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THE LIPID-LOWERING TREATMENT AFTER ACUTE CORONARY SYNDROME IN THE REAL CLINICAL PRACTICE: POSSIBLE ROLE OF THE PHARMACOGENETIC INTERACTIONS

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ГИПОЛИПИДЕМИЧЕСКАЯ ТЕРАПИЯ У БОЛЬНЫХ С ОСТРЫМ КОРОНАРНЫМ СИНДРОМОМ В РЕАЛЬНОЙ КЛИНИЧЕСКОЙ ПРАКТИКЕ: ВОЗМОЖНАЯ РОЛЬ ФАРМАКОГЕНЕТИЧЕСКИХ ВЗАИМОДЕЙСТВИЙ

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The study aimed to assess the possibility of individualizing lipid-lowering therapy in patients after acute coronary syndrome (ACS). The study included 1408 patients from the ORACUL II study, who has undergone ACS for the first time (60.5 % of men, average age 65.18±12.81 years), discharged from the hospital. Statins were prescribed to 1315 (93.4 %) patients at

discharge from the hospital. During the first year of observation 778 (55.2 %) patients use statins regularly, 394 (27.9 %) had low adherence to treatment, 236 (16.7 %) refused statins in a month after discharge. Among patients highly adhere to statin treatment, compared with patients without statins or having poor adherence to lipid-lowering therapy, the lower frequency of coronary events (8.1 % and 19.0 % of patients, respectively, p<0.001) was noted and a lower average expected time before coronary outcome (805.9±9.92 vs. 751.3±10.61 days, p=0.002). A significant decrease of statins effect on cardiovascular risk was observed in carriers of A allele of *ANXA2* gene, which initially had a higher level of low-density lipoprotein cholesterol than patients without A allele in the genotype (4.18±2.602 mmol/L vs. 3.12±1.197 mmol/L, p=0.017).

Keywords: acute coronary syndrome, statins, adherence, gene ANXA2

Исследование посвящено оценке возможности персонификации гиполипидемической терапии статинами у больных, перенесших острый коронарный синдром (ОКС). В исследование включены 1408 больных с ОКС из исследования ОРАКУЛ II (60,5 % мужчин, средний возраст 65,18±12,81 лет), выписанных из стационара после первичной госпитализации. При выписке из стационара статины были рекомендованы 1315 (93,4 %) больным. По данным первого года наблюдения 778 (55,2 %) пациентов лечились регулярно, 394 (27,9 %) имели низкую приверженность лечению, 236 (16,7 %) прекратили прием препаратов через месяц после выписки. Среди больных, получавших статины, было достоверно меньше лиц, перенесших коронарные события, по сравнению с больными, не получавшими статины или имевшими плохую приверженность лечению (8,1 и 19,0 % больных соответственно, p<0,001). В анализе Каплана – Мейера среднее ожидаемое время до развития коронарного исхода у лиц на статинотерапии и не принимавших статины составило 805,9±9,92 и 751,3±10,61 дней соответственно (p=0,002). Существенное снижение эффективности статинов отмечено у больных – носителей аллеля А гена *ANXA2*, имевших исходно более высокий уровень холестерина липопротеинов низкой плотности (4,18±2,602 и 3,12±1,197 ммоль/л, p=0,017).

Ключевые слова: острый коронарный синдром, статины, приверженность, ген ANXA2

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ACS – acute coronary syndrome
AH – arterial hypertension
ANXA2 – annexin A2
CAD – coronary artery disease
CV – cardiovascular
GFR – glomerular filtration rate
HDL-C – high-density lipoproteins cholesterol
HF – heart failure
LDL – low-density lipoproteins
LDL-C – low-density lipoproteins cholesterol
MI – myocardial infarction
PCI – percutaneous coronary intervention
PCSK9 – proprotein convertase subtilisin/kexin type 9
PE – pulmonary embolism

Lipid-lowering treatment is an essential component of acute coronary syndrome (ACS) management. In a meta-analysis of 26 RCTs of a statin vs. control or a more vs. less intensive statin regimen, for each 1.0 mmol/L reduction in low-density lipoprotein cholesterol (LDL-C) statin/more statin reduced major cardiovascular (CV) events (myocardial infarction (MI), coronary artery disease (CAD) death, any stroke or coronary revascularization) by approximately 22 %. The proportional effects (per mmol/L reduction in LDL-C) on major vascular events were similar in all subgroups examined, so the absolute risk reduction was proportional to the absolute baseline risk. The relative benefits were half as large in the first year as compared to subsequent years. Statins are recommended to all patients with previous ACS, regardless of the initial (baseline) LDL-C level [1].

