Boytsov S.A.[1], Shakhnovich R.M.[1], Tereschenko S.N.[1], Erlikh A.D.[2], Kukava N.G.[1], Pevsner D.V.[1], Rytova Yu.K.[1]

[1] Chazov National Medical Research Centre of Cardiology, Moscow, Russia

[2] Bauman Municipal Clinical Hospital #28, Moscow, Russia

The prevalence of hyperlipidemia and features of lipid-lowering therapy in patients with myocardial infarction according to the Russian register of acute myocardial infarction REGION-MI

Aim	To study the prevalence of hyperlipidemia in patients with myocardial infarction (MI) in the Russian Federation; to assess the compliance with clinical practice guidelines of the lipid-lowering therapy prescribed upon discharge from the hospital; and to determine the number of patients who are indicated for the combination lipid-lowering therapy to achieve the low-density lipoprotein cholesterol (LDL-C) goal.
Material and methods	REGION-MI is Russian rEGIstry Of acute myocardial iNfarction, a multicenter, retrospective and prospective observational study. The observation period was divided into 3 stages: observation during the stay in the hospital and at 6 and 12 months after the inclusion in the registry. Plasma total cholesterol (TC) and LDL-C were measured in all patients on admission. Evaluation of the prescribed lipid-lowering therapy included the intensity of the treatment.
Results	The study included 3620 patients; 62.4 of them had hyperlipidemia on admission. Mean TC on admission was 5.29 mmol/l and LDl-C level was 3.35 mmol/l. Upon discharge, 95.4% of patients after myocardial infarction continued on or were prescribed statin therapy; ezetimibe was prescribed to 1.22% of patients. Patients with an extremely high level of LDL-C >5 mmol/l accounted for 10.7% of patients with hyperlipidemia. The target level of LDL-C ≤1.4 mmol/l cannot be achieved with the statin and ezetimibe combination therapy in these patients; drugs from the group of PCSK9 inhibitors are indicated for them.
Conclusion	According to the data of the Russian registry of acute myocardial infarction, REGION-MI, a high incidence of hyperlipidemia is observed in patients with acute MI. Despite multiple studies that have proven the importance of achieving a low LDL-C level and good tolerance and safety of ezetimibe and PCSK9 inhibitors, the prescription frequency of combination therapy remains unreasonably low. Results of a simulation study that was conducted in Sweden and the data of the REGION-MI registry showed that PCSK9 inhibitors as a part of the combination therapy are indicated for many patients. The combination therapy is presently the most powerful type of lipid-lowering treatment that allows, in most cases, achievement of the LDL-C goal.

Keywords	Cardiovascular diseases; ischemic heart disease; acute coronary syndrome; myocardial infarction; acute myocardial infarction registry; hyperlipidemia; lipid-lowering therapy
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Corresponding author	Rytova Yu.K. E-mail: rytova_julia@mail.ru

Cardiovascular diseases are the leading cause of death in most of the world. They rank first by a significant margin among the causes of disability and death in the Russian Federation. Coronary artery disease (CAD) is a leader among causes of death. According to the Russian Statistics Agency (Rosstat), 508,657 people died of CAD in Russia in 2020, of whom 58,079 died of myocardial infarction (MI). Although, the possibilities of treating MI patients have increased significantly over the past decade the due to the common use of drugs with proven efficacy, and the use of invasive treatments [1, 2], short-term and long-term prognosis after MI is still unfavorable.

The accumulation of low-density lipoprotein (LDL) cholesterol in the artery walls is a key element of atherogenesis underlying CAD and MI, and its persistent decrease in blood plasma reduces the risk of adverse cardiovascular events [3].

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Elevated plasma levels of total cholesterol (TC) were named the main risk factor for the development of CAD in the early reports of the Framingham Heart Study, which began in 1948 [4]. It was also demonstrated back then that the risk of CAD was two times higher in patients with TC>6.76 mmol/L than in patients with TC<5.72 mmol/L [5]. Reducing the plasma levels of TC is one of the most important elements of secondary prevention of CAD.

The Russian Register of Acute Myocardial Infarction (REGION-MI) is a multicenter retrospective and prospective observational study that excludes any interference in clinical practice. The inclusion of patients began in 2020 and will continue for 24 months. The register was created to collect data on the diagnosis and treatment of patients with acute MI in Russian hospitals, treatment results, short-term and long-term outcomes (6 and 12 months after the diagnosis of MI). One of the important tasks of the register is to study lipid metabolism disorders in Russian patients with MI and administered lipid-lowering therapy and to compare the results with similar data from the international studies [6].

The objectives of this study, which is based on the analysis of data obtained from the REGION-IM register, are to study the prevalence of hyperlipidemia in Russian patients with MI, to assess the conformity of lipid-lowering therapy prescribed at discharge to the clinical recommendations, and to predict the number of patients to whom combination lipid-lowering therapy is indicated to achieve the target levels of LDL cholesterol.

Material and methods

The Russian Register of Acute Myocardial Infarction (REGION-MI) is a multicenter retrospective and prospective observational study. The register includes all patients admitted to hospitals from day 1 to day 10 of each month with the acute ST-segment elevation MI (STEMI) and non-ST-segment elevation MI (NSTEMI) diagnosed according to the ESC Guidelines on Fourth Universal Definition of Myocardial Infarction (2018).

