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Predicting the development of adverse events in patients with acute coronary syndrome including genetics in the long-term follow-up

Цель	To study a relationship of several factors (clinical and genetical markers) with unfavorable outcomes in patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) in long-term follow-up.
Material and methods	This full-design, prospective study included 415 patients with NSTE-ACS. 266 patients were evaluated for the presence of multifocal atherosclerosis (MFA). Typing of polymorphic variants *rs1041981 LTA, rs1800629 TNF, rs4986790*, and *rs498679 TLR4*, and also *rs3024491* and *rs1800872 IL10* was performed. Follow-up period lasted for 67±4 months. By the end of this period, information about clinical outcomes for 396 patients became available.
Results	During the entire follow-up period, unfavorable outcomes were observed in 239 (57.5%) patients with NSTE-ACS. The following clinical signs were associated with unfavorable outcomes: history of myocardial infarction, age >56 years, left ventricular ejection fraction (LV EF) ≤50% and GRACE score ≥100, significant stenosis of brachiocephalic arteries, MFA, carriage of genotype *A/A rs1041981 LTA* (OR, 6.1; p=0.02) and allele A (OR, 1.9; p=0.01). According to results of a multifactorial analysis, the most significant predictors included LV EF <50%, MFA, and carriage of genotype A/A rs1041981 LTA.
Conclusion	Stratification of patients with NSTE-ACS into groups of high or low risk for having an unfavorable outcome within the next 6 years is possible using the prognostic model developed and presented in this study. The model includes the following signs: LV EF <50%, MFA, and carriage of genotype *A/A rs1041981 LTA*.

Keywords	Non-ST-segment elevation acute coronary syndrome; multifocal atherosclerosis; unfavorable outcomes; long-term follow-up; rs1041981 LTA
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Despite the high mortality rates in infections and cancers, cardiovascular diseases (CVDs) such as acute coronary syndrome (ACS) are the leading cause of death in adults [1]. ST-elevation ACS has a high hospital mortality rate, and in fact is considered the most threatening form of cardiovascular disease. However, the mortality rate in patients with non-ST elevation acute coronary syndrome (NSTE-ACS) is twice as high four years after the event [2].

Long-term follow-up of patients with NSTE-ACS showed that the rate of fatal outcomes in five years was 56%, provided that only patients with non-ST elevation myocardial infarction (MI) were registered [3]. It was determined that if modern approaches to treatment are used, about 8.5% of patients hospitalized with progressive angina pectoris showed signs of myocardial necrosis at the hospital stage, and MI developed in 39% of cases in the long-term follow-up period [4]. Thus, it is relevant to find out which risk factors are associated with the adverse course of the disease in the long-term period in the current paradigm of medical care for patients with ACS. It should be noted that the influence of risk factors, which include carriership of alleles / genotypes of polymorphic genes, is not triggered by the development of ACS. However, the long-term follow-up of the patient cohort can reveal the relationship of genetic components with the development of repeat ACS and death outcomes in this particular category of patients.

The objective of this study was to investigate the relationship of factors (clinical and genetic markers) with adverse outcomes in patients with NSTE-ACS in the long-term follow-up period.

Materials and Methods

A full-design prospective study was conducted that included 415 patients with NSTE-ACS who were consecutively hospitalized within 12 months. Inclusion criteria: patient consent to participate in the study; age from 40 to 80 years; anginal syndrome with typical electrocardiographic changes (ST depression more than 1 mm and/or T-wave inversion). The diagnosis of non-ST elevation MI was established in cases of elevated levels of troponin T at admission or over time. The absence of elevated levels of cardiac-specific enzymes determined the final diagnosis of progressive angina pectoris. Patients with ST-elevation were not included in the study. Patients were included in a genetic testing group at the end of the hospital period. 266 patients in the total sample were examined for signs of multifocal atherosclerosis (MFA) using coronary angiography and color-flow duplex scanning of brachiocephalic arteries (BCAs) and lower extremity arteries (LEAs). This study evaluated the incidence of cardiovascular adverse events (ACEs), which included cases of MI, progressive angina pectoris, ischemic stroke, and patient death. The seven deaths at the hospital follow-up stage were not included in further analysis. The follow-up period was 67±4 months, by the end of which the clinical outcomes of 396 patients on the register were reported.