New dyslipidemia guidelines from the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) advocate a «lower is a better» and risk-based approach for LDL cholesterol, with a stronger emphasis on lipid-lowering than specified before [2]. According to this document, in secondary prevention for patients after ACS being at very high CV risk, an LDL-C reduction of ≥50 % of baseline and LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended [2]. During the present study period the LDL-C target of <1.8 mmol/L (<70 mg/dL) was approved. In real practice, only about 20 % of patients treated with lipid-lowering drugs reach the target level of LDL-C, which emphasizes the need for some patients to have lipid-lowering treatment that is more active [3].

Treatment problems include low adherence to statins, the use of insufficient doses, and the risks associated with adverse effects of statins in some clinical conditions of the patients.

Recently, a new class of drugs that affect the level of blood lipids has become available – antibodies to the proprotein convertase subtilisin/kexin type 9 (PCSK9) – enzyme, involved in the control of the LDL receptor and lipid metabolism in general [4]. Preliminary data from phase 3 trials suggested a reduction of CV events in line with LDL-C reduction achieved [2]. However, because of the cost of the treatments and limited data on long-term safety, these drugs are likely to be considered cost-effective only in those patients at very high risk of atherosclerotic cardiovascular disease. Moreover, their use may not be possible in some countries with limited healthcare resources, making us look for additional options to optimize lipid-lowering treatment.

Data on genetic variants associated with the pathogenesis of atherosclerosis and its complications could help to personify cardiovascular risks and treatment. One of the recently discovered genetic markers is polymorphism rs17845226 of the type 2 annexin (*ANXA2*) gene. Annexin A2 is an endogenous inhibitor of PCSK9, which

binds the R1 domain of PCSK9, changing the enzyme conformation and making it unable to trigger LDL receptor degradation, and therefore affects the level of LDL-C [5]. These effects allow to considering the *ANXA2* gene as a candidate for analysis of statins pharmacogenetics.

The aim of the study was to evaluate the possibility of personification of the lipid-lowering treatment with statins in patients after acute coronary syndrome based on clinical and genetic data.

Material and Methods. The data from the observational, initiative, multi-center registry ORACLE II (registration number NCT04068909 at ClinicalTrials.gov), designed and organized by the Department of Internal Diseases, Cardiology and Functional Diagnostics of the Central State Medical Academy of the Department of Presidential Affairs were used. The patients with ACS having indications for percutaneous coronary intervention (PCI) during hospitalization were enrolled in the study, regardless of whether the invasive treatment was performed or not. The inclusion criteria have been described in detail in previous publications [6]. From 2014 to 2017, 1655 patients from four centers in Moscow, Astrakhan, Krasnodar, and Kazan were included.

This article presents the analysis of data from 1408 patients discharged from the hospital after the primary hospitalization. 909 (64.5 %) patients had ACS without ST-segment elevation, 499 (35.5 %) – ACS with ST-segment elevation. The examined group consisted of 556 (39.5 %) women and 852 (60.5 %) men, the average age – 65.2±12.81 years. 1235 (87.8 %) patients suffered from arterial hypertension (AH), 1039 (73.8 %) – from coronary artery disease. 438 (31.1 %) patients had a history of myocardial infarction (MI). 845 (60.0 %) had undergone PCI during the index episode of ACS, 183 (13 %) had undergone it previously. 698 (49.6 %) patients suffered from heart failure (HF), 320 (22.7 %) patients – from diabetes mellitus. An aortic stenosis was detected in 76 (5.4 %) patients, GFR<30 ml/min/1.73 m^2 – in 138 (9.8 %) patients. 261 (18.5 %) patients used statins before the index hospitalization.