Patients are included in the study after they or their representatives have signed the informed consent to participate in the study and the personal data processing consent. The program has been developed and is carried out following the ethical principles of the Declaration of Helsinki, the ICH harmonized tripartite guideline, and the Russian GOST standard on Good Clinical Practice. The study design involves the collection of patients' personal data. By virtue of the observational nature of the study, the protocol, the case report form, and the information provided to patients is not subject to the approval of the Ministry of Healthcare of the Russian Federation and the Council on Ethics under the Ministry of Healthcare.

The study is carried out in the Quinta CRM platform. Case report form contains the following data: contact information; demographic characteristics; body weight, height; social status; medical history and concomitant diseases; information on the current case of MI (the time of onset of the first symptoms; the time of the first contact with health-care professionals and admission to the hospital; physical examination findings, hemodynamics at the time of hospitalization); clinical signs and symptoms; laboratory findings at admission and during the first 24 hours of hospital stay; clinical examination findings (electrocardiography, echocardiography, computed tomography angiography, stress test); findings of coronary angiography and percutaneous coronary intervention (PCI); in the case of coronary artery bypass grafting, the date of surgery, the number of grafts; information on the thrombolytic therapy; drug therapy (medicines administered at the time of admission, before hospitalization, and during hospital stay); clinical outcomes of the in-hospital treatment. The follow-up period is divided into 3 stages: observation during hospital stay, 6 and 12 months after inclusion in the register.

Venous blood samples are collected from all patients at admission to the hospital, including to determine the plasma levels of TC and LDL cholesterol. TC>5 mmol/L or LDL cholesterol>3 mmol/L are the criteria of hyperlipidemia [7]. The levels of TC in patients who took statins at the time of hospitalization are calculated using a correction factor of 1.3 [8]. The intensity of treatment is also assessed during the analysis of the administered lipid-lowering therapy. The following lipid-lowering treatment options are highly intensive: high-dose statins (atorvastatin 40–80 mg/day, rosuvastatin 20–40 mg/day, simvastatin 40–80 mg/day, pitavastatin 2–4 mg/day), combination therapy with statins and ezetimibe, PCSK9 inhibitors.

Simulation study provides the determination of the levels of LDL cholesterol, at which the target level of LDL cholesterol ≤1.4 mmol/L cannot be achieved using the combination of statins and ezetimibe therapy, to assess the percentage of patients who need the highest intensive lipid-lowering therapy and the administration of PCSK9 inhibitors. The calculations were based on the fact that, during the use of high-dose statins, a decrease in lipid levels could be expect by up to 60%, and additionally by 20% when adding ezetimibe [8].

Thus, with the baseline levels of LDL cholesterol >5 mmol/L, it is impossible to achieve the target levels LDL cholesterol ≤1.4 mmol/L without administering PCSK9 inhibitors.

The following data processing methods were used: descriptive statistics (mathematical expectation, standard deviation (SD), median, quartiles, minimum/maximum) to summarize the primary results obtained from case report forms; confidence assessment (mathematical expectation,

SD) that allows assessing the parameters of interest with the specified reliability; statistical data processing was carried out using IBM SPSS Statistic version 24.

All anamnestic, clinical, and laboratory data obtained were processed using variation statistics. The quantitative parameters were expressed as means (M), mean square deviation, errors of mean (m), standard deviations (SD), medians (Me), 95% confidence intervals (CI). The frequency of a sign or an event was determined for the qualitative data. The non-parametric Mann-Whitney test was used to determine the effect of various factors on the level of LDL cholesterol. A proportion z-test was applied to compare the frequencies of statin administration in the groups of patients with risk factors and co-morbidities. In some cases, a t-test was used to compare the means in the patient groups.

Results

Clinical and demographic characteristics of patients

The study involves 86 hospitals included in the «MI Network» in the Central, Ural, Siberian, and Far Eastern Federal Districts (a total of 41 Russian regions). From 01.11.2020 to 30.10.2021, a total of 3,620 patients were included in the REGION-IM register, 70% of whom were male. The mean age patients included in the study was 60 and 71 years for male and female patients, respectively. 17.5% of the patients had a history of MI, and the rest of the patients had new onset MI. 74% of the entire cohort were patients with STEMI. 33.7% of the patients were previously diagnosed with angina pectoris, 18.9% of the patients had a burdened medical history, 82.8% of the patients had arterial hypertension, and 34.1% of the patients were obese (Table 1).

Table 1. Clinical and demographic characteristics of the included patients (n=3,620)

Parameter	Value
Mean age of all patients, years (min–max)	63.01 (18.93–97.24)
Male, %	70.0
Female, %	30.0
Mean age of all male patients, years (min–max)	60.01 (18.93–95.63)
Mean age of all female patients, years (min–max)	71 (24.76–97.24)
Patients without a history of MI, %	81.8
Patients with recurrent MI, %	17.5
Smokers, %	39.2
Patients with arterial hypertension, %	82.8
Patients with angina pectoris, %	33.7
Patients with CHF, %	24.3
Patients with increased BMI, %	42.7
Patients with obesity, %	34.1
Patients with family history of CAD, %	18.9
STEMI, %	74

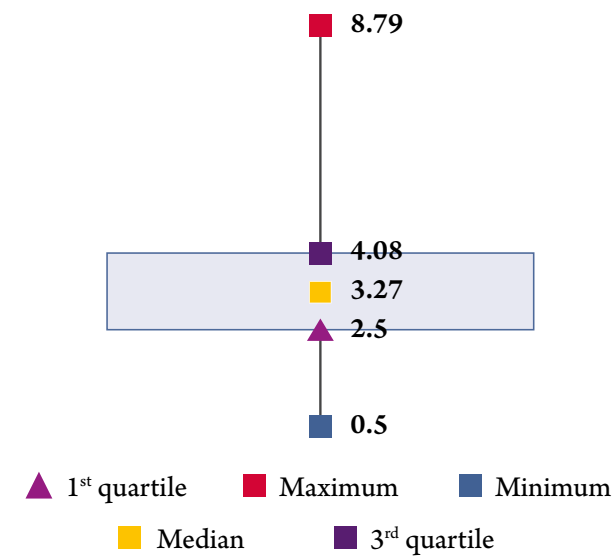
MI, myocardial infarction; CHF, chronic heart failure; BMI, body mass index; CAD, coronary artery disease; STEMI, ST-segment elevation myocardial infarction.