Clinical characteristics of the sample: 60% of the patients were male with a mean age of 61 years. 90% had hypertension, 17.8% type 2 diabetes, 39.8% MI, and 121% had been subject to a cerebrovascular accident. The majority of patients (78.5%) noted having previously experienced clinical signs of angina pectoris.

In this study, the variability of the *rs1041981, rs1800629, rs3024491, rs1800872, rs4986791*, and *rs4986790* polymorphisms in representatives of the Caucasian population of the Kemerovo region was studied. The ethnicity of the patients was determined based on questionnaire and passport data, and representatives of the indigenous population of Kuzbass were not included in the study. Genotyping was performed in 96--well format using the TaqMan assays (LifeTechnologies, USA) with real-time detection using the ViiATM 7 real-time PCR System (LifeTechnologies, USA) under the manufacturer's instructions. No deviation from the Hardy – Weinberg equilibrium was registered.

The findings were statistically processed using MedCalc v.11.0 (Software, Belgium). The rate and percentages of quality indicators were estimated. Quantitative indicators are represented as the median and interquartile range (25th and 75th percentiles). The quantitative signs were compared using the Mann-Whitney U-test whereas the qualitative signs were compared using the 2×2 and 2×3 contingency tables and the calculation of the Pearson chi-squared test or Fisher's exact test. The odds ratio (OR) with a 95% confidence interval (CI) was calculated. The multivariate analysis and the construction of the prediction model were carried out using binary logistic regression with stepwise selection of signs. The ROC (receiver operating characteristic) curves were used to determine the quantitative threshold and compare the prediction capacity of the reference (GRACE score) and our predictive models. The differences in the groups compared were considered statistically significant with $p<0.05$.

Results

Adverse outcomes were reported in more than half of patients with NSTE-ACS: 239 (57.5%) patients had ACEs by the end of the scheduled follow-up period. Fatal outcomes were observed in 64 (15.4%) patients, with 47 (73.4%) due to cardiovascular causes. The first year was the worst: 102 (42.6%) patients developed adverse cardiovascular events, including the largest number of fatal outcomes (25 (39.0%) cases), repeat MI (18 (50%) cases), and hospitalizations due to progressive angina pectoris (60 (52.2%) cases). In subsequent years, the same number of adverse outcomes were reported, but the incidence of ischemic strokes increased to 11 (35.5%) cases by the sixth year of follow-up.

The outcome analysis at the end of the sixth year of follow-up divided all patients included in the study into two groups: favorable outcome (Group I, n=157) and adverse outcome (Group II, n=239) (Table 1).

The development of adverse events in the long-term follow-up period was generally associated with older age and higher risk based on the GRACE score. Moreover, the development of ACEs was associated with such factors as the history of MI and a decrease in LVEF. Age >56 years ($p=0.001$; sensitivity (Sen) – 75.9%, specificity (Spe) – 40.5%), LVEF ≤ 50% ($p=0.001$; Sen – 33.1%, Spe – 78.3%), and the estimated GRACE index ≥100.0 points ($p=0.002$; Sen – 54.1%, Spe – 60.6%) were predictive of adverse outcomes.

In this study, the data describing the main characteristics of the coronary arteries in groups with different outcomes did not differ significantly during the six-year follow-up stage (Table 2).

It was reported that, in the hospital period, coronary artery imaging was performed in 80% of cases, and significant stenosis of three or more coronary arteries (CAs) was detected in about 30% of patients with NSTE-ACS. Due to the lack of a relationship between the nature of coronary artery lesions at the hospital stage and the development of ACEs in the long-term follow-up period,

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Table 1. Comparison of clinical factors in patient groups with NSTE-ACS based on disease outcome by the sixth year of follow-up

