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Влияние ингибиторов пропротеиновой конвертазы субтилизин/кексин типа 9 на выживаемость пациентов экстремального сердечно-сосудистого риска в реальной клинической практике

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АННОТАЦИЯ

Обоснование. Среди неинфекционных заболеваний сердечно-сосудистые патологии занимают лидирующее место по количеству смертей в развитых странах, включая Россию. В клинической практике Российской Федерации применяют практически все современные методы и средства лечения пациентов с сердечно-сосудистыми заболеваниями, в том числе инновационные гиполипидемические препараты, такие как ингибиторы пропротеиновой конвертазы субтилизин/кексин типа 9 — алирокумаб и эволокумаб. Однако на данный момент нет полной информации о том, как эти препараты влияют на выживаемость пациентов, находящихся в группе экстремального сердечно-сосудистого риска, как во всем мире, так и в России. В связи с этим изучение данного вопроса является важной и актуальной задачей.
Цель — оценить эффективность и безопасность ингибиторов пропротеиновой конвертазы субтилизин/кексин типа 9, а также влияние этих препаратов на выживаемость у пациентов экстремального сердечно-сосудистого риска.
Материал и методы. В исследование включены 104 пациента экстремального сердечно-сосудистого риска и разделены на две группы: основную (53 человека) и контрольную (51 человек). В контрольной группе получали стандартную гиполипидемическую терапию статином в максимальной переносимой дозе и/или эзетимибом, а в основной группе стандартная гиполипидемическая терапия дополнена препаратами ингибиторов пропротеиновой конвертазы субтилизин/кексин типа 9.
Выполнен анализ результатов лабораторных методов исследования в динамике, а также оценена частота побочных эффектов. Регистрировали все случаи сердечно-сосудистых событий, включая смерть. На основании полученных данных проведен анализ выживаемости и частоты больших сердечно-сосудистых событий.
Результаты. В основной группе через месяц после начала терапии ингибиторами пропротеиновой конвертазы субтилизин/кексин типа 9 уровень липопротеинов низкой плотности у всех пациентов снизился более чем на 50 % от исходного значения. Целевого уровня липопротеинов низкой плотности достигли 42 из 53 наблюдаемых пациентов. Эти результаты оставались стабильными до конца исследования. За период применения ингибиторов пропротеиновой конвертазы субтилизин/кексин типа 9 не зафиксированы случаи гепатотоксичности, миопатий или других местных побочных эффектов. В контрольной группе липидограмма пациентов не претерпела значимых изменений в ходе исследования. Кроме того, наблюдали больше случаев повторных сердечно-сосудистых событий, включая смерть от всех причин, у пациентов контрольной группы.
Заключение. В реальной клинической практике ингибиторы пропротеиновой конвертазы субтилизин/кексин типа 9 продемонстрировали высокую эффективность и безопасность у пациентов экстремального сердечно-сосудистого риска. Благодаря применению этих препаратов удалось достичь целевых показателей уровня липопротеинов низкой плотности и повысить приверженность к лечению, что улучшило прогноз для пациентов данной категории.

Ключевые слова: ингибиторы пропротеиновой конвертазы субтилизин/кексин типа 9; ингибиторы PCSK9; экстремальный сердечно-сосудистый риск; выживаемость.

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The effect of proprotein convertase subtilisin/kexin type 9 inhibitors on the survival of patients at extreme cardiovascular risk in real clinical practice

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ABSTRACT

BACKGROUND: Among non-communicable diseases, cardiovascular diseases occupy a leading position in terms of mortality rate in developed countries, including Russia. In the clinical practice of the Russian Federation, almost all modern methods and means of treating patients with cardiovascular diseases are used. In particular, innovative lipid-lowering drugs are used, such as proprotein convertase inhibitors subtilisin/kexin type 9—alirocumab and evolocumab. However, at the moment there is no complete information on how these drugs affect the survival of patients at extreme cardiovascular risk, both worldwide and in Russia. In this regard, the study of this issue is an important and urgent task.

AIM: To evaluate the efficacy and safety of proprotein convertase inhibitors subtilisin/kexin type 9 in patients at extreme cardiovascular risk. Also, to assess the effect of these drugs on the survival of patients of this category of cardiovascular risk.

