has decreased significantly primarily due to the widespread implementation of percutaneous coronary interventions [2–4], mortality rates in the later period of myocardial infarction have been decreasing at a slower rate, although there is also a positive trend [5]. In the LIS-3 study, over an observation period of 14–35 months, 12.5% of patients died [6], and in the later PROFILE-IM register, 10% of patients died over a 1.5-year observation period [5]. Similar data were obtained in the Polish register of acute coronary syndrome (ACS) and acute myocardial infarction in patients with left ventricular ejection fraction ≤ 40% [7]. According to the authors, such an improvement in long-term mortality is exclusively due to the improvement in the quality of secondary prevention [5, 7]. However, the effectiveness of the latter is largely associated not only with the adherence of patients to treatment but also with genetically determined drug resistance [8], which determines both death and adverse cardiovascular events in a particular patient. This fact determines the significant interest in the assessment of possible associations of genetic factors and prognosis.

In accordance with clinical guidelines, if there are no contraindications, all patients with MI should receive drugs that have been proven to improve the prognosis [9] (subject to their use by the patient). In this connection, in our opinion, it is preferable to determine the relationship between polymorphisms of genes that are responsible for the metabolism of these groups of medications and the prognosis in patients who are highly adherent to drug therapy, and when forming a sample of patients for the study, to focus on high potential adherence to treatment, which can be quantified using the QAQ-25 adherence questionnaire [10].

Goal of the study: to investigate associations of polymorphisms of genes involved in the metabolism of drugs

that improve prognosis in MI, with the risk of developing a combined endpoint (CEP) in highly adherent patients after MI.

Material and Methods

From September 1, 2018, to May 1, 2019, 250 patients hospitalized for MI were enrolled in the prospective single-center study.

Inclusion criteria:

- signed informed consent;
- established diagnosis of current MI;
- a high level (more than 75%) of potential adherence to drug therapy, as determined by the QAQ-25 [10].

Patients were enrolled in the study on days 1–3 after their transfer to the general ward from the intensive care unit.

The study had the following exclusion criteria:

- absolute contraindications to angiotensin-converting enzyme inhibitors (ACE inhibitors), beta-blockers (BB), statins, antiplatelet agents;
- mental illnesses;
- alcohol and drug abuse.
- low and medium potential adherence to drug therapy according to the QAQ-25 questionnaire) [10].

The study was approved by the local ethics committee and registered at ClinicalTrials.gov with identification number NCT04424368.

All patients received atorvastatin at a dose of 40 mg per day, ACE inhibitors, BB, clopidogrel as part of dual antiplatelet therapy (DAPT). The patients were given dietary recommendations.

For all patients enrolled in the study, at the time of enrollment, polymorphisms Thr174Met and Met235Thr were determined in the angiotensinogen gene (*AGT*), Arg389Gly and Ser49Gly in the beta-1 adrenergic receptor gene (*ADRB1*), Ser447Ter in the lipoprotein lipase gene (*LPL*) and Leu28Pro in the apolipoprotein E gene (*APOE*), Trp212Ter (*3) and G681A (*2) in the cytochrome P450 gene of family 2 of subfamily C number 19 (*CYP2C19*) via polymerase chain reaction with an electrophoretic scheme for detecting the result "SNP-EXPRESS" (NPF "Litekh", Russia) Subsequently, after 3, 6 and 12 months, the patients were contacted by telephone to assess their level of adherence. After 12 months of follow-up, all of the enrolled patients were adherent to drug therapy. Twelve months after MI, information about the events combined in the CEP was collected for each patient: death, non-fatal MI and cerebral strokes (CS), emergency revascularization of coronary arteries. Then the analysis of the associations of the studied polymorphisms was performed: Thr174Met and Met235Thr in gene *AGT*, Arg389Gly and Ser49Gly in gene *ADRB1*, Ser447Ter in gene *LPL* and Leu28Pro in gene *APOE*, Trp212Ter (*3) and G681A (*2) in gene *CYP2C19* with the risk of developing CEP.

The choice of candidate genes in the study was determined by the known data on the relationship between their polymorphisms and the metabolism of drugs that improve the prognosis, the ambiguity of results of previous studies in groups of patients with MI without considering their adherence to treatment or the absence of such studies according to the literature [11–13]. Clopidogrel was chosen as the second component of DAPT prescribed to patients after MI because of its greater availability for patients and, consequently, the greater frequency of its prescription and use in clinical practice [14–16].