Cholesterol and the prevalence of hyperlipidemia

At admission, the mean level of TC was 5.29 (4.3–6.1) mmol/L and mean LDL cholesterol was 3.35 (2.0–4.1) mmol/L. The distribution of patients based on LDL cholesterol levels is shown in Figure 1 and Figure 2. LDL cholesterol >2.5 mmol/L was observed in 75% of hospitalized patients, more than 50% of the patients had LDL cholesterol >3.37 mmol/L at admission. Only 5% of hospitalized patients had LDL cholesterol levels<1.4 mmol/L.

The mean level of LDL cholesterol in female patients who received lipid-lowering therapy and who did not take statins was 3.1 mmol/L and 3.6 mmol/L, respectively. The mean level of LDL cholesterol in male patients who received lipid-lowering therapy and who did not take statins was 2.9 mmol/L and 3.3 mmol/L, respectively.

Figure 1. Distribution of patients by the LDL cholesterol levels (mmol/L)



LDL, low density lipoprotein.

Among all patients hospitalized with MI, the highest level of LDL cholesterol was detected in 51–55-year-old female patients (4.0 mmol/L) and 36–40 year old male patients (3.8 mmol/L). The levels of LDL cholesterol tend to increase in patients up to 65 years old, after which a mild decrease is observed in patients over 70 years old (Figure 3).

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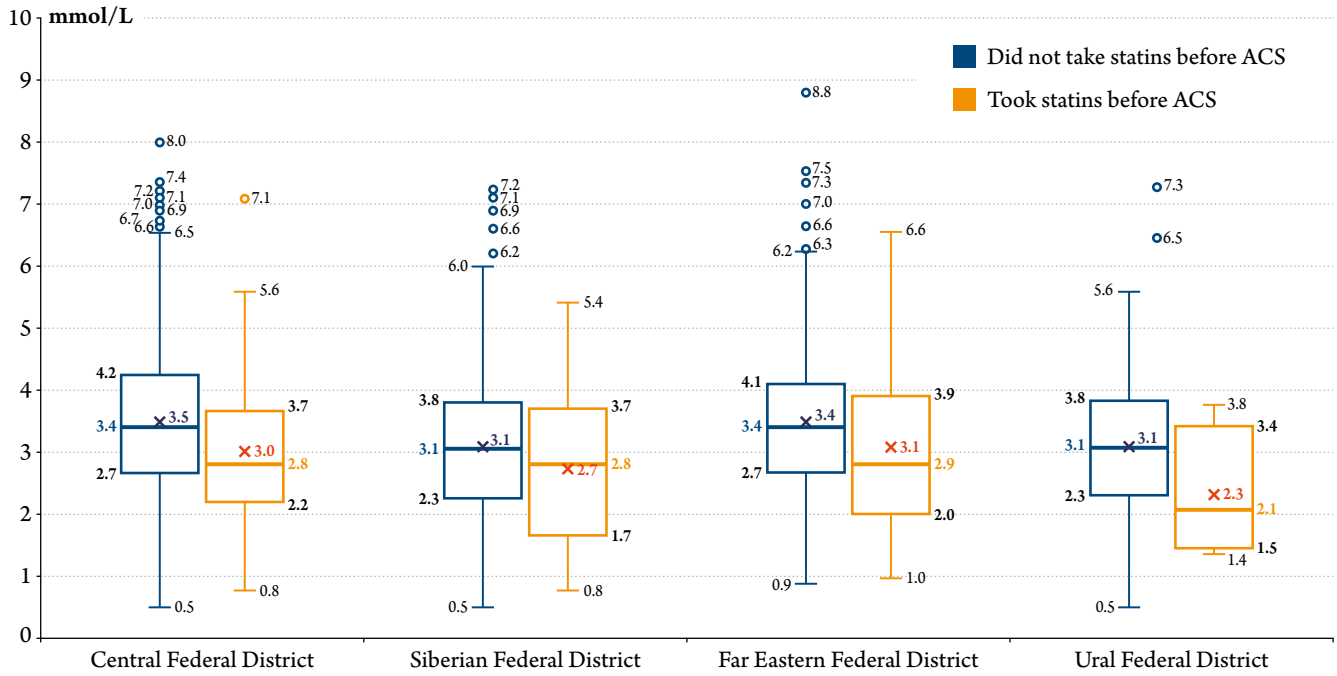
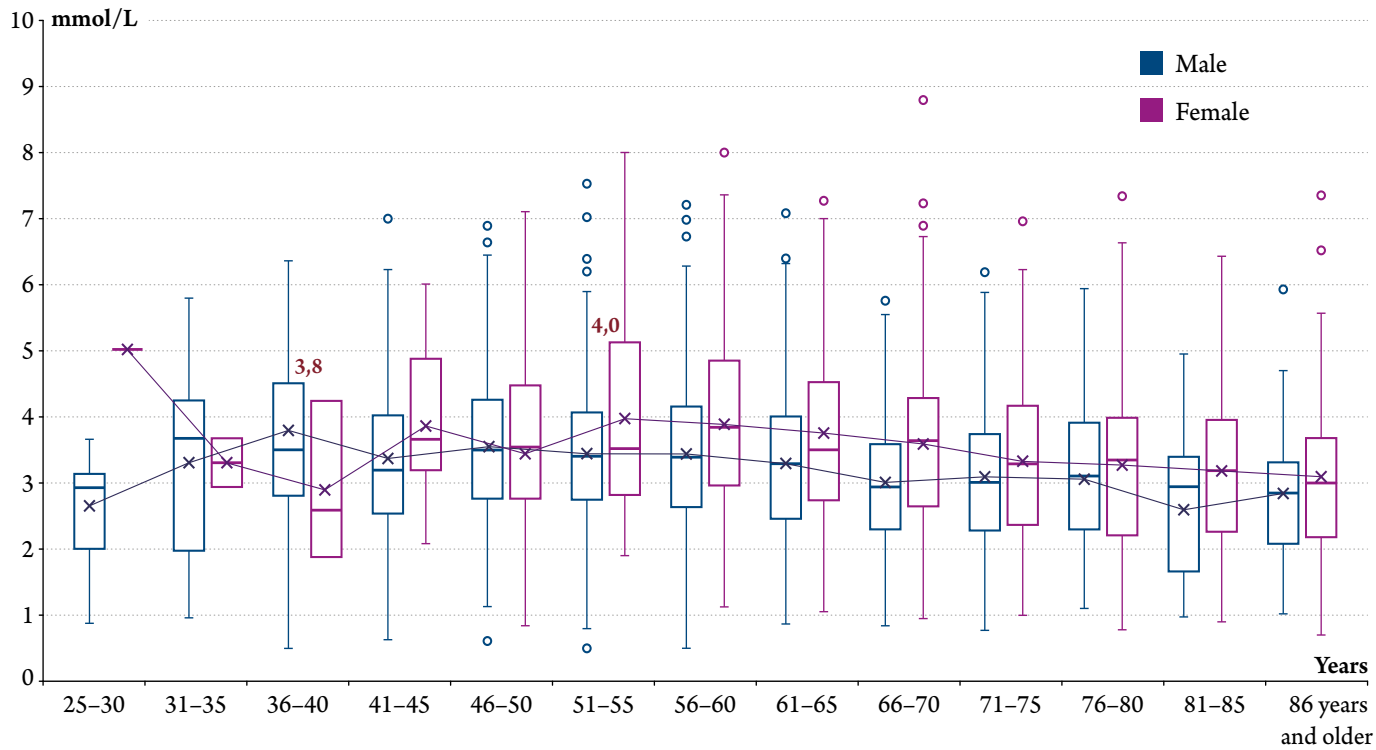
Figure 2. LDL cholesterol levels in patients by the Russian Federal Districts based on statin administration before the onset of ACS (mmol/L)