Parameter	Group I, n=157	Group II, n=239	p
Male, n (%)	96 (61.2)	134 (56.1)	0.308
Age, years, Me (Q25; Q75)	59.0 (52; 68)	62.0 (56; 70)	0.001
Diagnosed MI, n (%)	79 (50.2)	122 (51.1)	0.948
History of MI, n (%)	45 (28.5)	98 (41.1)	0.021
History of stroke, n (%)	18 (11.3)	30 (12.6)	0.898
Previous PCI, n (%)	13 (8.3)	26 (10.9)	0.521
Previous CAB, n (%)	4 (2.51)	18 (7.49)	0.060
Type 2 DM, n (%)	23 (14.7)	51 (21.4)	0.136
History of CHF, n (%)	19 (12.0)	44 (18.5)	0.135
History of hypertension, n (%)	135 (86.0)	220 (92.1)	0.143
History of angina pectoris, n (%)	120 (76.5)	190 (79.5)	0.684
Active smoking, n (%)	75 (47.8)	85 (35.4)	0.017
BMI, kg/m^2, Me (Q25; Q75)	28.5 (25.4; 39.5)	28.8 (25.2; 32.7)	0.413
GRACE risk, Me (Q25; Q75)	94 (78; 115)	103 (87; 122)	0.003
ST depression, n (%)	88 (56.0)	139 (58.1)	0.847
LVEF, %, Me (Q25; Q75)	61 (52; 65)	56 (48; 63)	0.002
LVEF <40%, n (%)	10 (6.36)	30 (12.5)	0.072
GFR using MDRD, Me (Q25; Q75), ml/min/1.73^2	69.5 (56.8; 85.7)	67.6 (54.8; 80.1)	0.329

MI, myocardial infarction; PCI, percutaneous coronary intervention; CBS, coronary bypass surgery; DM, diabetes mellitus; CHF, chronic heart failure; BMI, body mass index; LVEF, left ventricular ejection fraction; GFR, glomerular filtration rate; Me (Q25; Q75), the median and the 25th and 75th percentiles; p, level of statistical significance.

Table 2. Features of coronary and peripheral atherosclerosis in patients with NSTE-ACS at the hospital stage in groups with different outcomes by the sixth year of follow-up

Sign	Group I, n=157	Group II, n=239	p
Number of patients who underwent coronary angiography, n (%)	125 (79.7)	187 (78.3)	0.670
Coronary stenosis, n (%)	111 (70.6)	167 (69.7)	0.965
Multi-vessel coronary artery disease, n (%)	39 (24.9)	58 (24.3)	0.902
LCA trunk lesion>50%, n (%)	12 (7.65)	15 (6.28)	0.792
Hospital PCI, n (%)	58 (37.2)	87 (36.5)	0.934
Number of CBS scheduled, n (%)	25 (16.0)	33 (13.9)	0.632
Complete myocardial revascularization within the first 6 months of onset of ACS, n (%)	97 (90.6)	140 (91.5)	0.987
Assessment of peripheral arteries			
Number of patients who underwent BCA CFDS	138	207	-
IMC thickness, Me (Q25; Q75), mm	1.2 (1.0; 1.3)	1.2 (1.1; 1.3)	0.207
BCA stenoses, n (%)	37 (26.8)	84 (40.5)	0.012
BCA stenoses >50%, n (%)	8 (5.7)	27 (13.0)	0.045
Number of patients who underwent LEA CFDS	121	171	-
LEA stenoses, n (%)	23 (19.0)	48 (28.1)	0.101
LEA stenoses >50%, n (%)	14 (11.5)	28 (16.3)	0.325
Number of patients who underwent the assessment of 3 arterial systems	103	147	-
Presence of MFA, n (%)	36 (35.0)	72 (49.1)	0.037

LCA, left coronary artery; PCI, percutaneous coronary intervention; CBS, coronary bypass surgery, ACS, acute coronary syndrome; CFDS, color-flow duplex scanning; BCA, brachiocephalic arteries; IMC, intima-media complex; LEA, lower extremity arteries; MFA, multifocal atherosclerosis; p, level of statistical significance; Me (Q25; Q75), the median and the 25the and 75the percentiles.

the rate of complete myocardial revascularization within the first year after ACS is high (about 90%) in both study groups.

It was found that only a limited number of patients (about 55%) regularly took the drugs, and the differences in the frequency of major cardiac drug groups were not identified. During the first year of follow-up, about 80% of patients took statins in both favorable and adverse outcome groups. However, only 35% of patients were able to name the drugs by the sixth year of follow-up, with no significant differences between the groups with different outcomes.

The incidence of MFA within the six years of follow-up was significantly higher in the group of patients with the adverse course of the disease due to the presence of carotid stenosis. For example, more than 50% of patients with an adverse remote outcome in the sixth year of follow-up had stenosis of BCA.