Microsoft Excel 2010 and StatsoftStatistica10.0 were used to analyze the results of the study. Methods of descriptive and nonparametric statistics were fundamental. The results are presented as frequencies (%). The distribution of all quantitative traits differed from normal; the data are presented as the median and interquartile range of Me (Q1; Q3).

The significance of differences in the frequencies of genotypes and alleles of two unrelated groups was determined by the methods of nonparametric statistics depending on the number of observations (chi-square Pearson test, chi-square test with Yates' correction for continuity and Fisher's exact test). Differences were considered significant at $p < 0,05$.

The strength of the identified associations was assessed by the odds ratio (OR) and its 95% confidence interval (95% CI). The CI not including one, i.e. where both values of its limits were above or below one at a significance level of $p < 0.05$, was considered statistically significant.

The determination of the comparability of the distribution of the genotypes of the studied polymorphic genes in the studied sample in relation to the population was carried out by assessing the correspondence to the Hardy — Weinberg equilibrium using software available online http://ihg2.helmholtzmuenchen.de/cgi-bin/hw/hwa1.pl.

Distribution of genetic information in the studied sample corresponded to the Hardy — Weinberg equilibrium for all genes, except for AGT gene (Thr174Met) ($\chi^2 = 4.0$, $p = 0.045$) and ADRB1 (Arg389Gly) ($\chi^2 = 4.4$, $p = 0.037$).

Results

Among the 250 enrolled patients, 68.8% were males (172). 83.6% (209) of patients had a history of hypertension, 30.8% (77) — ischemic heart disease, including 26.4% (66) with a history of MI. In the past, 8.8% (22) of

patients underwent stenting of coronary arteries. Chronic heart failure and atrial fibrillation were observed in 88.8% (222) and 20.8% (52) of patients, respectively. Diagnosis of "diabetes mellitus" or "impaired glucose tolerance" was established in 26.4% (66) of cases. 71.6% (179) of patients had Q-MI at the time of enrollment. Median age was 62.8 (54.7;71.4) years (Table 1).

During one year of follow-up, 11.6% (29) of patients out of 250 died of all causes; 86.2% (25) of them died from cardiovascular causes. One-year survival rate was 88.4%. In one year, 4.8% (12) of patients had MI, which was fatal in three cases, and in 2.4% (6) patients, MI was fatal in one case 10.8% (27) of patients underwent unplanned coronary revascularization. Only 28.0% (70) of patients underwent CEP.

There was a statistically significant difference in the frequency of occurrence of CYP2C19 gene genotypes (G681A) and A allele of the CYP2C19 gene (G681A) between patients with and without registered events.

Data on the distribution of genotypes and the frequency of occurrence of alleles of the analyzed genes among patients with registered events combined in CEP and without such events are presented in Table 2.

Significant associations with the course of the postinfarction period were noted for *CYP2C19 (G681A)* gene polymorphism both at the level of genotypes and at the level of alleles (see Table 3). In individuals with registered events combined in CEP, the GA genotype of*CYP2C19 (G681A)* gene was more common than in the group without events (OR 1.97; CI 95% 1.05–3.69, p = 0.03), and GG genotype was less common (OR 0.51; CI 95%, 0.28–0.95, p = 0.03).

The AA genotype did not have a statistically significant relationship with the prognosis due to the small size of the group of patients with this genotype (n = 3) (OR 1.29; CI 95%, 0.12–14.46, p = 0.63).

For A allele of *CYP2C19 (G681A)* gene, OR of the risk of developing CEP was 1.96 (CI 95%, 1.06–3.64, p = 0.03). For G allele of *CYP2C19 (G681A)* gene, OR of the risk of developing CEP was statistically insignificant and amounted to 0.78 (CI 95%, 0.07–8.70, p = 0.63).

Discussion

The association of minor alleles *2 of the *CYP2C19* gene with an increased risk of developing CEP shown by our study is largely consistent with both the first Russian meta-analysis of the effect of polymorphism of the *CYP2C19* gene on the risk of MI, stent thrombosis, ischemic stroke, transient ischemic attack and cardiovascular death [17], and the latest international studies published in 2018–2019 [18, 19].

