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Current approaches to the treatment of patients with dyslipidemia in the real practice in the outpatient stage

Aim	To evaluate the frequency and structure of lipid-lowering therapy and of achieving the goal of low-density lipoprotein cholesterol (LDL–C) in patients with very high cardiovascular risk (CVR) who were monitored at the outpatient stage.
Material and Methods	A retrospective snapshot analysis was performed by continuous sampling method for 136 medical records of outpatient patients (71 men, 65 women) aged 42 to 91 years [median, 68 years; 25th and 75th percentiles (59; 78)].
Results	134 (98,53%) patients took statins; 8 (5.88%) patients took a combination of statin and ezetimibe; 2 (1.47%) patients took proprotein convertase subtilisin/kexin type 9 enzyme inhibitors (PCSK9): 2 (1.47%) patients took evolocumab and 1 (0.74%) of 2 PCSK9-treated patients took a combination of PCSK9 inhibitor and statin. Atorvastatin at a dose of 20 (20; 40) mg as recommended at the hospital was the most frequently prescribed statin. 5 (3.68%) patients achieved the goal LDL–C of ≤1.4 mmol/l.
Conclusion	Statins prevail in the structure of lipid-lowering therapy in patients with very high CVR. The frequency of combination therapy (statin/ezetimibe, 5.88%; PCSK9 inhibitor/statin, 0.74%) and PCSK9 inhibitors was noted to be low. Only 3.68% of patients achieved the goal LDL–C during the lipid-lowering treatment.

Keywords	Dyslipidemia; statins; lipid-lowering therapy
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Introduction

From 2000 to 2019, the incidence of cardiovascular diseases (CVDs) doubled in the Russian Federation, which is seen to be one of the key factors contributing to unfavorable demographics [1]. The World Health Organization claims that the implementation of various preventative measures may prevent up to 50% of all cardiovascular deaths [2]. The timely correction of lipid metabolism disorders is one of the priority prevention strategies for reducing the incidence of CVDs and mortality [3].

The majority of patients with high and very high cardiovascular risk, including those with atherosclerosis-related CVDs and a history of myocardial infarction (MI), do not meet the Russian Atherosclerosis Society's recommended low-density lipoprotein (LDL) cholesterol targets in real-world clinical practice [3]. Only 10 to 30 percent of patients with very high cardiovascular risk who require dyslipidemia correction achieve LDL cholesterol levels less than 1.8 mmol/L [4, 5], despite the availability of a wide range of therapeutic options, such as statins, ezetimibe, and highly effective lipid-lowering agents (alirocumab/evolocumab/inclisiran) [6].

Objective

Our study's objective was to evaluate the frequency and composition of lipid-lowering therapy and the achievement of the LDL cholesterol targets in patients with very high cardiovascular risk during outpatient management.

Material and methods

A retrospective, cross-sectional analysis of 136 outpatient records (71 male patients, 65 female patients, from 42 and 91 years old) was conducted by continuous

sampling [median 68 (59; 78) years]. The inclusion criteria for the patient examination results were as follows:

Very high cardiovascular risk (SCORE ≥10%): documented coronary artery disease (CAD)[1]; diabetes mellitus + organ damage[2]; severe chronic kidney disease (CKD)[3].

Outpatient management

Blinded patient data were entered into a specially designed case report form and an electronic database. The information was analyzed within the framework of the initiative research «Study of the Structure of Morbidity, Demographic Characteristics and Risk Factors of the Main Chronic Non-Communicable Diseases (NCDs) in Multimorbid Patients» approved by the local ethical committee of the N. I. Pirogov Russian National Research Medical University. Patient's informed consent was not required for this study.

Statistical data processing was conducted in SPSS Statistics v. 20.0 (IBM, USA). Qualitative variables are presented as the absolute numbers and percentages, and continuous quantitative variables are expressed as the medians (Me) and the 25th and 75th percentiles.

Results

The study group included 1 (0.74%) male patient of 42 to 44 years, 34 (25%) patients of 45 to 59 years (24 (70.6%) male and 10 (29.4%) female), 57 (41.91%) patients of 60 to 74 years (31 (54.39%) male and 26 (45.61%) female), and 43 (31.62%) patients of 75 to 89 years (15 (34.88%) male and 28 (65.12%) female). There was also 1 (0.74%) female patient of 90 years old.

In this cohort, 12 (8.82%) patients were smokers. Arterial hypertension (AH) was documented in 133 (97.79%) patients, 91 (66.91%) patients had a history of MI, 88 (64.71%) patients – a history of stroke, 45 (33.09%) patients had CKD, 28 (20.59%) – type 2 diabetes mellitus, 24 (17.65%) – obesity, 72 (52.94%) – carotid atherosclerosis, and 52 (38.24%) patients had peripheral artery atherosclerosis. Median time from cardiovascular event (stroke, myocardial infarction) was 3 (2; 3) months.

Statins were administered to 134 (98.53%) patients, the combination of a statin and ezetimibe – 8 (5.88%) patients, PCSK9 inhibitors – 2 (1.47%) patients: evolocumab was administered to 2 (1.47%) patients, the combination of a PCSK9 inhibitor and a statin – 1 (0.74%) patient. Atorvastatin in the recommended dose 20 (20; 40) mg was the most commonly administered statin in hospital. The target levels of LDL cholesterol of ≤ 1.4 mmol/L were achieved in 5 (3.68%) patients. Total cholesterol (TLC) was 5.34 (4.24; 6.49) mmol/L, LDL cholesterol – 2.13 (1.61; 2.84) mmol/L, and high-density lipoprotein (HDL) cholesterol – 1.11 (0.99; 1.47) mmol/L. Before a cardiovascular event, LDL cholesterol was 3.30 (2.50; 4.32) mmol/L, HDL – 1.25 (1.03; 1.55) mmol/L.