There is growing interest in studying the association between carriership of polymorphic protein genes involved in atherogenesis and the outcomes of diseases. In this study, the association of several genes related to the inflammatory response with remote adverse outcomes in patients after NSTE-ACS was investigated (Table 3).

The carriership of the A/A *rs1041981* LTA genotype (OS 6.1; p=0.02) and A allele (OR 1.9; p=0.01) is significantly associated with the development of ACEs within the six years of follow-up of patients after ACS. No

Table 3. Frequency of genotypes and alleles of polymorphic genes depending on an outcome in the long-term follow-up period in patients after NSTE-ACS

Genotypes, alleles	Group II, n (%)	Group I, n (%)	p
rs1041981 LTA			
A/A	15 (15.5)	2 (2.9)	0.02
A/C	44 (45.4)	30 (43.5)	
C/C	38 (39.2)	37 (53.6)	
A	74 (38.1)	34 (24.6)	0.01
C	120 (61.9)	104 (75.4)	
ORA 1.89 [95% CI: 1.16–3.06]; ORC 0.53 [95% CI: 0.33–0.86]			
rs1800629 TNF			
A/A	0	1 (1.4)	0.28
A/G	25 (26.0)	13 (18.6)	
G/G	71 (74.0)	56 (80.0)	
A	25 (13.0)	15 (10.7)	0.52
G	167 (87.0)	125 (89.3)	
ORA 1.25 [95% CI: 0.63–2.46]; ORG 0.8 [95% CI: 0.41–1.58]			
rs3024491 IL10			
A/A	14 (14.6)	12 (16.7)	0.84
A/C	51 (53.1)	35 (48.6)	
C/C	31 (32.3)	25 (34.7)	
A	79 (41.1)	59 (41.0)	0.97
C	113 (58.9)	85 (59.0)	
ORA 1.01 [95% CI: 0.65–1.56]; ORC 0.99 [95% CI: 0.64–1.54]			
rs1800872 IL10			
G/G	50 (51.0)	39 (53.4)	0.85
G/T	39 (39.8)	29 (39.7)	
T/T	9 (9.2)	5 (6.8)	
G	139 (70.9)	107 (73.3)	0.63
T	57 (29.1)	39 (26.7)	
ORA 0.89 [95% CI: 0.55–1.43]; ORC 1.13 [95% CI: 0.70–1.82]			
rs4986791 TLR4			
C/C	84 (86.6)	64 (87.7)	0.98
C/T	13 (13.4)	9 (12.3)	
T/T	0	0	
C	181 (93.3)	137 (93.8)	0.84
T	13 (6.7)	9 (6.2)	
ORC 0.91 [95% CI: 0.38–2.20]; ORT 1.09 [95% CI: 0.45–2.63]			
rs4986790 TLR4			
A/A	78 (82.1)	61 (84.7)	0.88
A/G	15 (15.8)	10 (13.9)	
G/G	2 (2.1)	1 (1.4)	
A	171 (90.0)	132 (91.7)	0.64
G	19 (10.0)	12 (8.3)	
ORA 0.82 [95% CI: 0.38–1.75]; ORG 1.22 [95% CI: 0.57–2.61]			

p, level of statistical significance. LTA, lymphotaxin-α; TNF, tumor necrosis factor-α; IL10, interleukin-10; TLR4, toll-like receptor-4, OR, odds ratio; CI, confidence interval.

Table 4. Variable coefficients and model constants

Factor	OR (95% CI)	Coefficient	p
LVEF <50% (a)	5.96 (1.2–28.1)	1.79	0.024
MFA (b)	2.40 (1.2–4.81)	0.97	0.014
A/A *rs1041981 LTA* (c)	7.18 (2.2–19.6)	1.95	0.0008
Constant (k)	–	-0.34	–

LVEF, left ventricular ejection fraction; MFA, multifocal atherosclerosis; LTA, lymphotaxin-α, k, constant value determined using the statistical software when building the model; p, level of statistical significance.

other similar associations with other studied polymorphic genes were identified.

The significance of adverse outcome predictors within the six years of follow-up was determined by binary regression analysis. The baseline regression analysis included all the parameters that were significant at the previous stages of the study: age>56 years, history of MI, LVEF < 50%, BCA stenosis>50%, presence of MFA, and carriership of the A/A *rs1041981* LTA genotype. The final prognostic model for adverse outcomes included three predictors: LVEF < 50%, MFA and carriership of A/A *rs1041981* LTA (Table 4).