Nevertheless, an extensive review published in 2019 on the pharmacogenetics of clopidogrel unequivocally states that the routine clinical genotyping of patients for non-functioning alleles *CYP2C19* is not recommended due to the lack of prospective evidence of the effectiveness of this approach [20]. The large randomized study "Tailored Antiplatelet Initiation to Lessen Outcomes due to Decreased Clopidogrel Response after Percutaneous Coronary Intervention" that ended in 2020 revealed no differences in the effect on the primary endpoint between routine antiplatelet therapy and tailored therapy based on genotyping data [21].

Table 1. *Clinical characteristics of patients included in the studies*

Parameter	Patients included in the study (n=250)
Median age, years	62,8 (54,7; 71,4)
Men, % of n	68,8 (172)
Obesity, % of n	30,0 (75)
Diabetes mellitus/impaired glucose tolerance, % of n	22,4 (56)
History of coronary heart disease, % of n	30,8 (77)
Repeated MI, % of n	26,4 (66)
History of PCI, % of n	8,8 (22)
AH, % of n	83,6 (209)
CHF, % of n	88,8 (222)
AF, % of n	20,8 (52)
Q-positive MI, % of n	71,6 (179)
Q-negative MI, % of n	28,4 (72)
Kidney diseases, % of n	26,3 (81)
COPD, % of n	2,4 (6)
Diseases of the gastrointestinal tract, % of n	26,0 (65)
Thyroid diseases, % of n	2,0 (5)

Note: MI — myocardial infarction, PCI — percutaneous coronary intervention, AH — arterial hypertension, CHF — chronic heart failure, AF- atrial fibrillation

Table 2. *Data on the distribution of genotypes, the frequency of occurrence of alleles of the analyzed genes in individuals who have reached and have not reached the combined endpoint*

Genotype/ Allele	Combined endpoint +, % от n=70 (Absolute value)	Combined endpoint –, % от n=180 (Absolute value)	p
ThrThr	65,7 (46)	63,3 (114)	0,72
ThrMet	34,3 (24)	34,4 (62)	0,98
MetMet	0,0 (0)	2,2 (4)	–
Thr	100 (70)	97,8 (176)	–
Met	34,3 (24)	38,9 (70)	0,50
MetMet	25,7 (18)	22,8 (41)	0,83
MetThr	51,4 (36)	57,2 (103)	0,41
ThrThr	22,9 (16)	20,0 (36)	0,37
Met	77,1 (54)	80,0 (144)	0,62
Thr	74,3 (52)	70,2 (139)	0,62
SerSer	69,8 (44)	67,1 (110)	0,81
SerGly	22,2 (14)	29,9 (49)	0,25
GlyGly	7,9 (5)	3,0 (5)	0,11
Ser	82,9 (58)	88,3 (159)	0,25
Gly	27,1 (19)	30,0 (54)	0,66
ADRB1 (Arg389Gly)			
ArgArg	47,1 (33)	57,2 (103)	0,15
ArgGly	47,1 (33)	40,0 (72)	0,30
GlyGly	5,7 (4)	2,8 (5)	0,22
Arg	94,3 (66)	97,2 (175)	0,22
Gly	52,9 (37)	42,8 (77)	0,15
APOE (Leu28Pro)			
LeuLeu	97,1 (68)	96,7 (174)	0,60
LeuPro	2,9 (2)	3,3 (6)	
Leu	100 (70)	100 (180)	–
Pro	2,9 (2)	3,3 (6)	0,60
LPL (Ser447Ter)			
SerSer	92,9 (65)	83,3 (150)	0,04
SerTer	7,1 (5)	16,7 (30)	
Ser	100 (70)	100 (180)	–
Ter	7,1 (5)	16,7 (30)	0,04
CYP2C19 (G681A)			
GG	67,1 (47)	80,0 (144)	**0,03**
GA	31,4 (22)	18,9 (34)	**0,03**
AA	1,4 (1)	1,1 (2)	0,63
G	98,6 (69)	98,9 (178)	0,63
A	32,9 (23)	20,0 (36)	**0,03**
CYP2C19 (Trp212Ter)			
TrpTrp	91,4 (64)	87,2 (157)	0,48
TrpTer	8,6 (6)	12,8 (23)	
Trp	100,0 (70)	100,0(180)	–
Ter	8,6 (6)	12,8 (23)	0,47