LDL, low-density lipoprotein; ACS, acute coronary syndrome.

The effects of CAD risk factors on the lipid composition of blood in patients with MI is shown in Figure 4. There were no statistically significant differences in the TC levels between smoking and non-smoking patients, patients with and without a burdened family history, and patients with or without arterial hypertension. The non-parametric Mann-Whitney test allowed detecting a statistically significant decrease in

Figure 3. LDL cholesterol levels (mmol/L) based on age and sex



LDL, low density lipoprotein.

LDL cholesterol in patients with recurrent MI (p<0.001), exertional angina (p<0.001), and diabetes mellitus (p=0.004) compared to patients without a respective history. However, there were little differences in the absolute mean values of LDL cholesterol levels. Statins were administered at admission by 13% of the entire cohort, 25% of the patients with a history of MI, and 17% of the patients with stable CAD (Figure 5).

Hyperlipidemia was detected at admission in 62.4% of all patients included in the study.

Lipid-lowering therapy

Statins were continued or prescribed to 95.4% of post-MI patients at discharge from the hospital. Atorvastatin was administered to 91% of the patients (Figure 6). High-intensity statin therapy was prescribed to most patients. In the atorvastatin subgroup, 96% of the patients received the doses of ≥ 40 mg/day. Among patients treated with rosuvastatin, 92% received ≥20 mg/day. In the simvastatin subgroup, all patients received the doses of ≥40 mg/day, and pitavastatin was administered at the doses of ≥2 mg/day. Only 9 (1.22%) patients received ezetimibe. This sample is insufficient for drawing preliminary conclusions.