Table 4 also lists ORs that demonstrate that these factors are highly related to adverse outcomes within the six years of follow-up, and the predictor factors used in the following formula to determine the y value, which is needed to calculate p, the probability of an adverse outcome, using the formula:

$$p = 1 / 1 + e^{-y}$$

where e, the base of the natural logarithm, is a constant equal to 2.71; y=k + A × coefficient a + B × coefficient b + C × coefficient c.

A standard regression equation:

$$y = -0.34 + A \times 1.79 + B \times 0.97 + C \times 1.95$$

where A is LVEF (< 50%=1; >50%=0); B is MFA (present=1; absent=0); C is the A/A genotype (*rs 1041981*) of the LTA gene (present=1; other genotypes =0).

The ROC curve is a graphical representation of the probability of a predicted event (Figure 1). This curve was used to find p, above which the risk of adverse outcomes increases. The ROC curve shows the relationship between the number of correctly classified positive examples and

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Figure 1. ROC curve of the prognostic model for adverse cardiovascular events within the six years of follow-up

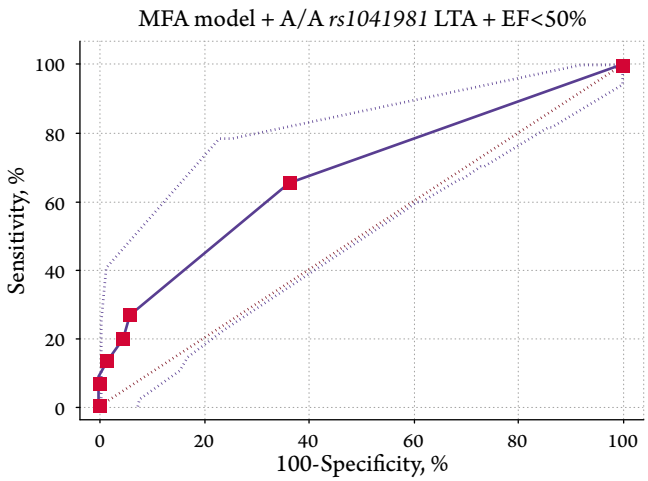
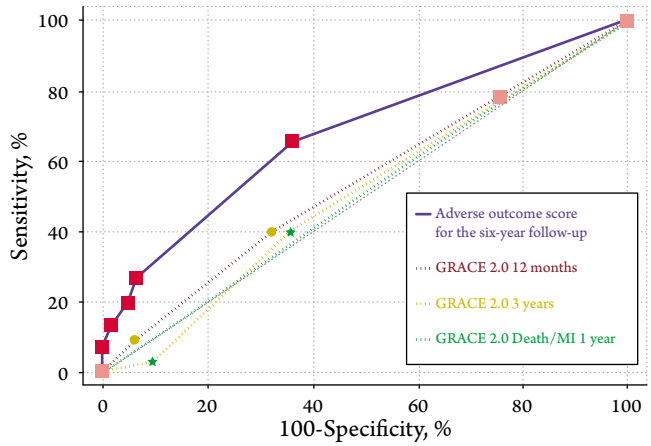


Figure 2. Comparison of ROC curves of the GRACE 2.0 score and the prediction model for the risk of adverse cardiovascular events in our study (p<0.05)



the number of incorrectly classified negative examples. It is assumed that the classifier has a specific parameter, whose differing value will allow the division of patients into two classes taking into account the values of the test sensitivity and specificity. This parameter is often referred to as a cutoff point. The statistical software allowed us to obtain the cutoff point p>0.415, indicating a high probability of adverse outcome. If the p value is less than the cutoff point, ACEs are unlikely to develop within six years.

A satisfactory quality model was developed with the correct classification percentage of 76.9% (AUC=0.679; sensitivity 65.9%, specificity 63.4%; p < 0.0001) with an optimal cutoff point of p>0.415.

Based on the classification characteristics, the combination of the three predictors presented can effectively divide patients into groups of high or low risk of adverse outcomes in the long-term follow-up period.

Figure 2 compares the ROC curves of the model developed as a result of this study and the GRACE 2.0 score, with the greatest area under the ROC curve used to determine the adverse outcome risk score developed in this study (AUC=0.679; p < 0.05).