MATERIAL AND METHODS: The study involved 104 patients at extreme cardiovascular risk. The patients were divided into two groups: the main group (53 people) and the control group (51 people). In the control group, the patients received standard lipid-lowering therapy: statin at the maximum tolerated dosage and/or ezetimibe, and in the main group, standard lipid-lowering therapy was supplemented with drugs of proprotein convertase inhibitors subtilisin/kexin type 9.

The results of laboratory research methods were analyzed in dynamics, and the frequency of side effects was evaluated. All cases of cardiovascular events, including mortality, were recorded. Based on the data obtained, we analyzed the survival rate and frequency of major cardiovascular events.

RESULTS: In the main group, month after starting therapy with proprotein convertase inhibitors subtilisin/kexin type 9, the level of low-density lipoproteins in all the patients decreased by more than 50% from the initial value. The target level of low-density lipoproteins was reached by 42 out of 53 observed patients. These results remained stable until the end of the study. No cases of hepatotoxicity, myopathy, or other local side effects were reported during the period of use of proprotein convertase inhibitors subtilisin/kexin type 9. In the control group, the lipidogram of patients did not change significantly during the study. In addition, there were more cases of recurrent cardiovascular events, including mortality, in the patients in the control group.

CONCLUSIONS: In real clinical practice, proprotein convertase inhibitors subtilisin/kexin type 9 has demonstrated high efficacy and safety in patients at extreme cardiovascular risk. Thanks to the use of these drugs, it was possible to achieve the target levels of low-density lipoproteins and increase patient's adherence to treatment. As a result, the prognosis for patients with an extreme risk of cardiovascular complications improved.

Keywords: proprotein convertase subtilisin/kexin type 9 inhibitors; PCSK9 inhibitors; extreme cardiovascular risk; survival.

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BACKGROUND

Cardiovascular diseases remain the leading cause of death worldwide and in the Russian Federation [1]. Management of modifiable risk factors, including dyslipidemia, is the main principle of primary and secondary prevention of cardiovascular disease [2, 3]. The literature shows that dyslipidemia is more common in Russia and is characterized by higher levels of atherogenic lipid fractions than in other European countries [4–6]. Therefore, it is important to optimize therapy, including lipid-lowering therapy, for patients with cardiovascular disease [7].

A wide range of lipid-lowering agents are available for the treatment of hyperlipidemia. However, statins are the most commonly used agents in real-world clinical practice [4, 8]. This is due to increasing evidence of statin efficacy in patients at high cardiovascular risk, as well as high availability and affordability of statins through reimbursement programs. It should also be noted that in most patients at high and very high cardiovascular risk, low-density lipoprotein (LDL) target levels can be achieved with the combination of statins at the maximum individually tolerated dose and ezetimibe [9, 10]. Despite optimal lipid-lowering therapy and/or achieving a target LDL of less than 1.4 mmol/L, a significant proportion of patients develop recurrent cardiovascular events within 2 years. This has led to identifying an extreme cardiovascular risk category. The target LDL level for these patients is no more than 1 mmol/L. To achieve this value, targeted therapies known as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, namely alirocumab and evolocumab, are used in addition to combination lipid-lowering therapy. Long-term use of PCSK9 inhibitors has been shown to be one of the most effective lipid-lowering therapy options for patients with atherosclerotic disease. It should be noted that prior to 2022 in Russia, PCSK9 inhibitors were used primarily in patients with heterozygous familial hypercholesterolemia.

The use of PCSK9 inhibitors in this population has been poorly studied in Russia due to new recently identified risk category of extreme cardiovascular risk and strict LDL target levels established.

The aim of the study was to evaluate the efficacy and safety of PCSK9 inhibitors and their impact on survival in patients at high cardiovascular risk.

MATERIALS AND METHODS

The study was conducted at the Departmental Clinic of the S.M. Kirov Military Medical Academy.

Inclusion criteria:

- Two or more cardiovascular events (acute coronary syndrome, ischemic stroke, acute lower limb ischemia, surgery in any vascular system) within 2 years in 2020–2023, despite receiving optimal lipid-lowering therapy (statins and/or ezetimibe) and/or achieving LDL levels below 1.4 mmol/L,
- Age 18 years and older,
- Written consent for study participation.

Non-inclusion criteria: refusal to participate, mental disorders, pregnancy and lactation, cirrhosis, and stage V chronic kidney disease.