Adverse outcomes and treatment were identified during the follow-up examination or through phone contact on 25, 90, 180, and 360 days after discharge from the hospital. The primary endpoint was death from all causes. Secondary endpoints included coronary outcomes (death from CAD or repeated ACS), new cases of stroke, complicated atherosclerosis, pulmonary embolism, bleeding, repeated coronary angiography and revascularization, hospitalization due to decompensation of heart failure.

When analyzing the therapy, the drugs are taken, and their dosage was recorded. If the patient noted the regular intake of drugs not at all visits or noted that he took the drug from time to time («on-demand»), adherence to treatment was considered low.

According to the classification of the American College of Cardiology, atorvastatin 40–80 mg and rosuvastatin 20–40 mg per day was considered a highly concentrated dose, atorvastatin 10-20 mg and rosuvastatin 5–10 mg per day were considered a moderately intensive dose, simvastatin 10–20–40 mg per day was considered a low-intensive dose [7]. Also, atorvastatin 5 mg/day was considered a low-intensity dose in this study.

The following reference values of biochemical blood markers were used during hospitalization: creatinine 53–115 μmol/L, total cholesterol 2.0–5.2 mmol/L, LDL-C up to 3.3 mmol/L, HDL-C 0.91–1.56 mmol/L, triglycerides 0.50–1.70 mmol/L. If the lipid profile was examined against the background of lipid-lowering treatment, the approach described by Besseling et al. was used to assess the level of LDL-C [8]. Glomerular filtration rate (GFR) was calculated using the MDRD formula.

To study the ANXA2 rs17845226 gene polymorphism, the ready-made qPCRmix-HS SYBR reaction mixture designed for real-time PCR with the intercalating dye SYBR Green I (Evrogen CJSC, Moscow) was used. Oligonucleotide primers were synthesized by «Evrogen» (Moscow). Genomic DNA was isolated from blood by extraction with a mixture of phenol and chloroform after incubation of blood samples with proteinase K in the presence of 0.1 % sodium dodecyl sulfate. Alleles of the polymorphic marker were identified using allele-specific PCR on a real-time CFX96 C1000 Touch thermocycler (Bio-Rad, USA) in 25 μl of the reaction mixture: qPCRmix-HS SYBR reaction mixture, 2.5 pmol of each primer, 25 ng of genomic DNA.

Amplification conditions for the DNA fragment: preliminary denaturation 95 °C/1 min, 95 °C/30 s, 59 °C/30 s, 72 °C/30 s – 35 cycles. The composition of the primers: direct (A) TGTCTTCAATAGGCCCAAAATCAA, direct (C) TGTCTTCAATAGGCCCAAAATCAC, reverse CCGGAGTGGTCAAAGACTCA.

Results and Discussion. Statins at discharge from the hospital were prescribed to 1315 (93.4 %) patients. In a month after ACS, 91.6 % of patients used lipid-lowering drugs, 4 % of patients did not take statins regularly. After a year of observation, 778 (55.2 %) patients reported taking statins daily, 394 (27.9 %) reported taking statins, not at all visits – low adherence, 236 (16.7 %) never use lipid-lowering drugs after the first visit.

Atorvastatin was the most often prescribed statin, rosuvastatin, and simvastatin were less frequent. At the stage of outpatient observation, two patients indicated fluvastatin and lovastatin among the drugs taken after 90 and 180 days, respectively.

Atorvastatin was prescribed mainly in doses of moderate-intensity – 10–20 mg (Table 1). Upon discharge from the hospital, rosuvastatin was recommended primarily in high doses, but at the outpatient stage, patients were often treated in the moderate-intensive (5–10 mg) regimen.

