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# Experience of the use of the PCSK9 inhibitor Alirocumab in patients with extremely high cardiovascular risk

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| *Aim* | To study the efficacy and safety of alirocumab in patients with high and very high cardiovascular risk in the Republic of Karelia and to evaluate their compliance with the alirocumab therapy. |
| *Materials and methods* | Study design: observational, noncomparative. The observation group consisted of 9 patients receiving alirocumab (Praluent®) (mean age, 48.6±4.7 years; 7 men). 7 patients had familial hypercholesterolemia of the type diagnosed by DLCN criteria; five patients had MI. Lipid profile, concentrations of transaminases, creatinine, glucose, and lipoprotein a (LP(a)) were measured at 3, 6, 12, and 18 months. Electrocardiography was performed, and the clinical picture (development of acute coronary syndrome, acute cerebrovascular disease, transient ischemic attacks, myocardial revascularization, and cardiovascular death) was evaluated. Efficacy criteria included the absence of these clinical conditions, the proportion of patients who achieved the LDL CS goal, and the decrease in LP(a). Safety was evaluated by clinical and laboratory data, such as levels of transaminases, total bilirubin, creatinine, and blood glucose. The observation lasted for 6 months to 1.5 years. |
| *Results* | LDL CS goals were achieved in 7 (77.8%) patients receiving alirocumab. The mean level of LP(a) decreased from 0.39 to 0.28 g/l; the degree of decrease ranged from 20 to 33%. No cases of IHD instability (acute coronary syndrome) or new cases of acute cerebrovascular disease and transient ischemic attacks were observed. None of the patients had to stop the alirocumab treatment; adverse effects, including local ones, were not observed. |
| *Conclusion* | LDL CS goals were achieved in 7 (77.8%) patients. The level of LP(a) decreased by 20-33% in patients receiving the PCSK9 inhibitor. In real-life clinical practice, the alirocumab treatment was characterized with high compliance and good tolerability without side effects, including local ones. |

*Keywords* Familial hypercholesterolemia; lipid-lowering therapy; cardiovascular diseases; alirocumab

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Low-density lipoprotein cholesterol (LDL-C) is known as the main predictor of the development of atherosclerotic cardiovascular diseases and catastrophes. The main goal of lipid-lowering therapy is to reduce LDL-C to target levels [1]. Genetic, epidemiological, and clinical trials show a direct relationship between the LDL-C levels and the risk of atherosclerotic cardiovascular diseases [1]. The so-called cumulative cholesterol burden, i.e., the time during which cholesterol level is elevated, is also important.

According to the European Society of Cardiology and the European Atherosclerosis Society's guidelines, the target LDL-C levels for patients at high and very high risk is less than 1.8 and 1.4 mmol/L, respectively. In this connection, achieving the target levels, i.e., reducing LDL-C by 50% from the baseline levels, is also recommended [2].

The use of statins in maximal tolerated doses to achieve target LDL-C levels leads to significant improvements in the prognosis for patients at very high risk, especially those with a history of acute coronary syndrome (ACS) [2-4]. High-intensity statin therapy is also essential for patients with familial hypercholesterolemia (FH). However, target LDL-C levels are rarely achieved in real-world clinical practice [5].

According to the EUROASPIRE IV trial conducted in real clinical settings in 2012-2015, only one-third of patients received high-dose statin therapy following ACS or scheduled coronary revascularization. Only 19.3% of patients achieved the target LDL-C levels of less than 1.8 mmol/L [6]. However, in the recent EUROASPIRE V study, a two-fold increase in the number of patients receiving high-dose statin therapy led to a modest 7% increase of in the achievement

of the target LDL-C levels of less than 1.8 mmol/L, amounting to only 32% [7].