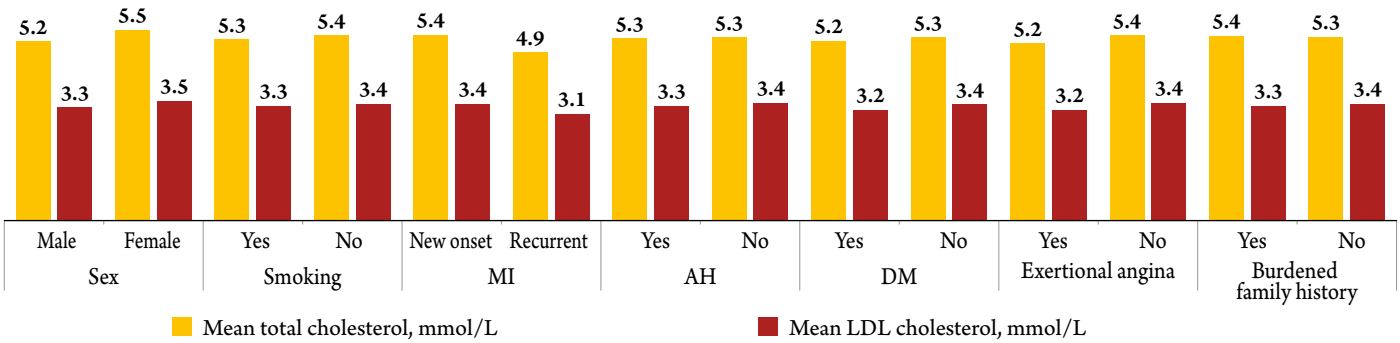
Simulation study

Some patients, who adhered to maximum-dose statin therapy prescribed at discharge, did not achieve target LDL cholesterol levels of ≤1.4 mmol/L due to limited lipid-lowering potential of the drugs.

We conducted a simulation study to determine the percentage of patients who needed the most intensive combination lipid-lowering therapy, which currently includes three different drug classes: statins, ezetimibe, and PCSK9 inhibitors. The calculations produced the data, according to which it was impossible for patients, who were naive to lipid-lowering therapy and had baseline LDL cholesterol levels >5 mmol/L, to achieve the target LDL cholesterol levels ≤1.4 mmol/L during the combination statin and ezetimibe therapy.

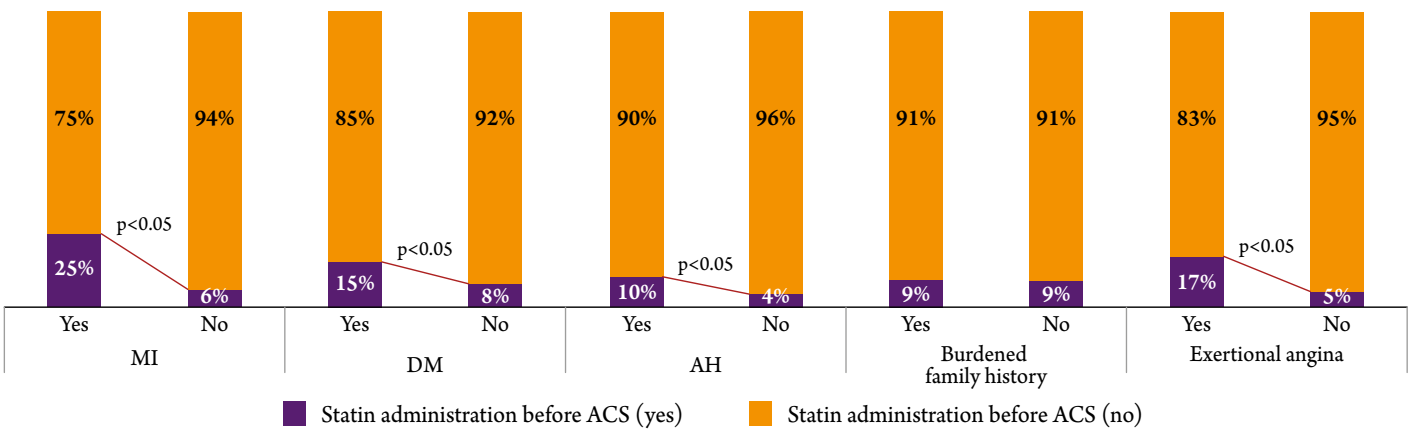
In the REGION-IM register, 10.7% of the patients with hyperlipidemia had extremely high LDL cholesterol levels of >5 mmol/L. PCSK9 inhibitors are indicated to this group of patients.

Figure 4. Lipid levels in patients with CAD risk factors and co-morbidities (mmol/L)



CAD, coronary artery disease; MI, myocardial infarction; AH, arterial hypertension; DM, diabetes mellitus; LDL, low-density lipoprotein.

Figure 5. Statin administration before hospitalization based on risk factors and co-morbidities



ACS, acute coronary syndrome; MI, myocardial infarction; AH, arterial hypertension; DM, diabetes mellitus.

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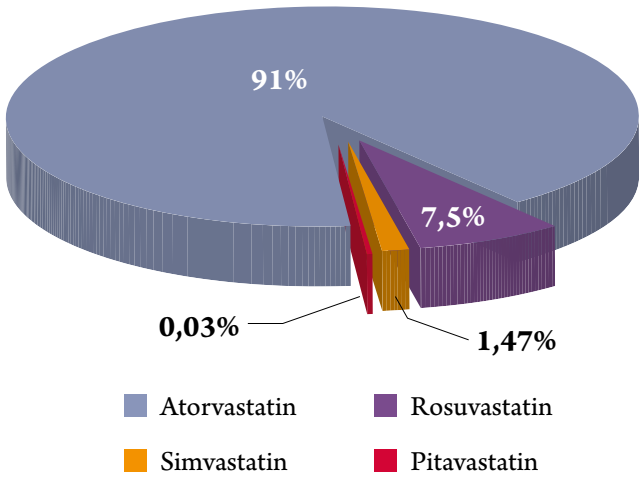
Figure 6. Administration of statins during hospital treatment



Long-term outcomes of lipid-lowering therapy

Preliminary data on the levels of LDL cholesterol in patients 6 months after MI were obtained in early February 2022. The study protocol did not include the evaluation of long-term changes in the TC levels, which is why the levels of LDL cholesterol were estimated 6 months after inclusion in the register in only 218 patients through telephone contacts.