Table 1

Statins dose during the observation period

The drug name	High dose	Moderate dose	Low dose
At discharge from the hospital			
Atorvastatin (89.2 %)	20.0 %	79.9 %	0.1 %
Rosuvastatin (8.8 %)	60.4 %	39.6 %	
Simvastatin (2.0 %)	–	84.6 %	15.4 %
After a month of observation			
Atorvastatin (85.3.9 %)	16.6 %	83.1 %	0.3 %
Rosuvastatin (12.9 %)	32.2 %	67.8 %	
Simvastatin (1.8 %)	–	82.4 %	17.6 %
After a year of observation			
Atorvastatin (78.2 %)	16.1 %	83 %	0.9 %
Rosuvastatin (18.4 %)	32.3 %	67.7 %	
Simvastatin (3.4 %)	–	87.1 %	19.4 %

Notes. Doses of high intensity were considered atorvastatin 40–80 mg/day, rosuvastatin 20–40 mg/day, moderate intensity – atorvastatin 10–20 mg/day, rosuvastatin 5–10 mg/day, simvastatin 20–40 mg/day, low intensity – simvastatin 10 mg/day, atorvastatin 5 mg/day.

A few patients received simvastatin in doses of mainly moderate intensity.

Among patients receiving statins, there were significantly fewer coronary outcomes (coronary death and recurrent ACS) compared with patients who did not receive statins or had poor adherence to treatment

(Table 2). The frequency of death from all causes in the studied groups did not differ significantly. In the group of high adherence to lipid-lowering treatment, there was a significantly higher frequency of death from other causes – cancer, pneumonia, and complications of diabetes. In the group of low adherence to treatment patients were comparatively older (average age 67.3±13.06 years and 63.4±12.6 years, respectively, p=0.009), there were fewer men (55.3 % and 65.6 %, respectively, p=0.028), more patients with diabetes (26.3 % and 18.9 %, p=0.034), PCI was less likely due to an index event (46.3 % and 66.5 %, respectively, p<0.001).

Table 2

Adverse outcomes in patients with high and low statin adherence

Outcomes	Total (n=1408)	Regular use of statin (n=778)	Low adherence/ no statins (n=630)	p	Regular use of statin (n=461)	Low adherence/ no statins (n=461)	p
	No randomization				After randomization		
All cause death	124 (8.8 %)	64 (8.2 %)	60 (9.5 %)	0.393	47 (10.2 %)	57 (12.3 %)	0.313
Coronary death	64 (4.5 %)	23(2.95 %)	41 (6.5 %)	0.002	**20 (4.33 %)**	**39 (8.45 %)**	**0.0106**
Fatal stroke	5 (0.35 %)	3 (0.38 %)	2 (0.31 %)	0.797	3 (0.65 %)	2 (0.43 %)	0.648
HF death	16 (1.1 %)	10 (1.3 %)	6 (0.95 %)	0.558	8 (1.7 %)	6 (1.3 %)	0.617
PE death	4 (0.28 %)	2 (0.25 %)	2 (0.31 %)	0.833	0 (0 %)	2 (0.43 %)	0.158
Other causes death	35 (2.48 %)	26(3.34 %)	9 (1.4 %)	0.022	16 (3.68 %)	8 (1.73 %)	0.068
Recurrent ACS	119 (8.4 %)	40(5.14 %)	79(12.5 %)	**<0.001**	28(6.1 %)	51 (11.4 %)	**<0.0044**
All coronary outcomes	183 (12.9 %)	63 (8.1 %)	120 (19.0 %)	**<0.001**	48 (10.4 %)	90 (19.5 %)	**<0.001**
Non-fatal stroke	25 (1.8 %)	10 (1.3 %)	15 (2.38 %)	0.130	9 (1.95 %)	12 (2.60 %)	0.503
FH hospitalization	41 (2.91 %)	21 (2.69 %)	20 (3.17 %)	0.598	15 (3.25 %)	16 (3.47 %)	0.853
Complicated atherosclerosis	11 (0.78 %)	8 (1.02 %)	3 (0.47 %)	0.251	6 (1.3 %)	3 (0.65 %)	0.315

Given the significant differences in the essential clinical parameters of patients with high and low adherence to treatment, the above groups were randomized according to these parameters. Two groups of 461 patients comparable by gender, age, diabetes mellitus, and frequency of PCI were obtained. The analysis of the rate of the adverse outcomes in these groups is in Table 2.