Patients were divided into the study group and the control group according to their lipid-lowering therapy (with or without PCSK9 inhibitors).

During the study, all patients underwent the following procedures:

- Lipid profile testing (total cholesterol, high-density lipoprotein [HDL], LDL, non-HDL),
- Blood chemistry (aspartate aminotransferase, alanine aminotransferase, total bilirubin, glucose, creatinine),
- Glycated hemoglobin in patients with diabetes mellitus,
- Body sizes (weight, body mass index),
- Echocardiography,
- Medical history, including smoking status and family history of atherosclerotic cardiovascular disease.

All baseline data were collected through retrospective analysis of medical records and patient interviews at the time of the second event. Follow-up data were collected at the end of the study or at the end of participation in the study (e.g., death, missing, refusal to participate, or discontinuation of treatment). In addition, the study group had their lipid profile monitored one month after starting treatment with PCSK9 inhibitors.

Efficacy of the PCSK9 inhibitors was assessed by achieving target LDL levels, and safety was assessed by changes in markers of liver and skeletal muscle injury and the presence of allergic reactions. A conclusion about the impact of PCSK9 inhibitors on prognosis in patients at extreme cardiovascular risk was based on the group comparison.

SPSS Statistic for Windows 11.0 (version 25.0) and Microsoft Excel 2019 were used for statistical data processing.

Kolmogorov–Smirnov test was used to determine normality of distribution of quantitative parameters. In the case of normal distribution, data are presented as arithmetic mean and standard deviation. Parameter comparisons were made using a paired or unpaired Student's *t*-test.

In the case of non-normal distribution, parameters were presented as median and interquartile range. Non-parametric tests were used to compare parameters over time.

Qualitative parameters are presented as the number of cases and their incidence as a percentage. Pearson's chi-square test or a Fisher's exact test was used for statistical testing of differences between parameters.

The Kaplan–Meier method was used to estimate the survival function, and a log-rank test was used to assess statistical significance of differences between groups.

Differences were considered statistically significant at $p < 0.05$.

RESULTS

The study included a total of 104 patients, divided into the study group (53 patients) and the control group (51 patients).

Both groups were comparable except for the presence of confirmed heterozygous familial hypercholesterolemia, which was diagnosed in 6 patients in the study group at baseline and was not reported in the control group ($p = 0.027$).

Table 1 shows the baseline characteristics of the patients.

At baseline, atorvastatin and rosuvastatin were prescribed at individually tolerated doses (40–80 mg/day and 20–40 mg/day, respectively). All patients were also prescribed ezetimibe at 10 mg/day in addition to statins. Despite the use of this treatment regimen, most patients in the study and control groups did not achieve target LDL levels of less than 1.4 mmol/L, including 51 (98.1%) patients in the study group and 46 (90.2%) patients in the control group.

In the study group, the median time of initiation of PCSK9 inhibitor therapy was 5 months after the last cardiovascular event. Patients received alirocumab at 150 mg every 2 weeks (48 patients) or evolocumab at 140 mg every 2 weeks (4 patients). Patients who initially received evolocumab were switched to alirocumab after 8–13 months. PCSK9 inhibitors were added to the baseline treatment regimen, and in the outpatient setting, cardiologists adjusted the treatment regimen based on LDL monitoring by discontinuing ezetimibe and/or reducing statin doses. Treatment regimen was adjusted only in patients with a significant decrease in LDL levels (below 0.5–0.7 mmol/L) during the first month of alirocumab therapy. Figure 1 provides detailed data on the final lipid-lowering regimens of the enrolled patients.

In the control group, 3 patients also received fenofibrate as part of combination lipid-lowering therapy. The remaining patients continued their baseline lipid-lowering treatment at the maximum tolerated dose throughout the study. To manage co-morbidities, all patients received treatment according to current clinical guidelines.

Data showed a statistically significant decrease in triglyceride levels in all patients.

In the control group, there were no statistically significant changes in total cholesterol, HDL and LDL levels during the follow-up period.