Note: for ADRB1 gene (Ser49Gly), n = 227; statistically significant differences are shown in bold

Table 3. *Comparative analysis of the probability of the combined endpoint in patients with MI within 1 year, depending on the genotype/allele*

Genotype/ Allele	Combined endpoint +, % от n=70 (Absolute value)	Combined endpoint -, % от n=180 (Absolute value)	P	OR (95% CI)
		AGT (Thr174Met)		
ThrThr	65,7 (46)	63,3 (114)	0,72	1,11 (0,62–1,98)
ThrMet	34,3 (24)	34,4 (62)	0,98	0,99 (0,56 — 1,77)
MetMet	0,0 (0)	2,2 (4)	–	–
Thr	100 (70)	97,8 (176)	–	–
Met	34,3 (24)	36,7 (66)	0,72	0,91 (0,51 — 1,61)
		AGT (Met235Thr)		
MetMet	25,7 (18)	22,8 (41)	0,83	0,32 (0,62–2,24)
MetThr	51,4 (36)	57,2 (103)	0,41	0,79 (0,46– 1,38)
ThrThr	22,9 (16)	20,0 (36)	0,37	1,19 (0,61 — 2,31)
Met	77,1 (54)	80,0 (144)	0,62	0,84 (0,43 — 1,64)
Thr	74,3 (52)	70,2 (139)	0,62	0,85 (0,45 — 1,62)
		ADRB1 (Ser49Gly)		
SerSer	69,8 (44)	67,1 (110)	0,81	0,32 (0,61 — 2,13)
SerGly	22,2 (14)	29,9 (49)	0,25	0,73 (0,37 — 1,45)
GlyGly	7,9 (5)	3,0 (5)	0,11	2,74 (0,76 — 9,82)
Ser	82,9 (58)	88,3 (159)	0,25	0,64 (0,30 — 1,38)
Gly	27,1 (19)	30,0 (54)	0,66	0,87 (0,47 — 1,61)
		ADRB1 (Arg389Gly)		
ArgArg	47,1 (33)	57,2 (103)	0,15	0,67 (0,38 — 1,16)
ArgGly	47,1 (33)	40,0 (72)	0,30	1,30 (0,75 — 2,27)
GlyGly	5,7 (4)	2,8 (5)	0,22	2,12 (0,55 — 8,14)
Arg	94,3 (66)	97,2 (175)	0,22	0,47 (0,12 — 1,81)
Gly	52,9 (37)	42,8 (77)	0,15	1,50 (0,86 — 2,61)
		APOE (Leu28Pro)		
LeuLeu	97,1 (68)	96,7 (174)	0,60	1,17 (0,23 — 5,95)
LeuPro	2,9 (2)	3,3 (6)		0,85 (0,17 — 4,33)
Leu	100 (70)	100 (180)	–	–
Pro	2,9 (2)	3,3 (6)	0,60	0,85 (0,17 — 4,33)
		LPL (Ser447Ter)		
SerSer	92,9 (65)	83,3 (150)	0,04	2,6 (0,97 — 7,00)
SerTer	7,1 (5)	16,7 (30)		0,39 (0,14 — 1,04)
Ser	100 (70)	100 (180)	–	–
Ter	7,1 (5)	16,7 (30)	0,04	0,39 (0,14 — 1,04)
		CYP2C19 (G681A)		
GG	67,1 (47)	80,0 (144)	**0,03**	**0,51 (0,28 — 0,95)**
GA	31,4 (22)	18,9 (34)	**0,03**	**1,97 (1,05–3,69)**
AA	1,4 (1)	1,1 (2)	0,63	1,29 (0,12 — 14,46)
G	98,6 (69)	98,9 (178)	0,63	0,78 (0,07 — 8,70)
A	32,9 (23)	20,0 (36)	**0,03**	**1,96 (1,06 — 3,64)**
		CYP2C19 (Trp212Ter)		
TrpTrp	91,4 (64)	87,2 (157)	0,48	1,56 (0,61 — 4,02)
TrpTer	8,6 (6)	12,8 (23)		0,64 (0,25 — 1,65)
Trp	100,0 (70)	100,0(180)	–	–
Ter	8,6 (6)	12,8 (23)	0,47	0,64 (0,25 — 1,65)

Note: for *ADRB1* gene (Ser49Gly), n = 227; statistically significant differences are shown in bold

However, despite this, when taking clopidogrel, the Russian clinical guidelines for the management of patients with MI and ACS indicate that "pharmacogenetic testing of *CYP2C19* can be carried out to predict reduced laboratory sensitivity to clopidogrel" [22, 23].