In the Kaplan – Meier analysis, the average expected time to the development of coronary outcome was 805.9±9.92 days in patients highly adhered to treatment, in patients not using statins – 751.3±10.61 days (p=0.002) (Fig. 1).

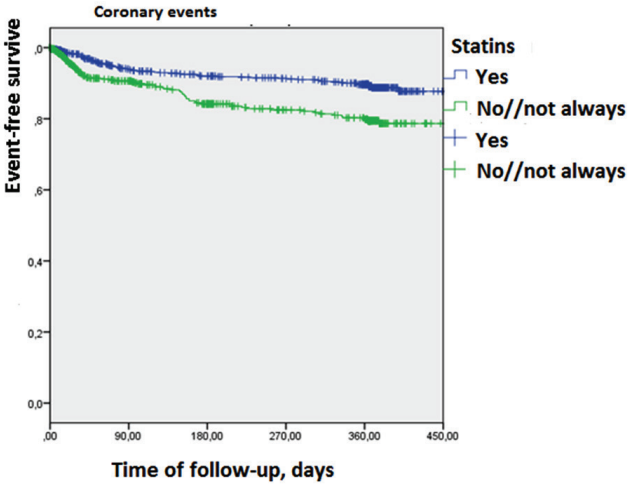

Fig. 1. The risk of adverse coronary outcomes depending on the lipid-lowering treatment in patients after ACS

The preventive effect of statins regarding the frequency of coronary outcomes was studied in different clinical groups. In the group with normal GFR statins were quite effective, while in patients with GFR<30 ml/min/1.73 m^2, lipid-lowering treatment failed to prevent coronary events, as well as in patients with aortic stenosis and carriers of A allele of the *ANXA2* gene (Fig. 2).

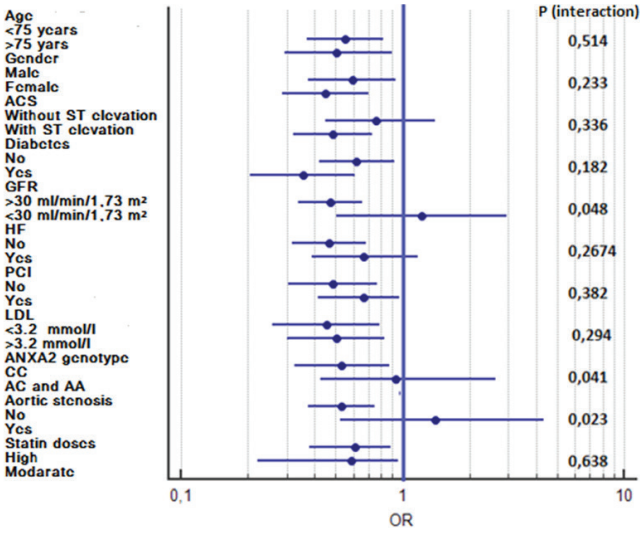

Fig. 2. Reduction of the adverse coronary outcomes risks after ACS on the background of continuous statin therapy in the selected clinical groups

The LDL-C level during the index hospitalization was significantly higher in carriers of the AC and AA genotypes of the *ANXA2* gene (3.66±1.649 mmol/L and 4.18±2.602 mmol/L, respectively), than in carriers of the CC genotype (3.12±1.197 mmol/L, p=0.017), while the level of total cholesterol, triglycerides, and HDL-C did not differ in the compared groups. A dose of statins prescribed to patients with different genotypes of the *ANXA2* gene did not differ significantly. For example, patients with CC genotype received atorvastatin 23.07±10.43 mg per day, carriers of the AC genotype – 21.67±8.04 mg, AA genotype – 18.33±4.08 mg (p=0.311). Similar data were obtained with rosuvastatin and simvastatin.