In the PCSK9 inhibitor group, LDL levels decreased by 69.42% ± 9.89% ($p < 0.001$) one month after treatment initiation. At the end of the study, this parameter did not change significantly and was 64.77% ± 8.87%. A statistically significant increase in HDL levels was also reported in this group (12.06% ± 11.72%; $p < 0.001$). A total of 79.3% of patients in the study group achieved the target LDL level of less than 1.0 mmol/L. Of these, nearly half (45.3%) achieved this level with a combination of PCSK9 inhibitors and atorvastatin.

Transaminase levels remained normal in all patients throughout the follow-up period. Uric acid levels, glycemic profile, and left ventricular contractility also did not change significantly. No allergic reactions and no signs of myopathy were observed. Table 2 provides detailed data on changes in laboratory parameters over time. Table 3 shows the lipidogram changes over time in the study group.

More cases of combined recurrent nonfatal cardiovascular events were reported in the control group than in the study group (37.5% vs. 17.7%; log-rank test: $p = 0.013$) at 27.4 ± 7.8 months after the second event. The survival rates in the study and control groups were 96.7% and 64.6%, respectively (log-rank test: $p = 0.037$). All deaths were due to acute cardiovascular events such as decompensation of chronic heart failure and recurrent myocardial infarction.

DISCUSSION

Patients at extreme cardiovascular risk are the most vulnerable category of patients with cardiovascular disease. Cardiologists and general practitioners at all levels of the healthcare system are challenged to manage the risk factors of this patient population. The study shows that with standard lipid-lowering therapy (statin and/or ezetimibe), almost all subjects did not achieve target LDL levels due to factors such as hypertension (100% of patients), type 2 diabetes mellitus (65.4%), hyperuricemia (28.8%), obesity and overweight (83.7%). Low adherence to statin therapy and lack of physician awareness of heterozygous familial hypercholesterolemia should also be considered [11].

By the end of the first month of treatment, addition of PCSK9 inhibitors to lipid-lowering therapy reduced LDL levels to 1 mmol/L or lower in 79.3% of patients. At the end of the study, this parameter remained unchanged, demonstrating the rapid and stable effects of PCSK9 inhibitors. The results presented are consistent with current concepts in lipidology such as *the lower the better*, *the faster the better*, and *the longer the better*.

The failure to achieve the target lipid profile with combination lipid-lowering therapy with PCSK9 inhibitors in the remaining patients in the study group appears to be due to complex co-morbidities, decreased adherence to standard lipid-lowering therapy due to the use of an advanced treatment modality, and non-adherence to non-drug lipid-lowering measures (weight loss, lipid-lowering diet, physical activity, smoking and alcohol cessation).

Clinical practice establishes strategy of de-intensifying lipid-lowering therapy by discontinuing ezetimibe and