One of the significant factors explaining this situation is the failure of physicians to accomplish the target levels of lipid parameters, as well as low patient cooperation with lipid-lowering therapies in some cases [8]. In any case, severe hypercholesterolemia (including genetically determined forms) is quite common, especially among patients with a history of ACS at a young age. The prevalence of severe hypercholesterolemia (LDL-C ≥5.0 mmol/L) reaches 10% in Russian patients hospitalized due to ACS [9]. At the same time, only 2.3% of patients with FH who received high-intensity statin therapy achieved the target LDL-C levels of less than 1.8 mmol/L [10].

Another significant problem arises in the form of statin intolerance. The rate of adverse reactions, most frequently due to myalgia, can reach 17% or more; this is often accompanied by a reduction of doses or withdrawal of the drug [11-13]. Statin intolerance, identified in 1.65% of patients, was associated with an increased rate of coronary events (recurrent myocardial infarction (MI) or coronary revascularization) by 43% and recurrent MI by 36% compared to patients showing high compliance with statin therapy [14].

The search for new ways to reduce the LDL-C levels, especially in patients with high and very high cardiovascular risk, patients with FH and statin intolerance, determined the development of a new group of specific drugs – monoclonal antibodies to proprotein convertase subtilisin / kexin type 9 (PCSK9) enzyme regulating the expression of LDL-C receptors. Two drugs of this class (alirocumab and evalocumab) have been registered in Russia, Europe, and the United States.

Alirocumab (Praluent®) is a fully human monoclonal antibody (IgG1) demonstrating high affinity and specificity for PCSK9. By inhibiting the binding of circulating PCSK9 to LDL-C receptors on the surface of hepatocytes, the use of alirocumab leads to an increase in the number of these receptors and active removal of LDL-C from the systemic circulation. Since LDL-C receptors also bind very-low-density triglyceride-rich (TG) remnant lipoproteins and intermediate-density lipoproteins, alirocumab can reduce levels of apolipoprotein B, non-high-density lipoprotein cholesterol, and TG. Despite the low affinity of LDL-C receptors to this lipoprotein, alirocumab can also be used to reduce the level of lipoprotein(a) [Lp(a)]. However, the exact mechanism of this effect is not yet known [15].

Registered in the Russian Federation in 2017, alirocumab is marketed as a solution for subcutaneous injection with a dosage of 75 or 150 mg/mL. The efficacy and safety of alirocumab were established in major international clinical research program ODYSSEY [8]. The objective of the present study was to analyze the efficacy and safety of alirocumab in patients at high and very high cardiovascular risk in the Republic of Karelia, as well as assessing patient compliance with alirocumab therapy.

## Material and Methods

The study design was observational and non-comparative. The follow-up group consisted of nine patients treated with alirocumab (Praluent®); the mean age was 48.6±4.7 years; seven patients were male. Of these, seven patients had FH, while five patients had a history of MI. Before starting alirocumab therapy, eight patients received intensive statin therapy equivalent to rosuvastatin 20-40 mg/day, while one patient received only ezetimibe due to statin intolerance (rhabdomyolysis). Safety was evaluated based on clinical and laboratory data such as the levels of transaminase, total bilirubin, creatinine, and glucose.

The lipid profile, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, glucose, and Lp (a) levels were evaluated in all patients at 3, 6, 12, and 18 months. Electrocardiogram (ECG) was performed and the clinical picture was evaluated (acute coronary syndrome, acute cerebrovascular accident, transient ischemic attacks, myocardial revascularization, cardiovascular death). Efficacy criteria consisted in the absence of the above-mentioned clinical manifestations, the percentage of patients who achieved target LDL-C levels, and a decreased level of Lp (a). The follow-up lasted for 6 to 18 months.

In patients at very high risk, the lipid spectrum target levels were LDL-C less than 1.4 mmol/L, while in patients at high risk the target levels were less than 1.8 mmol/L [2]. Our study complied with the Declaration of Helsinki and was approved by the local ethics committee. All patients signed an informed consent form prior to being included in the study.