Because a significant percentage of individuals in our study had GA genotype of the *CYP2C19* gene (distribution of genotypes and alleles of the gene *CYP2C19* in our study corresponded to the Hardy Weinberg equilibrium), which was associated with an unfavorable outcome, the recommendation to conduct pharmacogenetic testing can be considered valid and consistent with our results. This genotype (GA of *CYP2C19* gene) determines the need to apply all possible measures to prevent an adverse outcome, including careful selection of DAPT in patients with MI where currently acetylsalicylic acid and a drug from the group of P2Y12 -receptor inhibitors, primarily ticagrelor or prasugrel, should be included [22, 23]. According to clinical guidelines, clopidogrel should be prescribed only when its use is safer for the patient [22, 23]. However, data from actual clinical practice suggest otherwise — clopidogrel is mostly prescribed for patients with MI. In the Russian register "RECORD-3", clopidogrel was prescribed at discharge in 67% of cases, and ticagrelor — in 12% [14]; in one of the registries conducted in the USA, 72.9% of patients received clopidogrel, 17.6% — prasugrel, and 9.5% — ticagrelor [15]; in the analysis of case histories conducted by M. R. Atabegashvili et al (2019), of 854 patients with ACS hospitalized from January to December 2017, clopidogrel was prescribed to 73% of patients, and ticagrelor — to 27% [16].

In such a situation, which implies the prescription of clopidogrel in the absence of contraindications for ticagrelor and prasugrel, the results of genetic testing can be considered an indicator of the safety of its prescription [22, 23]. The cost of the latter (as of May 2021) ranges from 960 to 2,600 rubles depending on the time of analysis, region, laboratory (data from open sources — price lists of laboratories providing the service) and is economically justified [24, 25]. When genotypes associated with the risk of an unfavorable outcome are identified, the results of genotyping will allow the prescription of ticagrelor and prasugrel to such patients, the use of other drug and non-drug methods to improve the prognosis, thereby reducing possible expenses associated with hospitalization, disability, and death of the patient. If a genotype that is not associated with the risk of an unfavorable outcome is identified, genotyping results will allow the prescription of clopidogrel to such patients with a lower risk. The cost of genetic testing will be comparable to the difference in the cost of drugs and will be recovered within the first few months of treatment.

Unlike a number of other authors, we obtained no statistically significant data on the relationship between polymorphisms of other genes that we studied and the prognosis. In the study by M. V. Solodun et al. (2016), the carrier status of allele Ser of polymorphic gene *ADRB1 Ser49Gly* was associated with an increase in the incidence of adverse cardiovascular events within 12 months after STEMI [26]; in another study with hypertrophic cardiomyopathy, genotype ArgGly gene *ADRB1* (polymorphism *Arg389Gly*) was more favorable, since it had a lower chance of being complicated by the development of atrial fibrillation than other genotypes [27].

The distinctive feature of our study, which began in 2018, was the inclusion of patients with only a high level of potential adherence to drug therapy and remote monitoring of adherence to therapy after 3, 6 and 12 months. This study methodology allowed the enrollment of highly adherent patients in the study and the assessment of the associations of gene polymorphisms and prognosis exclusively in patients taking drugs whose metabolism is affected by the studied genes.

Conclusion

The association of a poor prognosis with GA genotype of *CYP2C19* gene, which is involved in the metabolism of clopidogrel, shown by the study among highly adherent patients with MI, suggests the need for a tailored approach to the choice of medication from the group of P2Y12-receptor inhibitors for DAAT and, when clopidogrel is prescribed, consideration of the advisability of pharmacogenetic testing according to CYP2C19.

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