Discussion

Thus, statins predominate in the structure of lipid-lowering therapy for patients with very high cardiovascular risk, according to real-world outpatient data. It was found that the combination lipid-lowering treatment and monoclonal antibodies, such as PCSK9 inhibitors, were rarely used. Only 3.68% of patients who receive this type of treatment achieved the target levels of LDL cholesterol.

The findings show that it is necessary to raise physicians' awareness of the significance of escalating lipid-lowering therapy after 4–6 weeks of the outpatient management if the target LDL cholesterol levels are not achieved with the maximum tolerated doses of statins [6].

In some cases, according to Ray et al., it is necessary to prescribe early combination lipid-lowering therapy (statin and ezetimibe) to achieve the target levels of LDL cholesterol more quickly, and if ineffective, add PCSK9 targeted therapy (alirocumab, evolocumab, inclisiran) [7].

Our findings are consistent with those of many researchers. In particular, the study of the effectiveness of lipid-lowering therapy during the outpatient management of 1,671 hospitalized CAD patients of 67.0 (59.0; 74.0) years old, point to the use of statin monotherapy in the majority of patients (99.2%) and insufficient use of combination therapy (statin/ezetimibe in 0.8%). Moderate-dose atorvastatin was the most commonly prescribed statin (74.6% of all orders). The target levels of LDL cholesterol were achieved in 37.5% of patients [8].

Similar results are presented in the Familial Hypercholesterolemia Register (n=1208, 54±13 years), according to which 27% of patients received lipid-lowering therapy, among them 3% received a statin/ezetimibe combination, target levels of the lipid profile were achieved in 6% of patients with very high cardiovascular risk [9].

It is well-known that the percentage of the LDL cholesterol levels decreases during the combination lipid-lowering therapy, as ezetemibe additionally decrease LDL cholesterol by 15–20%, and with the three-component lipid-lowering therapy (statin, ezetimibe,

[1] Documented cardiovascular disease (CVD)—a history of myocardial infarction, acute coronary syndrome, coronary revascularization, etc., arterial revascularization, stroke, transient ischemic attack, aortic aneurysm, peripheral vascular disease.

[2] Organ damage—proteinuria and/or + significant risk factor: smoking/hypercholesterolemia/arterial hypertension.

[3] Chronic kidney disease—glomerular filtration rate (GFR) <30 ml/min/1.73 m^2.

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ЗНАЮ. ВИЖУ. СНИЖАЮ?

Снижение уровня ХС ЛНП на 1 ммоль/л [illegible] **риск сердечно-сосудистых катастроф** [illegible]

PCSK9 inhibitor) by 85%, which once again emphasizes the necessity of correct evaluation of the lipid profile, cardiovascular risks, and an individual approach to choosing between treatment options keeping in mind the potential adherence [3, 10].

According to the Russian experts in atherosclerosis and lipid-lowering therapy, the main reasons for failure to achieve the targets of lipid-lowering therapy in patients with very high cardiovascular risk are the following:

- Insufficient continuity between inpatient and outpatient stages of medical care for patients with a history of acute coronary syndrome (ACS);
- Insufficient continuity between physicians of different specialties, such as, internists, cardiologists, endocrinologists, geriatricians, etc.;
- High incidence (up to 10%) of severe hypercholesterolemia, including familial forms, especially among young patients with a history of ACS;
- Insufficient awareness of physicians and the population about familial hypercholesterolemia;
- Poor tolerance of statins in multimorbid patients, especially those with complicated diabetes mellitus, chronic kidney disease, liver disease [11, 12].

The current guidelines for lipid-lowering therapy include «aggressive» control of LDL cholesterol levels even when using stepwise combined lipid-lowering therapy, with the total cardiovascular risk being the reference point for its appointment. In most cases, treatment is initiated with statin monotherapy at the maximum recommended/tolerated dose. If the target LDL cholesterol level is not achieved, ezetemibe is added to statin therapy. If the target LDL cholesterol level is also not achieved again, the addition of PCSK9 targeted therapy (alirocumab/evolocumab/inclisiran) is indicated. At the same time, it is important to remember the importance of adherence to treatment, as this essential for the achievement the target levels of LDL cholesterol. In this regard, lipid-lowering therapy should be chosen individually, and if patients with very high cardiovascular risk have insufficient adherence affecting LDL cholesterol, inclisiran should be preferred. It is administered by 3 subcutaneous injections in year 1 and 2 injections in year 2 and following, which is unprecedented in cardiology and ensures high adherence to treatment among patients. Moreover, such a treatment regimen can significantly reduce the burden on health professionals due to fewer patient visits to clinics [6, 13].

It is important to remember that timely prevention of cardiovascular and other chronic diseases is essential, since it is lack of prevention that leads to disability of patients, necessitates the use of intensive and expensive medical treatment, and leads to economic losses. Thus, many aspects of prevention are a priority for physicians, general practitioners, cardiologists, and other primary care physicians [14].

Conclusion

Our findings showed that 96.3% of patients with very high cardiovascular risk do not achieve the target levels of LDL cholesterol. Statins are the most commonly used lipid-lowering agents in the treatment of this category of patients, and the combination lipid-lowering therapy, including a statin and ezetimibe or a PCSK9 inhibitor and a statin, as well as monoclonal antibodies, such as PCSK9 inhibitors, are administered only in rare cases. Lipid-lowering therapy and the principles of its use within the outpatient management should be subjected to a more detailed comprehensive analysis with the inclusion of larger numbers of patients to address the existing limitations. Increasing physicians' awareness of current approaches to lipid-lowering therapy and improving patients' understanding of the disease and the prevention principles can help to bring LDL cholesterol levels closer to the target range.

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