Our prediction model has advantages over the GRACE 2.0 clinical score as it includes risk factors that are unmodifiable over time. Thus, it is more relevant in determining the long-term prognosis for patients with NSTE-ACS.

Discussion

The literature now shows that the mortality of high-risk NSTE-ACS (GRACE score) is about 25% in the first year and reaches 56% after ten years of follow-up [3, 5]. In 2016, the Federal State Statistics Service (Rosstat) reported that cardiovascular mortality was falling [1]. At the same time, foreign observational studies showed an increase in fatal outcomes after ACS in the long-term follow-up period [6]. In respect to this, the results of our study showing the high incidence of repeated non-fatal cardiovascular events in the first year after NSTE-ACS are consistent with several follow-up registries of patients with NSTE-ACS in the European population [7, 8]. In our recent study on the rate and time of the development of ACEs, we provided detailed data on the follow-up of patients with NSTE-ACS within the five years after their admission [9]. Interestingly, the highest incidence of ischemic stroke was observed in the sixth year of follow-up, which may be due to the presence of significant atherosclerotic lesions in brachiocephalic arteries as well as their progression during the follow-up period. Similar data were collected in the sample of patients with ACS in Tomsk, where cases of ischemic stroke were reported in the long-term follow-up period [10].

This study identified associations between several clinical factors and the adverse course of the disease. Recently, along with symptoms of senility, the age threshold of 65 years has been considered an adverse factor. An increasing number of arguments propose that older age should not be used as an excuse to cancel revascularization due to the high mortality of coronary events [11]. In this study, patients with favorable outcomes were somewhat younger than patients with ACEs. However, age did not prove to be an independent predictor of adverse outcomes in the presence of such combination of predictors as significantly reduced LVEF, the presence of MFA, and carriership of the high-risk A/A *rs1041981* genotype. In our opinion these predictors have advantages over the GRACE clinical model, which

is based mainly on age, in identifying younger patients who might have previously been predicted as at low risk of experiencing a fatal cardiovascular event.

The presence of previous incidences of MI in patients is not only directly associated with the development of adverse outcomes in patients with ACS [12] but also affects the decrease in LVEF. The decrease in global LV contractility, in turn, increases the risk of congestive heart failure and repeat coronary incidents, with an adverse impact stemming from even a relatively small decrease in LVEF to 56% [13]. The relevance of complete myocardial revascularization in multi-vessel coronary lesions is unquestionable [14]. The approach to the management of NSTE-ACS patients adopted in our facility dictates that routine myocardial revascularization procedures are performed within the six months after discharge from the hospital. Thus, the majority of patients underwent either a transcutaneous coronary intervention or coronary artery bypass surgery at the second stage, and complete myocardial revascularization was achieved. In our opinion, this explains the absence of the relationship between the severity of coronary lesions, the rate of emergency interventions at the hospitalization stage, and the development of adverse outcomes in the long-term period.

Multifocal atherosclerosis was considered a predictor of the adverse course of the disease both in stable coronary artery disease and ACS [15]. For example, the presence of MFA was identified as a risk factor for an adverse prognosis within twelve months of follow-up in patients with STE-ACS. Thus, KemScore-1 was created. This score is based on a combination of such predictors as a refusal of percutaneous coronary intervention, older age, congestive heart failure, and reduced global LV contractility of < 40%. Moreover, we made an attempt to increase the predictive value of the GRACE score by adding such predictors as MFA [16].

A significant association between the adverse course of the disease and the carriership of the A/A *rs1041981* LTA genotype was identified as a genetic factor in the long-term follow-up period. It is known from the literature that *rs1041981* LTA is associated with the development of an adverse outcome after ACS [17]. Moreover, the A allele and the A/A genotype are present in 40% and 16.5% of the world population, respectively [18]. Several papers demonstrate that the A/A *rs1041981* LTA genotype is significantly associated with coronary atherosclerosis and the development of MI [19]. This risk factor is useful for the stratification of the risk of severe coronary complications in the long-term period after NSTE-ACS. We have previously identified that the presence of the A allele and A/A *rs1041981* LTA genotype in patients with NSTE-ACS is associated with the development of adverse cardiovascular events in a five-year follow-up period [20]. Follow-up beyond five years showed that the *rs1041981* genotype retains its negative influence both in combination with and independently of other predictors. The use of a comprehensive prognostic approach, where narrower genetic markers are used along with traditional risk factors, improves the quality of long-term prediction in patients with NSTE-ACS.