Statistical processing of the findings was performed using the STATISTICA v.10.0 software suite (StatSoft Inc., USA). The data are expressed as M ± SD. The Student's t-test was used to estimate the intergroup differences.

## Limitations

The present study represents the first results of a registry of patients receiving PCSK9 inhibitors


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**Table 1.** Changes in laboratory findings during alirocumab therapy

| Follow-up period | TC, mmol/L | LDL-C, mmol/L | HDL-C, mmol/L | TG, mmol/L | Lp (a), g/L | Creatinine, μmol/L | ALT, MU/L | AST, MU/L | Glucose, mmol/L |
|---|---|---|---|---|---|---|---|---|---|
| Baseline | 7.4 ± 1.3 | 4.8 ± 0.9 | 1.2 ± 0.4 | 1.7 ± 0.8 | 0.39 ± 0.04 | 76.8 ± 3.6 | 29 ± 1.2 | 31 ± 2.4 | 4.7 ± 0.8 |
| 3 months | 4.37 ± 1.46 | 2.6 ± 0.87 | 1.21 ± 0.35 | 1.6 ± 0.4 | 0.28 ± 0.03 | 74.5 ± 3.7 | 27 ± 1.1 | 30.5 ± 2.7 | 4.8 ± 0.7 |
| 6 months | 4.34 ± 1.2 | 2.6 ± 0.78 | 1.3 ± 0.33 | 1.55 ± 0.45 | 0.27 ± 0.03 | 73.6 ± 4.8 | 28 ± 1.3 | 30.4 ± 3.6 | 4.9 ± 0.6 |
| 12 months | 4.4 ± 1.1 | 2.8 ± 0.9 | 1.3 ± 0.42 | 1.54 ± 0.5 | 0.27 ± 0.02 | 74.1 ± 3.7 | 26.9 ± 1.2 | 29.7 ± 3.4 | 5.1 ± 0.7 |
| 18 months | 4.45 ± 1.3 | 2.81 ± 1.1 | 1.32 ± 0.44 | 1.55 ± 0.3 | 0.27 ± 0.04 | 72.8 ± 3.9 | 27.4 ± 1.8 | 31.5 ± 2.7 | 5.0 ± 0.4 |

TC, total cholesterol, LDL-C, low-density lipoprotein cholesterol, HDL-C, high-density lipoprotein cholesterol, Lp(a), lipoprotein (a).

(PCSK9i). At the time of preparing this article, 18 patients were included on the register in the Republic of Karelia. Long-term results were evaluated in patients receiving therapy for 6 to 18 months.

## Results

Baseline laboratory findings and their changes during alirocumab therapy are presented in Table 1. None of the patients stopped alirocumab therapy during the follow-up period. There were no side effects, including those of topical nature. Target LDL-C levels were achieved in 7 (77.8%) patients when alirocumab was included in the treatment.

Two (28.6%) patients with FH failed to achieve the target LDL-C levels corresponding to the risk category with a dose of 75 mg twice a month. This was due to objective difficulties in lipid-lowering therapy due to high baseline lipid profile levels (n=1) and statin intolerance (n=1). At the same time, these patients exhibited a 50% decrease in LDL-C relative to the baseline levels. The decision was taken to increase the dose of alirocumab to 150 mg twice a month.

The Lp (a) levels were evaluated in 8 (88.7%) patients. Seven patients had elevated Lp (a) levels, with a normal Lp (a) concentration of less than 0.3 g/L. The decrease in Lp (a) levels during PCSK9i therapy, which reached 20-33%, from 0.39 to 0.28 g/L, was observed in all patients by month 3 from the start of the therapy, reaching a minimum by month 6.

Neither destabilization of CHD (new events of MI and unstable angina) nor new cases of acute cerebrovascular accident or transient ischemic attacks were reported during the PCSK9i therapy. Given the limited experience of using PCSK9i in Russia, we believe it is appropriate to review case studies of the use of PCSK9i in various clinical situations.