Of the 218 patients, only 23% achieved the target levels of LDL cholesterol ≤1.4 mmol/L during lipid-lowering therapy. The target levels of TC were achieved by 21% of the patients in the statin monotherapy group and 44% in the group of statin+ezetimibe combination therapy, but the absolute numbers were very low.

Among the 218 patients with known levels of LDL cholesterol at month 6 of monitoring, high-dose and low-dose statins were administered to 86% and 14%, respectively.

Discussion

Cholesterol levels

Only 25% of the included patients had acceptable (but not ideal) levels of LDL cholesterol<2.5 mmol/L, 50% of the patients had very high LDL cholesterol>3.27 mmol/L, and 25% had extremely high LDL cholesterol >4.08 mmol/L. LDL cholesterol ≤1.4 mmol/L was detected in only 5% of the patients.

According to the Pharmacoepidemiologic General Research eXtension (PGRx) ACS register (France), the mean level of LDL cholesterol in patients with MI at admission was 2.9 mmol/L, i.e., significantly lower than in our patients (3.35 mmol/L), and the number of patients with LDL cholesterol ≥5 mmol/L was more than 2 times lower (4.6%) [9]. In order to evaluate the efficacy of secondary post-MI prevention, a PATIENT-CARE register was created in Germany. The mean level of LDL cholesterol at the time of inclusion in post-ACS patients was also lower than in our study (2.49±0.83 mmol/L) [10]. In the large TERCET register (Poland), TC in patients hospitalized with ACS at admission was higher than in France and Germany, but lower than in the patients included in our register. The mean levels of LDL cholesterol were 3 mmol/L and 2.69 mmol/L in patients with STEMI and NSTEMI, respectively [11]. According to the MAINTAIN ACS register (US), mean LDL cholesterol at admission was 2.6 mmol/L [12].

Higher levels of TC in patients with MI in the Russian Federation compared to the USA and the European countries is likely to be largely due to dietary habits. In Russia, unlike these countries, food ration contains more saturated animal fats rich in cholesterol and less fish and vegetables. Thus, there is high incidence and mortality associated with CAD/MI and other atherosclerotic manifestations. Such differences are also due to less common administration of statins in patients in the Russian Federation. Only 25% of the patients with risk factors or a history of CAD received statins before hospitalization. The influence of genetics on the TC levels in patients of different ethnic origin cannot be excluded.

Our findings that the highest levels of LDL cholesterol are observed in male patients younger (36–40 years) than female patients (51–55 years) correlate with the previous studies. In a large population-based study (US), LDL cholesterol levels were higher in male patients from 20 to 59 years old than in female patients of the same age group, and they were higher in female patients older than 60 years. A significant increase in LDL cholesterol was observed in female patients after the age of 50 [13]. This natural increase in the levels of plasma TC in female patients older than 50 years is due to menopause, which significantly contributes to the development of hyperlipidemia [14, 15].

In our register, we see a trend similar to other studies' findings that levels of TC decrease as people age [16, 17]. Several factors associated with aging and pathological conditions contribute to lower levels of TC and LDL cholesterol in elderly and senile patients. Senile asthenia, gastrointestinal disorders, malnutrition are nutrition-related factors that lead to a decreased intake of exogenous cholesterol [16]. Cancer, liver diseases, as well as a concomitant pathological conditions and chronic diseases lead to a reduced synthesis of endogenous cholesterol [18].

Lipid-lowering therapy

In the REGION-IM register, patients with recurrent MI, angina pectoris, and diabetes mellitus had significantly lower levels of LDL cholesterol at admission than those without such conditions, although there were no differences in the absolute values between the groups. These data show that some patients with risk factors and a history of CAD used statins before hospitalizations, however, the percentage of such patients was small that the intensity of lipid-lowering therapy was low.

At the time of index hospitalization, only 25% of the patients with a history of MI received statins. This indicates that although while there are clear-cut indications for intense lipid-lowering therapy, in real-world clinical practice, patients with a previous diagnosis of CAD either do not receive lipid-lowering drugs at the outpatient stage or the severity of this therapy is inadequate. This is obviously a matter a low rate of prescribing drugs and poor adherence to treatment. According to the Research eXtension (PGRx) register (France), 75% of patients who had indications for lipid-lowering therapy before the index event, were taking statins at the time of hospitalization [9].

At discharge, 95.4% of the subjects of our study received intensive lipid-lowering therapy with high-dose statins, mainly atorvastatin with a proven efficacy in ACS patients [19]. Rosuvastatin was the second most common;y administered drug, and the rest of this group of drugs was prescribed very rarely. Although the majority of the patients in our study received high-dose statins or statin + ezetimibe combination after discharge, only 23% of the patients who continued taking lipid-lowering drugs were able to achieve the target levels of LDL cholesterol of ≤ 1.4 mmol/L.

Overall statin prescription rate at discharge was relatively lower than in the Russian part of the EUROASPIRE V trial (95.4% vs. 98%) and significantly higher than in the general population of this international multicenter register with statins being prescribed to only 85% of the patients at discharge. High-intensity lipid-lowering therapy was administered to patients at discharge much less frequently in the EUROASPIRE V register than in the REGION-IM register: 60.3% of subject in the general study cohort and 54.0% of the patients in the Russian sites received high-intensity lipid-lowering therapy [20].