Among the carriers of A allele of *ANXA2* gene, patients without lipid-lowering treatment tend to dominate. Moreover, these patients have significantly higher levels of LDL-C.

The main lipid-lowering drugs for CAD are statins. One of the main problems is the low adherence to statins [9], resulting in a high residual risk of CAD complications. In the Swedish register of ACS (49.857 participants) 2001-2012, 20.2 % of patients used high doses of statins after ACS, while 42.7 % did not take lipid-lowering treatment after discharge from the hospital. Moreover, the statins, at any dose, reduced the risk of adverse events [10].

In New Zealand, registry statins were recommended at discharge to 95 % of patients with ACS. 92 % of patients continued with statins for three months, 75 % – for a year, 67 % – for three years. Among the main predictors for low adherence to treatment were young age and lack of lipid-lowering treatment before index hospitalization [11]. In the Chinese registers CPACS-1 and CPACS-2 only 72 % of patients continue with statins in 6 months after ACS. Moreover, the relative risk of adverse coronary events was higher by 27 % with low adherence to treatment regardless of the other risk factors [12]. In the Russian registry of ACS – RECORD-3, 84 % of patients used statins at discharge, 66 % – 6 months and 69 % – 12 months after discharge from the hospital [13].

In our study, lipid-lowering treatment was recommended for more than 90 % of patients at discharge, while in a year only 55 % of patients regularly used statins, about 27 % did it occasionally (low adherence), and about 17 % did not use statins at all.

In addition, with the recommended intensive treatment with high doses of statins after ACS, insufficient doses of drugs are often prescribed in real practice, resulting in a small number of those patients who achieved target LDL-C levels and decreased the prophylactic effect of treatment. In the sizeable Chinese registry, which included more than 80,000 patients with acute coronary syndrome, 90 % of patients received moderate dose of statins after ACS and revascularization, while only 36.1 % reached the target LDL-C levels [14]. In the Polish registry of ACS – TERCET (Hyperlipidaemia Therapy in tERtiary Cardiological cEnTer), 91.8 % of patients use statins at discharge from the hospital, among them 37.6 % received intensive lipid-lowering treatment and 32.4 % reached target LDL-C levels [15].

In our study, moderate doses of statins were common, although it should be noted that the continued use of that doses could reduce the differences in risk for adverse coronary outcomes in carriers of different genotypes of the *ANXA2* gene. There were no significant differences in the level of CV risk reduction regarding the treatment with moderate and low doses of statins.

In the present study, lipid-lowering treatment with statins was associated with a reduced risk of specific adverse coronary outcomes, but not all-cause mortality. This may be due to insufficient follow-up. Similar data were obtained in the Swedish ACS register 2001–2012 [16]. A reduction in the risk of recurrent coronary events, but not of all causes mortality, was also confirmed by the Cochrane meta-analysis, which included 14303 patients who initiate treatment by statins in the first 14 days after hospitalization for ACS [17].

Our study revealed several groups of patients with the insufficient effect of lipid-lowering treatment on CV risk. These are patients with GFR<30 ml/min/1.73 m^2. Similar data have already been published previously; for example, the data from the Japanese ACS registry [18]. There are also opposing data on the high efficacy of statins in ACS patients with pre-dialysis CKD [19]. Perhaps, the poor effect of the lipid-lowering treatment on CV risk in our study is associated with a low frequency of statins prescription to patients with reduced renal function.

The insufficient effect of statins on CV risk in patients with aortic stenosis may be due to the predominant death from heart failure in the death structure of this group [20], as well as due to a relatively small number of patients with this pathology.

The data obtained have revealed an association of the minor allele of the *ANXA2* gene with a higher level of LDL-C, which corresponds to the previous data [21]. Carriage of a rare allele has been associated with a decrease in the effectiveness of the statin. This fact can be associated not only with different initial LDL-C levels in patients with different genotypes of the *ANXA2* gene. The initial LDL-C level alone was not significantly related to the effect of lipid-lowering treatment on CV risk. The link between annexin-2 activity and risk of atherosclerotic events can be mediated by the fibrinolysis system (an inhibitor of the fibrinogen activator), inflammation and the level of matrix metalloproteinases expression. In the experimental model the statins inhibited the expression of annexin-2, which may underlie their antiatherosclerotic effect [22].