Table 1. Basiline patients' characteristics

Таблица 1. Исходная характеристика пациентов

Parameter	The study group	The control group	*p*-value
Male/female, *n* (%)	36/17 (67.9/32.1)	38/13 (74.5/25.5)	0.459
Age, years	63.4 ± 7.3	65.24 ± 9.97	0.288
Left ventricular ejection fraction, %	52.6 ± 4.9	53.5 ± 4.44	0.337
BMI, kg/m^2	29.4 ± 4.5	28.6 ± 4.24	0.333
Smoking, *n* (%)	11 (20.8)	12 (23.5)	0.733
Family history of cardiovascular disease, *n* (%)	10 (18.9)	8 (15.7)	0.668
History of multiple cardiovascular events (≥3), *n* (%)	18 (34.0)	14 (27.5)	0.472
Comorbidity			
Essential hypertension, *n* (%)	53 (100)	51 (100)	1.0
Diabetes mellitus, *n* (%)	39 (73.6)	29 (56.9)	0.073
Atherosclerosis of lower limbs, *n* (%)	9 (17)	7 (13.7)	0.646
Significant brachiocephalic atherosclerosis (stenosis ≥50% of area), *n* (%)	28 (52.8)	34 (66.7)	0.151
Multiple atherosclerotic lesions (≥2 arterial systems), *n* (%)	33 (62.3)	34 (64.7)	0.639
Cancer, *n* (%)	2 (3.8)	5(9.8)	0.265
Chronic obstructive pulmonary disease, *n* (%)	6 (11.3)	4 (7.8)	0.742
Asthma, *n* (%)	3 (5.7)	0 (0.0)	0.243
Obesity and overweight, *n* (%)	45 (84.9)	42 (82.4)	0.582
• Overweight (BMI ≥25 kg/m^2 and <30 kg/m^2), *n* (%)	21 (39.6)	23 (45.1)	
• Grade I obesity (BMI ≥30 kg/m^2 and <35 kg/m^2), *n* (%)	19 (35.8)	14 (27.5)	
• Grade II obesity (BMI ≥35 kg/m^2 and <40 kg/m^2), *n* (%)	3 (5.7)	5 (9.8)	
• Grade III obesity (BMI ≥40 kg/m^2), *n* (%)	2 (3.8)	0 (0.0)	
Chronic heart failure, *n* (%)	49 (92.5)	42 (82.4)	0.26
• Ejection fraction ≥50%, *n* (%)	35 (66)	36 (70.6)	
• Ejection fraction ≥40% and <50%, *n* (%)	13 (24.5)	6 (11.8)	
• Ejection fraction <40%, *n* (%)	1 (1.9)	0 (0.0)	
Iron deficiency anemia, *n* (%)	6 (11.3)	11 (21.6)	0.158
Glomerular filtration rate <60 mL/min/1.73 m^2 (stage 3a, 3b, and 4 chronic kidney disease), *n* (%)	10 (18.9)	12 (24)	0.525
History of symptomatic chronic coronary syndrome, *n* (%)	20 (37.7)	15 (29.4)	0.369
Atrial fibrillation, *n* (%)	9 (17)	8 (15.7)	0.858
Hyperuricemia, *n* (%)	13 (24.5)	17 (33.3)	0.389
Confirmed heterozygous familial hypercholesterolemia, *n* (%)	6 (11.3)	0 (0.0)	0.027
Autoimmune thyroiditis, *n* (%)	4 (7.5)	3 (5.9)	1.0
Statin intolerance, *n* (%)	7 (13.2)	2 (3.9)	0.161

Note: BMI, body mass index.

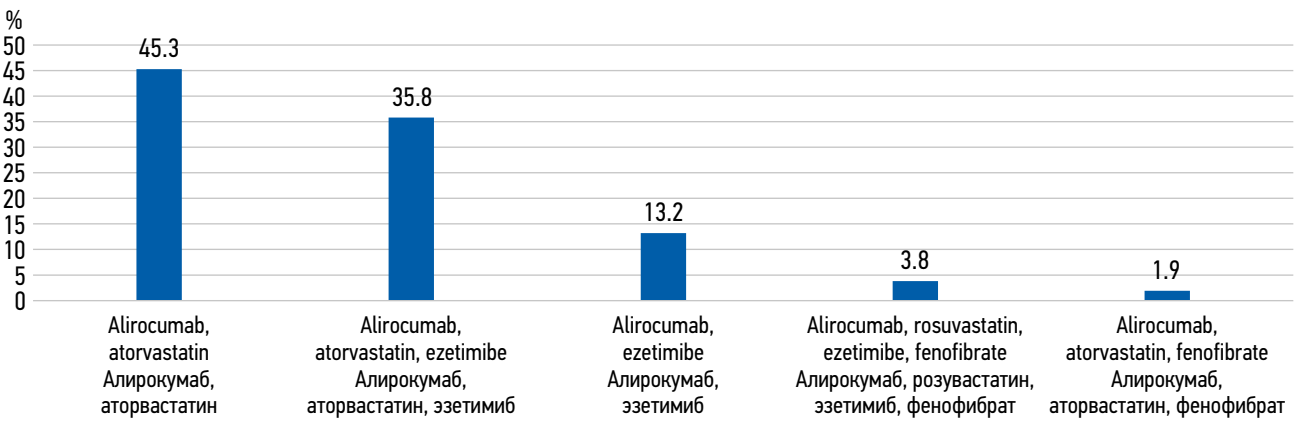

Fig. 1. Characteristics of the final schemes of lipid-lowering therapy in the patients of the main group

Рис. 1. Характеристика окончательных схем гиполипидемической терапии у пациентов основной группы

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Table 2. Dynamics of laboratory data during the study