In contrast to the REGION-IM register, high-dose statins were prescribed at discharge to only 56% of the subjects of the PGRx register, and only 1% received combination therapy with statins and ezetimibe. At the time of enrollment (2013–2016), the target level of LDL cholesterol, according to the ESC Guidelines for the Management of Dyslipidaemias, was ≤ 1.8 mmol/L [21]. Only 32% of the patients achieved the target level after 3 months of follow-up, and only 15% achieved LDL cholesterol levels ≤ 1.4 mmol/L, which is less than in our register [9]. In the PATIENT-CARE register, statins were prescribed at discharge to 96.7% of the patients (atorvastatin 40 mg – 66.9%, simvastatin 40 mg/day – 38.2%). Interestingly, ezetimibe was prescribed significantly more often (10.6%) than in our study. However, despite initially lower TC levels and a more frequent use of the combination of statins and ezetimibe, 41.9% of the patients were able to achieve LDL cholesterol levels ≤ 1.8 mmol/L 1.5 months after the index event [10]. In the TERCET register (Poland), statins were prescribed less frequently at discharge (91.6%) than in our study, atorvastatin was also the most commonly used drug. However, intensive lipid-lowering therapy with high-dose statins was prescribed to less than 50% of the patients with ACS, and the combination therapy was administered in only 3% of cases. After 12 months of treatment, LDL cholesterol levels decreased to ≤1.8 mmol/L in 32.4% of the patients with STEMI and 29.9% of the patients with NSTEMI [11]. In the MAINTAIN register (US), lipid-lowering therapy was prescribed at discharge less frequently (89%) than in our study. Medium-dose statins were administered in 77% of the patients, with only 6.6% receiving maximum doses of statins. At 12 months, target LDL cholesterol levels of ≤1.8 mmol/L were achieved in 31% of the patients [12]. In the Danish population-based study, more than 89.4% of the patients hospitalized with ACS had LDL cholesterol>1.8 mmol/L. Only 29.7% of the patients received intensive lipid-lowering therapy after discharge. Only 39% of the patients achieved the target levels of LDL cholesterol ≤ 1.8 mmol/L 12 months after ACS [22]. Thus, although most patients with ACS receive intensive statin therapy, sometimes in combination with ezetimibe, the rate of achieving target LDL cholesterol levels is very low.

Intensive lipid-lowering therapy in patients with myocardial infarction

The MIRACL study, which included patients with ACS without ST segment elevation, was first to show the efficacy of early statin administration 20 years ago. It was determined that prescribing statins within the first 24–96 hours of hospitalization resulted in a significant decrease in the incidence of cardiovascular adverse events within 4 months after ACS [23]. The ARMYDA-ACS study showed that statin administration in patients with ACS before PCI resulted in a significant decrease in the incidence of cardiovascular adverse events (the incidence of death, MI, emergency revascularization was 5% in the atorvastatin group and 17% in the placebo group; p=0.01) [24].

Large multicenter randomized clinical trial (RCT) PROVE IT – TIMI 22 demonstrated not only the importance of early initiation of statins, but also the need for intensive lipid-lowering therapy, such as the administration of statins at maximum tolerated doses. Patients with ACS included in the study were divided into two groups: Group 1 – pravastatin 40 mg/day and Group 2 – high-intensity therapy with atorvastatin 80 mg/day. The incidence of cardiovascular adverse events was lower in the atorvastatin group than in the pravastatin group by 16% (95% CI 5–26; p=0.005) [19]. The PROVE IT-TIMI 22 study also demonstrated that patients with a recent history of ACS who achieved lower LDL cholesterol levels also experienced a larger decrease in the risk of developing cardiovascular adverse events. This trend was observed up to LDL cholesterol levels of 1.0 mmol/L and lower [25]. This hypothesis was also confirmed in the IMPROVE-IT study, which showed a direct linear correlation between a decrease in LDL cholesterol of<1.8 mmol/L and

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a decrease in the risk of developing cardiovascular adverse events (95% CI 0.89–0.99; p=0.016) [26]. A retrospective analysis of data obtained from the SWEDEHEART register (Sweden) showed that a more than 50% decrease in LDL cholesterol from initial levels, a decrease in LDL cholesterol to ≤ 1.8 mmol/L lead to a significant reduction in the risk of developing cardiovascular adverse events [27].

The findings of the above studies contributed to the fact that the «the lower the better» strategy was approved in the 2019 ESC Guidelines for the Management of Dyslipidaemias, according to which the target levels of LDL cholesterol in patients at very high risk is ≤ 1.4 mmol/L and a decrease of at least 50% from the initial levels [8]. This position was supported in the Russian Guidelines for the management of chronic CAD, STEMI, ACS without ST-segment elevation [28–30].

In the PROVE-IT study, about 30% of the patients with a history of ACS did not achieve the target levels of LDL cholesterol during treatment with atorvastatin 80 mg/day [25]. In the European observational study of lipid-lowering therapy DA VINCI, only 18% of patients at very high risk (including patients with MI) achieved target LDL cholesterol levels of ≤1.4 mmol/L. The most common lipid-lowering regimen was medium-intensity monotherapy with statins, and patients receiving combination therapy including a PCSK9 inhibitor achieved target levels more often [31].

Many studies of lipid-lowering drugs and registers demonstrated that the high incidence of failure to achieve the target levels of LDL cholesterol was not only associated with non-intensive therapy or low adherence to treatment. It was mainly due to the fact that it is impossible to achieve the treatment targets using statin monotherapy in patients with very high initial levels of LDL cholesterol. The expected level of LDL cholesterol decreases during the therapy with of atorvastatin and rosuvastatin at maximum doses is 53–55% of the initial level. However, if initial LDL cholesterol is more than 3.9 mmol/L, it should be decreased by at least 60% to achieve the target levels of ≤1.4 mmol/L [21].