These data allow considering the *ANXA2* gene as a gene – candidate associated with the lipid-lowering treatment effects.

Conclusions. The data obtained highlight the importance of lipid-lowering treatment after ACS for patients' prognosis. The minor allele of the *ANXA2* gene is associated with higher LDL-C levels, requiring a more intensive approach to lipid-lowering therapy. Genetic typing data could be used to select patients for intense and combined treatment of dyslipidemia, especially in the case of homozygous carriage of a minor allele of the *ANXA2* gene. These data could also be used to create additional motivation for lipid-lowering treatment in patients after ACS.

The limitations of the study: an observational nature without randomization, a relatively short follow-up period. Besides, the study did not suggest the dynamic control of the blood lipids.

Disclosures:
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References

1. Ibanez B., James S., Agewall S., Antunes M. J., Bucciarelli-Ducci C. [et al.] ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur. Heart J.* 2018;39(2):119-177. https://doi.org/10.1093/eurheartj/ehx393
2. Mach F., Baigent C., Catapano A. L., Koskinas K. C., Casula M. [et al.] 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). *Eur. Heart J.* 2019;ehz455. https://doi.org/10.1093/eurheartj/ehz455
3. Kotseva K., Wood D., De Bacquer D., De Backer G., Rydén L. [et al.]; EUROASPIRE Investigators. EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. *Eur. J. Prev. Cardiol.* 2016;23(6):636-48. https://doi.org/10.1177/2047487315569401