Таблица 2. Динамика лабораторных данных в ходе исследования

Parameter	The study group				The control group				
	Baseline (1)	At the end of the study (2)	Decrease/increase in the parameter (3)	p_{1-2}	Baseline (4)	At the end of the study (5)	Decrease/increase in the parameter (6)	p_{4-5}	p_{3-6}
Total cholesterol, mmol/L	4.56 ± 0.86	2.9 ± 0.43	−35.57 ± 6.91	<0.001	4.28 ± 0.96	4.15 ± 0.85	1.3 (−15.53–11.45)	0.3	<0.001
Triglycerides, mmol/L	1.98 ± 0.9	1.74 ± 0.73	−10.88 ± 8.2	<0.001	1.41 (1.08–2.0)	1.41 ± 0.57	−4.47 ± 30.52	0.005	0.967
High-density lipoprotein, mmol/L	1.1 (0.98–1.3)	1.25 ± 0.22	12.06 ± 11.72	<0.001	1.17 ± 0.27	1.22 (1.0–1.45)	10.51 ± 21.82	0.098	0.251
Low-density lipoprotein, mmol/L	2.5 ± 0.65	0.85 ± 0.26	−64.77 ± 8.87	<0.001	2.41 ± 0.83	2.29 ± 0.75	−0.45 (−20.23–26.22)	0.255	<0.001
Uric acid, mmol/L	342.66 ± 102.71	326.53 ± 92.15	−0.44 (−8.32–5.34)	0.069	358.46 ± 96.31	356.69 ± 97.37	−2.59 (−6.84–8.76)	0.756	0.738
Glomerular filtration rate, mL/min/1.73 m^2	75.35 ± 18.68	72.94 ± 17.04	−3.56 ± 6.31	0.002	79.86 ± 19.39	74.43 ± 20.97	−4.36 (−12.33–2.1)	<0.001	<0.001
Fasting glucose, mmol/L	6.9 (5.4–8.6)	6.9 (5.55–8.2)	−3.94 ± 14.49	0.032	5.8 (5.1–6.9)	5.7 (5–6.8)	−3.92 (−7.46.1–5.66)	0.139	0.215
Body mass index, kg/m^2	29.43 ± 4.49	29.73 ± 4.86	−0.67 (−2.06–0.65)	0.061	28.6 ± 4.24	28.93 ± 4.2	−0.96 (−2.59–0.37)	0.086	0.691
Glycated hemoglobin, %	6.7 (6.1–7.7)	6.7 (6–7.65)	−1.72 (−4.53–3.83)	0.418	6.7 ± 0.77	6.84 ± 0.91	2.38 ± 10.81	0.371	0.135
Left ventricular ejection fraction, %	52.57 ± 4.89	54 (50–58.5)	2.56 (−4.04–9.98)	0.02	53.47 ± 4.39	55.33 ± 6.95	1.96 (−1.92–6.67)	0.039	0.256
Alanine aminotransferase, IU/L	23 (18.5–31)	23.76 ± 8.99	−3.92 ± 24.46	0.104	20.1 (17–28)	20 (17–30)	2.1 ± 23.06	0.692	0.372
Aspartate aminotransferase, IU/L	24.35 ± 8.73	22.42 ± 7.41	−8.57 (−22.07–0)	0.036	21 (15.6–28.8)	19 (16–27)	0.68 ± 32.54	0.435	0.518
Total bilirubin, mmol/L	10.79 ± 2.97	10.28 ± 2.43	−6.67 (−14.84–9.55)	0.124	9 (8–11)	9 (7–11.1)	−5.8 (−12.94–9.09)	0.142	0.320

Table 3. Dynamics of the lipidogram of the main group during therapy with proprotein convertase inhibitors subtilisin/kexin type 9

Таблица 3. Динамика липидограммы основной группы на фоне терапии ингибиторами пропротеиновой конвертазы субтилизин/кексин типа 9