When the target levels of LDL cholesterol cannot be achieve achieved with the maximum doses of statins, combination lipid-lowering therapy with statins and other classes of drugs is required [32]. In the IMPROVE-IT study [26], the combination of simvastatin and ezetimibe was shown to be more effective than statin monotherapy and provided a significant decrease in the incidence of severe complications in patients with ACS without ST-segment elevation. This was mainly due to a decrease in the incidence of non-fatal MI and repeated revascularization procedures.

According to the latest ESC Guidelines for the Management of Dyslipidemias [8], the most potent lipid-lowering drugs, PCSK9 inhibitors, are indicated when the combination therapy with the maximum doses of statins and ezetimibe fail to achieve the target levels of LDL cholesterol. Their efficacy was demonstrated in the ODYSSEY OUTCOMES and FOURIER studies [33]. In the FOURIER study, the risk of developing severe cardiovascular adverse events decreased from 16% in the first year of evolocumab therapy to 25% when the drug was used for more than a year [34]. The EVOPACS study, which was the first clinical trial to evaluate the efficacy and safety of PCSK9 inhibitor evolocumab in the first 72 hours from the onset of ACS, demonstrated that the target LDL cholesterol levels ≤1.4 mmol/L were achieved by 90% of the patients during the combination therapy with atorvastatin 40 mg and evolocumab, and only about 11% of the patients receiving statin monotherapy [35]. Recently published results of the HUYGENS study confirmed the highest efficacy of lipid-lowering therapy with the combination of statins and evolocumab, such as a 80% decrease in LDL cholesterol from initial levels. The effect of PCSK9 inhibitors on the stabilization of atherosclerotic plaques in patients with ACS without ST-segment elevation was also studied. When combined with evolocumab statins were two times more effective in stabilizing a plaque than statin alone. According to optical coherence tomography measurements, the minimum thickness of a fibrous cap increased within a year by 21% during statin monotherapy and by 42.7% during the use of evolocumab [36].

A simulation study was conducted within the framework of the SWEDEHEART IM register (Sweden) in 2013–2017 based of the ESC Guidelines for the Management of Dyslipidaemias [37]. The objective was to estimate the number of patients who would fail to respond to the maximum doses statins and would require the combination lipid-lowering therapy to achieve the target TC levels. After discharge from hospital, 86.6% of the patients received high-dose statins. In 6–10 weeks, 82.9% of the patients included in the study had indications for more intense lipid-lowering therapy due to failure to achieve the target levels of LDL cholesterol (< 1.4 mmol/L or a more than 50% decrease from initial levels). In the simulation study, when ezetimibe was added to the maximum doses of statins, the percentage of patients who achieved the target levels increased to 50.3%. However, 50.7% of the patients would still require more intense drug therapy with PCSK9 inhibitors, which is significantly more than in our study. The target levels of LDL cholesterol were achieved during the combination therapy including PCSK9 inhibitors in more than 90% of the patients. In the simulation study based on data from the REGION-IM register, PCSK9 inhibitors were indicated to 10.7% of the patients. To achieve the target levels of LDL cholesterol as quickly as possible, the Russian Guidelines for the treatment of STEMI and NSTEMI suggest the possibility of early administration of alirocumab or evolocumab without the prior administration of ezetimibe in this group of the patients

[29, 30]. This recommendation is based on two positions. First, very few patients received ezetimibe in the ODYSSEY OUTCOMES and FOURIER studies, i.e., the main data on the benefits of PCSK9 inhibitor therapy were obtained in combination with statins. Second, if LDL cholesterol levels are significantly elevated, the combination therapy with statins and ezetimibe will not be adequate, and PCSK9 inhibitor will have to be added, although the statin + PCSK9 inhibitor combination will achieve the desired result in most cases. Thus, it is reasonable not to administer an optional drug, which is especially important given the number of drugs that are advised after MI.

Conclusion

According to the Russian register of acute myocardial infarction REGION-IM, the incidence of hyperlipidemia is high in patients with acute myocardial infarction. Higher levels of total cholesterol and low-density lipoprotein cholesterol are observed compared to the data obtained from European and American registers. Moreover, lipid-lowering therapy is not common in patients with risk factors for coronary artery disease at the outpatient stage.

Early, intensive and, if necessary, composite lipid-lowering therapy is the basis for secondary prevention of coronary artery disease. However, despite many studies that demonstrated the need to achieve low levels of low-density lipoprotein cholesterol in patients at very high risk, which was included in clinical guidelines, the good tolerability and safety of ezetimibe and PCSK9 inhibitors, the frequency of administration of the combination therapy remains unreasonably low in the Russian Federation and the rest of the world. More than 50% of the patients with a history acute coronary syndrome do not achieve the target levels of low-density lipoprotein cholesterol due to the limited efficacy. Given the data obtained in the simulation study conducted in Sweden and the findings of the REGION-IM register, PCSK9 inhibitors are indicated within the combination therapy to a large number of patients, as they are the most potent lipid-lowering drugs currently available that allow in most cases to achieve the target levels of low-density lipoprotein cholesterol.

Limitations

Only hospitals included in the «MI Network» participate in the register, which excludes the analysis of acute myocardial infarction cases in non-specialized hospitals; not all regions of the Russian Federation participate in the register; the study protocol does not include the evaluation of long-term changes in the TC levels, which is why the levels of LDL cholesterol were estimated 6 months and more after inclusion in the register in a limited number of patients via telephone calls.

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