The creation of complex models for the prognosis of long-term outcomes is now a relevant task, and genetic risk factors increase the prediction power, consequently influencing the choice of treatment strategy [21]. In 2017, a mathematical model was presented for the prediction of ACE risk within a year of NSTE-ACS diagnosis. It included such factors as the levels of serum C-reactive protein and carriership of the C/T *rs1376251* genotype of the TAS2R50 gene alongside standard clinical risk factors, increasing its predictive value [22]. Konenkov et al. (2015) demonstrated that a combination of laboratory- and genetic predictors has a high prognostic significance and can be used as criteria for the assessment of the efficacy of cell-based therapy in patients with chronic heart failure [23].

The ACE risk model presented in this study is capable of stratifying patients into a high-risk group and allows the personalization of secondary prevention measures, as well as contributing to the reduction of re-hospitalizations and fatal outcomes in patients with NSTE-ACS in the long-term period.

The assessment of the risk of repeated cardiovascular events in the long-term is interesting both to a patient and a consulting physician in choosing the optimal approach to patient management and drug therapy. Reduced patient awareness of the severity of the disease is the most significant factor in cases of decreased adherence to medication and lifestyle recommendations. Increase in patient adherence to regular drug administration was shown to be influenced by the explanation to the patient of his/her condition and the risk of the adverse course of the disease. The problem of patient adherence and the willingness to change their lifestyle after a cardiovascular event was addressed in a review of 44 European publications [24]. The importance of communication skills was emphasized in communicating effectively with ACS patients who, during hospitalization due to their diagnosis, experience initial stress as well as anxiety-depressive disorders later on, and as a result are often not willing to continue treatment at the outpatient stage. Positive adaptation and lifestyle changes after ACS, which can be demonstrated using prediction models developed for the outpatient period, was shown to be more readily

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*Более интенсивное снижение уровня ХС-ЛНП ассоциировано со снижением общей смертности у пациентов с исходным уровнем ХС-ЛНП ≥ 2,6 ммоль/л[1]

#В исследовании ODYSSEY OUTCOMES терапия алирокумабом была ассоциирована со снижением риска смерти от всех причин (ОР 0,85; 95% ДИ: 0,73-0,98; p=0,0261 [не скорректировано для множественных сравнений]).[2]

ОКС - острый коронарный синдром; ХС-ЛНП - холестерин липопротеинов низкой плотности; ОР - отношение рисков; ДИ - доверительный интервал; PCSK9 - пропротеиновая конвертаза субтилизин/кексин типа 9 (Proprotein Convertase Subtilisin/Kexin Type 9).