Parameter	Baseline (1)	After one moth of treatment (2)	At the end of the study (3)	Decrease/increase from baseline after one month of treatment, %	Decrease/increase from baseline at the end of the study, %	p_{1-2}	p_{2-3}
Total cholesterol, mmol/L	4.58 ± 0.86	2.8 ± 0.53	2.9 ± 0.43	−37.2 (от −42.5 до −33.96)	−35.57 ± 6.91	<0.001	0.003
Triglycerides, mmol/L	1.89 ± 0.9	1.66 ± 0.71	1.74 ± 0.73	−3.91 (от −6.65 до −1.38)	−10.88 ± 8.2	<0.001	<0.001
High-density lipoprotein, mmol/L	1.1 (0.98–1.3)	1.29 (1.16–1.43)	1.29 (1.15–1.44)	11.38 ± 12.85	12.06 ± 11.72	<0.001	0.065
Low-density lipoprotein, mmol/L	2.5 ± 0.65	0.78 ± 0.36	0.85 ± 0.26	−69.42 ± 9.89	−64.77 ± 8.87	<0.001	0.021

reducing statin doses when very low LDL levels are achieved in combination therapy with PCSK9 inhibitors. Despite strong evidence for *the lower the better* concept, patients with LDL levels below 0.7 mmol/L have virtually the same outcomes as patients with LDL levels between 0.8 mmol/L and 1.0 mmol/L. In this study, 24 patients were de-intensified from lipid-lowering therapy one month after initiation of PCSK9 inhibitors. After adjustment of the treatment regimen, their LDL levels remained within target levels until the end of follow-up.

Clinical and laboratory tests showed that PCSK9-targeting therapy did not result in liver or kidney function impairment, signs of myopathy, or allergic reactions. The results presented on the safety profile of PCSK9 inhibitors are consistent with data from global and Russian literature [12–17].

Currently, there is no reliable information on short- and long-term survival in extreme cardiovascular risk patients. Limited survival data are available for patients with recurrent myocardial infarction. According to the Registry of Myocardial Infarction of the Vascular Center (RIMIS), 64.1% (25 of 39) of patients with recurrent ST-elevation myocardial infarction died during a median follow-up of 71 months after the index event [18].

In this study, patients at extreme cardiovascular risk were followed for 27.4 ± 7.8 months. Overall survival rate during this time was 80.7%. PCSK9 inhibitors were found to have a positive effect on patient survival compared to the control parameter (log-rank test: $p = 0.037$). This suggests that the use of PCSK9 inhibitors may improve the prognosis of patients at extreme cardiovascular risk.

It should be noted that despite achieving LDL levels below 1 mmol/L, 5 patients experienced recurrent cardiovascular events. Further analysis showed that glycemic profile and body mass index remained unchanged throughout the follow-up period, despite all the measures taken to improve the metabolic syndrome. This may indirectly indicate that these patients did not follow recommendations for lifestyle modification and other non-drug methods to improve their metabolic syndrome.

This study is observational and does not randomize patients. This open design of the study is one of its limitations. The results add to evidence supporting the impact of PCSK9 inhibitors on survival rates in patients at high cardiovascular risk. This patient population is relatively new for clinical practice. In addition, the results help clinicians understand how to manage mortality in high-risk patients in real-world clinical practice.

The ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab) study followed approximately 18,000 patients for 2.8 years to demonstrate differences in survival rates [19, 20]. This study demonstrated the beneficial effect of PCSK9 inhibitors on survival in a cohort of 104 patients over 27 months. The reasons may be as follows:

1. The study included patients at high cardiovascular risk.
2. In the ODYSSEY OUTCOMES study, the mean age of patients was 58.5 years, which is lower than the mean age of patients in the current study (63.4 years in the study group). Absolute benefit increases with age [19].
3. In the ODYSSEY OUTCOMES study, the alirocumab dose was 75 mg every 2 weeks in most patients [20]. In the current study, the maximum doses of PCSK9 inhibitors were used (evolocumab 140 mg or alirocumab 150 mg every 2 weeks).
4. At the end of the follow-up period, the mean LDL level in the current study was 0.85 mmol/L, which is significantly lower than the mean LDL level in the ODYSSEY OUTCOMES study.
5. Patients who know in advance that they will receive expensive agents are more likely to use other types of pharmacological therapy for co-morbidities, which also affects their survival.

CONCLUSION

PCSK9 inhibitors have demonstrated efficacy and safety in patients at extreme cardiovascular risk. The addition of PCSK9 inhibitors to combination therapy for secondary prevention of cardiovascular events in patients at extreme cardiovascular risk not only helps achieve target LDL levels but also improves long-term prognosis.

ADDITIONAL INFORMATION

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Ethics approval. The present study protocol was approved by the local Ethics Committee of the Kirov Military Medical Academy (No. 274 dated 23.01.2023).

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Вклад авторов. Все авторы внесли равный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

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