### *Case study #1*

Patient P., 36 years old. Diagnosis: Familial hypercholesterolemia (DLCN definite). CAD, functional class (FC) 3 angina pectoris. Postinfarction cardiosclerosis (MI dated July 2017). Obliterating coronary atherosclerosis. Percutaneous coronary intervention and stenting of the right coronary artery dated 11/21/2017. Complications: Chronic heart failure, stage 2A, FC 2. Comorbidities: hypertensive heart disease, stage 3, risk class 4; obliterating brachiocephalic atherosclerosis.

The patient was referred for consultation to the Department of Intermediate Level Therapy, Phthisiology, Infectious Diseases, and Epidemiology of the Petrozavodsk State University due to MI at a young age (36 years).

The patient reported a past history of smoking. No diabetes was identified. He has a family history of cardiovascular pathology: his father had MI at 40 years old, recurrent MI at 60 years old (fatal). History since 2014: a transient increase in blood pressure (BP) to 140/100 mm Hg. The patient did not regularly measure BP or take hypotensives until 2017. Later, continuous use of perindopril 5 mg/day was commenced.

The onset of CAD on 21 July 2017, anterior-lateral Q-MI. Coronary angiography showed acute thrombotic occlusion of the anterior interventricular artery. Subocclusion of the circumflex artery, stenosis of the right coronary artery up to 70%, stenosis of obtuse marginal artery up to 60%. Thromboaspiration was performed. Next, stenting of the anterior interventricular artery with two holometallic stents and proximal balloon angioplasty were carried out. The distal part was not enhanced when performing control angiography. Attempts to catheterize the circumflex artery were unsuccessful. Cardiogenic shock developed during the procedure

The disease was also complicated by Dressler's syndrome (pericarditis, pleuritis, pneumonitis). The left ventricular ejection fraction at control echocardiographic monitoring was 28-37%. Papillary muscle dysfunction was detected. Mitral regurgitation grade 3 was recorded. PCI with the right coronary artery stenting was performed on 21 November 2017. Later, beta-blockers, antiplatelet agents, and high-dose statin therapy were used. However, clinical signs of angina pectoris remained. Triplex scanning of brachiocephalic arteries dated 2017: right carotid bifurcation stenosis was 40-45%, while left carotid bifurcation stenosis was 50-55%. Ostial stenosis of both internal carotid arteries was 40-45%. The patient was discharged on atorvastatin 80 mg/day (control lipid profile findings: TC 5.3 mmol/L, LDL-C 3.35 mmol/L, TG 1.2 mmol/L).

The patient reported increased TC to 9 mmol/L, LDL-C to 5 mmol/L. The examination revealed neither tendon xanthomata nor arcus lipoides corneae. Medical records (dated 3 October 2016) were subsequently provided: TC 12.1 mmol/L, LDL-C 6.48 mmol/L, HDL-C 1.5 mmol/L, TG 1.92. During the use of atorvastatin 80 mg/day: TC 5.3 mmol/L, LDL-C 3.35 mmol/L, TG 1.2 mmol/L. The patient had an elevated baseline Lp (a) level of 1.3 g/L, which is also a predisposing factor of early vascular catastrophes.

Thus, a certain FH was clinically diagnosed retrospectively and confirmed by genetic analysis (LDL-C receptor mutation).

Since, despite intensive lipid-lowering therapy (high dose statins), clinically diagnosed FH, obliterating multiple atherosclerosis, family history and MI at an early age, the target levels of lipid profile were not achieved, increased levels of Lp (a) (1.3 g/L at baseline) and therapy with PCSK9i alirocumab (Praluent®) were started at the dose of 75 mg/mL (every other week).