4. Nishikido T., Ray K. K. Non-antibody Approaches to Proprotein Convertase Subtilisin Kexin 9 Inhibition: siRNA, Antisense Oligonucleotides, Adnectins, Vaccination, and New Attempts at Small-Molecule Inhibitors Based on New Discoveries. *Front. Cardiovasc. Med.* 2019;5:199. https://doi.org/10.3389/fcvm.2018.00199
5. Seidah N. G., Poirier S., Denis M., Parker R., Miao B. [et al.] Annexin A2 is a natural extrahepatic inhibitor of the PCSK9-induced LDL receptor degradation. *PLoS One*. 2012;7(7):e41865. https://doi.org/10.1371/journal.pone.0041865
6. Averkova A. O., Brazhnik.V. A., Koroleva O. S., Zubova E. A., Hasanov N. R. [et al.] Acute coronary syndrome in young patients with familial hypercholesterolemia based on the results of ORACUL II observation trial. *Medical news of North Caucasus.* 2017;12(1):5-8. https://doi.org/10.14300/mnnc.2017.12001
7. Stone N. J., Robinson J. G., Lichtenstein A. H., Bairey Merz C. N., Blum C. B. [et al.] American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J. Am. Coll. Cardiol.* 2014;63(25PtB):2889-2934. https://doi.org/10.1016/j.jacc.2013.11.002
8. Besseling J., Kindt I., Hof M., Kastelein J. J., Hutten B. A. [et al.] Severe heterozygous familial hypercholesterolemia and risk for cardiovascular disease: a study of a cohort of 14,000 mutation carriers. *Atherosclerosis*. 2014;233(1):219-22. https://doi.org/10.1016/j.atherosclerosis.2013.12.020
9. Shalnova S. A., Belov V. N., Valiakhmetov M. N., Veselovskaya N. G., Voronina N. V. [et al.] Approaches to statin therapy adherence improvement. *Cardiovascular Therapy and Prevention.* 2018;17(2):81-87. http://dx.doi.org/10.15829/1728-8800-2018-2-81-87
10. Rockberg J., Jørgensen L., Taylor B., Sobocki P., Johansson G. Risk of mortality and recurrent cardiovascular events in patients with acute coronary syndromes on high-intensity statin treatment. *Prev. Med. Rep.* 2017;6:203-209. https://doi.org/10.1016/j.pmedr.2017.03.001
11. Kerr A. J., Turaga M., Grey C., Lee M., McLachlan A. [et al.] Initiation and maintenance of statins and aspirin after acute coronary syndromes (ANZACS-QI 11). *J. Prim. Health Care*. 2016;8(3):238-249. https://doi.org/10.1071/HC16013
12. Sun Y., Myint P. K., Patel A., Yang X., Li M. [et al.] Six-month adherence to Statin use and subsequent risk of major adverse cardiovascular events (MACE) in patients discharged with acute coronary syndromes. *Lipids Health Dis.* 2017;16(1):155. https://doi.org/10.1186/s12944-017-0544-0
13. Erlikh A. D. on behalf of the RECORD-3 registry workteam. Twelve months outcomes in patients with acute coronary syndrome, by the National Registry RECORD-3. *Russ. J. Cardiol.* 2018;3(155):23-30. https://doi.org/10.15829/1560-4071-2018-3-23-30
14. Xing Y., Liu J., Hao Y., Liu J., Huo Y. [et al.] CCC-ACS Investigators. Prehospital statin use and low-density lipoprotein cholesterol levels at admission in acute coronary syndrome patients with history of myocardial infarction or revascularization: Findings from the Improving Care for Cardiovascular Disease in China (CCC) project. *Am. Heart J.* 2019;212:120-128. https://doi.org/10.1016/j.ahj.2019.02.019
15. Dyrbus K., Gasior M., Desperak P., Nowak J., Osadnik T. [et al.] Characteristics of lipid profile and effectiveness of management of dyslipidemia in patients with acute coronary syndromes – Data from the TERCET registry with 19,287 patients. *Pharmacol. Res.* 2019;139:460-466. https://doi.org/10.1016/j.phrs.2018.12.002
16. Rockberg J., Jørgensen L., Taylor B., Sobocki P., Johansson G. Risk of mortality and recurrent cardiovascular events in patients with acute coronary syndromes on high intensity statin treatment. *Prev. Med. Rep.* 2017;6:203-209. https://doi.org/10.1016/j.pmedr.2017.03.001
17. Vale N., Nordmann A. J., Schwartz G. G., de Lemos J., Colivicchi F. [et al.] Statins for acute coronary syndrome. *Cochrane Database Syst. Rev.* 2014;(9):CD006870. https://doi.org/ 10.1002/14651858
18. Shibui T., Nakagomi A., Kusama Y., Atarashi H., Mizuno K. Impact of statin therapy on renal function and long-term prognosis in acute coronary syndrome patients with chronic kidney disease. *Int. Heart J.* 2010;51(5):312-318.
19. Natanzon S. S., Matetzky S., Beigel R., Iakobishvili Z., Goldenberg I. [et al.] Acute Coronary Syndrome Israel Survey (ACSIS) investigators. Statin therapy among chronic kidney disease patients presenting with acute coronary syndrome. *Atherosclerosis*. 2019;286:14-19. https://doi.org/10.1016/j.atherosclerosis.2019.05.002
20. Safaryan V. I., Brazhnik V. A., Minushkina L. O., Averkova A. O., Rogozhina A. A. [et al.] The prognostic value of calcified aortic stenosis in patients with acute coronary syndrome. Kremljovskaya Medicina. *Clinichesky Vestnik*. 2018;4: 8-15.
21. Fairoozy R. H., Cooper J., White J., Giambartolomei C., Folkersen L. [et al.] UCLEB consortium. Identifying low density lipoprotein cholesterol associated variants in the Annexin A2 (*ANXA2*) gene. *Atherosclerosis*. 2017;261:60-68. https://doi.org/10.1016/j.atherosclerosis.2017.04.010
22. Hwang J., Hodis H. N., Hsiai T. K., Asatryan L., Sevanian A. Role of annexin II in estrogen-induced macrophage matrix metalloproteinase-9 activity: the modulating effect of statins. *Atherosclerosis*. 2006;189(1):76-82. https://doi.org/10.1016/j.atherosclerosis.2005.11.026

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