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Краткая инструкция по применению препарата Пралуэнт. МЕЖДУНАРОДНОЕ НЕПАТЕНТОВАННОЕ НАИМЕНОВАНИЕ: алирокумаб. СОСТАВ: алирокумаб 75 мг/мл или 150 мг/мл. ФОРМА ВЫПУСКА: раствор для подкожного введения. ПОКАЗАНИЯ К ПРИМЕНЕНИЮ. 1). Препарат Пралуэнт показан взрослым пациентам для лечения первичной гиперхолестеринемии (несемейной гиперхолестеринемии и гетерозиготной формой семейной гиперхолестеринемии) или смешанной дислипидемии, включая пациентов с сахарным диабетом 2 типа, в дополнение к диете, для снижения концентрации холестерина липопротеинов низкой плотности (ХС-ЛПНП), общего холестерина (общего-ХС), холестерина липопротеинов, не являющихся липопротеинами высокой плотности (ХС-ЛПневП), аполипопротеина В (Апо В), триглицеридов (ТГ) и липопротеина а (ЛПа) и повышения концентраций холестерина липопротеинов высокой плотности (ХС-ЛПВП) и аполипопротеина А-1 (Апо А-1): в комбинации со статинами (ингибиторами ГМГ-КоА-редуктазы) в сочетании или без сочетания с другой липид-модифицирующей терапией при невозможности достижения у пациентов целевой концентрации ХС-ЛПНП при приеме максимально переносимой дозы статинов; в монотерапии или как дополнение к другой, не относящейся к статинам липид-модифицирующей терапии, у пациентов с непереносимостью статинов или при наличии противопоказаний к их применению; для уменьшения частоты проведения ЛПНП-афереза у пациентов с гетерозиготной формой семейной гиперхолестеринемии. 2). Препарат Пралуэнт показан взрослым пациентам с установленным атеросклеротическим сердечно-сосудистым заболеванием с целью снижения риска развития сердечно-сосудистых событий посредством снижения ХС-ЛПНП как дополнение к коррекции других факторов риска: в комбинации с максимально переносимыми дозами статинов в сочетании или без сочетания с другой липид-модифицирующей терапией; в монотерапии или как дополнение к другой, не относящейся к статинам, липид-модифицирующей терапии, у пациентов с непереносимостью статинов или при наличии противопоказаний к их применению. СПОСОБ ПРИМЕНЕНИЯ И ДОЗЫ. Начальная доза препарата Пралуэнт составляет 75 мг 1 раз каждые 2 недели. У пациентов, которым требуется большее снижение концентрации ХС-ЛПНП (> 60 %), начальная доза препарата Пралуэнт может составлять 150 мг, которую также вводят 1 раз каждые 2 недели или 300 мг 1 раз каждые 4 недели (ежемесячно). Дозу препарата Пралуэнт следует подбирать индивидуально на основании таких параметров как исходные значения ХС ЛПНП, цели терапии и ответ пациента на лечение. При необходимости дополнительного снижения концентрации ХС-ЛПНП у пациентов, которым препарат Пралуэнт назначался в дозе 75 мг 1 раз каждые 2 недели или 300 мг 1 раз каждые 4 недели, доза может быть скорректирована до максимальной дозы 150 мг 1 раз каждые 2 недели. ПРОТИВОПОКАЗАНИЯ. Повышенная чувствительность к алирокумабу или какому-либо вспомогательному веществу препарата; беременность; период грудного вскармливания; детский возраст до 18 лет. С ОСТОРОЖНОСТЬЮ. Почечная недостаточность тяжелой степени; печеночная недостаточность тяжелой степени. ОСОБЫЕ УКАЗАНИЯ. В клинических исследованиях сообщалось о развитии генерализованных аллергических реакций. При появлении симптомов и признаков серьезных аллергических реакций лечение препаратом Пралуэнт должно быть прекращено и следует начать проведение соответствующей симптоматической терапии. Данные о применении алирокумаба у пациентов старше 75 лет ограничены. Пралуэнт следует применять с осторожностью у пациентов с почечной или печеночной недостаточностью тяжелой степени. ПОБОЧНЫЕ ДЕЙСТВИЯ. Субъективные симптомы и объективные признаки со стороны верхних дыхательных путей, включая боль в ротоглотке, ринорею, чихание; кожный зуд; реакции в месте введения препарата. Для ознакомления с побочными эффектами, возникающими нечасто, редко и очень редко, ознакомьтесь с официальной инструкцией по медицинскому применению лекарственного препарата. ФАРМАКОЛОГИЧЕСКИЕ СВОЙСТВА. Полностью человеческое моноклональное антитело (IgG1). Ингибитор пропротеиновой конвертазы субтилизин-кексин типа 9 (PCSK9). Код АТХ: C10AX14. РЕГИСТРАЦИОННОЕ УДОСТОВЕРЕНИЕ В РФ: ЛП-004078. Дата регистрации: 16.01.2017. SARU.ALI.20.02.0312.

Материал для специалистов здравоохранения. Перед назначением ознакомьтесь с полной инструкцией по применению.

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accepted by patients to whom the pathogenic mechanisms and risks of adverse outcomes were explained multiple times [25].

Conclusion

Stratification of patients with NSTE-ACS into groups of high or low risk of adverse outcomes over the proceeding six years of follow-up can be performed based on the predictive model developed in this study, which includes such signs as LV50%, MFA, and carriership of the A/A genotype of the LTA gene (*rs1041981*); It is expected that if a patient is aware of the existence of unmodifiable risk factors of adverse outcomes in the five years following diagnosis, it will motivate him/her to more carefully adhere to medical advice. Moreover, for patients with severe risk factors at the outpatient follow-up stage patient education can enhance patient adherence to appropriate treatment and lifestyle changes.

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