The results of biochemical parameters following 3 months of combined therapy with atorvastatin 80 mg/day and alirocumab 75 mg twice a month were as follows: TC 3.12 mmol/L, LDL-C 1.6 mmol/L, HDL-C 0.98 mmol/L, TG 1.13 mmol/L, total bilirubin 15.4 mmol/L, direct bilirubin 3.8 mmol/L, ALT 21 U/L, AST 19 U/L, glucose 5.9 mmol/L (6.1 mmol/L), creatine phosphokinase 151 U/L. The level of Lp (a) decreased to 0.87 g/L (by 33% from the baseline level).

This was a peculiar case due to FH having been established retrospectively in a patient with a history of MI at a young age. According to Nanchen et al., the incidence of ACS at a young age in patients with FH is several times higher [9]. Increased Lp (a) levels additionally exacerbate the prognosis for cardiovascular diseases.

Considering MI at a young age and elevated Lp (a), PCSK9 inhibitors were recommended to the patient as the second step immediately after statins. In order to achieve the target LDL-C levels, it was recommended to increase the dose of alirocumab to 150 mg/day, which can provide an additional reduction in LDL-C by a mean of 14% from the baseline level (i.e., approximately 1.38 mmol/L can be achieved) [16].

### *Case study #2*

Patient B., 42 years old. The patient has not smoked since 2010. The patient has a family history of cardiovascular pathology: his father had MI at 63 years old. No diabetes mellitus or hypertension were reported by the patient.

The first onset of CAD was recorded in 2009 in the form of acute anterior non-Q-MI. The patient was treated in a central district hospital. Due to high-FC angina in 2020, a holometallic stent was implanted in the anterior descending artery (stenosis up to 90%) following coronary angiography. The patient was administered rosuvastatin 40 mg. Target LDL-C levels were not achieved.

Recurrent inferolateral Q-MI occurred in December 2015. The patient received thrombolytic therapy with alteplase. A holometallic stent was implanted in the posterior interventricular artery (stenosis up to 90%) on December 25, 2015. He was treated with acetylsalicylic acid, bisoprolol, ivabradine, angiotensin-converting enzyme inhibitor. Considering dyslipidemia (increased baseline TC 6.5 mmol/L, LDL-C 3.9–4.1 mmol/L), rosuvastatin 20 mg, ezetimibe 10 mg were prescribed. During the treatment: TC 3.85 mmol/L, LDL-C 2.63 mmol/L, TG 1.2 mmol/L, HDL-C 0.8 mmol/L. The level of Lp (a) 0.02 g/L was within reference values.

Deterioration in August 2018: recurrence of angina pectoris, anginal pain with little physical activity (100 m walking). He had no prolonged pain attacks, according to him. Recurrent MI was diagnosed by a positive troponin test. ECG findings: sinus rhythm; HR 58 bpm; focal of inferior and anteroapical lesions.

Coronary angiography: balanced coronary blood flow, subocclusive restenosis in the middle stent of the anterior descending artery, ostial stenosis up to 20% of the intermediate artery, minimal restenosis of the proximal stent, ostial stenosis up to 50%. Minimal restenosis of the distal stent. Stenting of the anterior descending artery and balloon angioplasty with drug-eluting stent (Biomatrix 3×18 mm) were performed. The patient's condition was stable with no anginal pains following the procedure. Shortness of breath was reported when climbing four floors. There were no


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cardiac arrhythmias or MI complications. BP profile: 100-120/70-80 mmHg.

Since the patient did not achieve the target LDL-C levels, twice-monthly alirocumab 75 mg was added to the therapy. Control of biochemical parameters after two months of hypolipidemic therapy was: TC 2.02 mmol/L, HDL-C 0.99 mmol/L, LDL-C 0.62 mmol/L, TG 1.1 mmol/L, creatinine 78.6 mmol/L, ALT 25 U/L, AST 24 U/L, glucose 4.7 mmol/L.

Thus, the three-component therapy (rosuvastatin 20 mg, ezetimibe 10 mg, alirocumab 75 mg twice a month) allowed the target LDL-C levels to be achieved.

According to current data, achieving the LDL-C level of 0.62 mmol/L is safe and does not require a correction of the dosage of the lipid-lowering agents [17, 18]. In the real-world clinical practice, intensive lipid-lowering therapy allowed low lipid profile levels to be achieved in patients with FH and those having a history of ACS. The relatively low current target LDL-C levels for this category of patients turned out to be safe.

According to the PLANET registry, only 15-18% of patients with FH in the Czech Republic and Slovakia achieve target LDL-C levels during high-dose statin therapy (atorvastatin, rosuvastatin). The number of patients with FH who achieve the target LDL-C levels increases 3-fold when using PCSK9 inhibitors [19].

The problem of residual cardiovascular risk is also being widely discussed. Even patients undergoing randomized clinical trials with high-dose statins along with a combination of statin and ezetimibe and other optimal therapy affecting the prognosis remain at a high residual risk of cardiovascular events following ACS. In the PROVE IT trial, a 2-year cumulative prevalence of major cardiovascular events was 22.4% in patients with a history of ACS receiving high-intensity atorvastatin therapy at a dose of 80 mg [20].

In 7 of 9 cases in our study, alirocumab was used at a dose of 75 mg. An increase to 150 mg was required in 2 patients with MI (a patient with FH and a patient with statin-associated rhabdomyolysis). It is important to emphasize that PCSK9 inhibitors have an additional important property of reducing Lp (a) levels. The observed decrease in Lp (a) during PCSK9i therapy of about 30% is consistent with the medical literature.

It has been shown that, along with a potent hypolipidemic effect and safety, alirocumab is also effective in reducing the risk of cardiovascular diseases. Thus, the ODYSSEY OUTCOMES trial showed that, in patients with a recent history of ACS who did not achieve the target LDL-C levels during high-intensity statin therapy, alirocumab therapy reduced the risk of major cardiovascular events, such as fatal CAD, non-fatal MI, ischemic stroke or unstable angina requiring hospitalization, as well as being associated with reduced total mortality. The greatest benefit of alirocumab was demonstrated in patients with baseline LDL-C levels more than 2.6 mmol/L and those with atherosclerotic lesions of three vascular systems. These subgroups showed a 24 and 36% reduction in the relative risk of major cardiovascular events, respectively. The relative risk of all-cause death, which decreased by 29% in the subgroup with baseline LDL-C >2.6 mmol/L, was reduced by 77% in patients when three vascular systems were involved [21].

The beneficial effect of alirocumab on total mortality was mediated by the reduced rate of non-fatal cardiovascular events, as well as decreased cardiovascular mortality. Thus, patients with fewer cardiovascular events are also at a lower risk of dying of non-cardiovascular causes [22].

According to the results of recent additional analyses of trials with alirocumab and evalocumab, the most clinically promising method may consist in the use of these drugs in patients with additional risk factors, such as multiple lesions, familial hypercholesterolemia, diabetes mellitus, etc., as well as clinically significant atherosclerosis. [23]. Thus, it is essential to make sure that these medications are available to patients to prevent recurrences effectively. It appears that the timely initiation of PCSK9i therapy after the first cardiovascular event – and, in some cases, before the development of clinically significant atherosclerosis – will help to prevent the occurrence of vascular catastrophes, especially in young patients with hereditary forms of hypercholesterolemia.

## Summary

1. Target LDL-C levels in alirocumab therapy were achieved by 77.8% of patients (all patients without FH and 71.4% of patients with FH). Two patients with FH did not achieve the target levels of LDL-C when using alirocumab 75 mg twice a month due to objective hypolipidemic therapy difficulties: high baseline lipid profile levels (n = 1), statin intolerance (n = 1). It was recommended that the alirocumab dose be increased to 150 mg twice a month.
2. During the administration of alirocumab, Lp (a) levels decreased by 0-30%.
3. In real-world clinical settings, alirocumab therapy is characterized by high compliance and good tolerability without adverse reactions, including those of a topical nature.

*No conflict of interest is reported.*

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