



Implemented models and perspectives of managing lipid metabolism disorders. Concept of rare lipid disease centers

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Despite the advances in lipidology over the past decade, the control of dyslipidemia at the population level in Russia, as in a number of European countries, remains unsatisfactory. The need for novel organizational approaches to solving the problem at the regional and federal levels is obvious. This publication provides an overview of the implemented projects and the successful practical experience of lipid centers in Russia, as well as the prospects for the development of novel models that will optimize the care provision for patients with lipid metabolism disorders at the population level.

Keywords: dyslipidemias, population-based strategy, lipid centers.

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Dyslipidemia is one of the key modifiable risk factors, delayed detection of which leads to an increase in cardiovascular morbidity and mortality. Despite the evidence of key role of lipid metabolism disorders in the development of atherosclerotic cardiovascular diseases (CVD) and the common position of European and Russian guidelines on the need to lower the low-density lipoprotein (LDL) cholesterol levels, the study results demonstrate insufficiently effective control of dyslipidemia at the population level. Thus, the DA VINCI study, which assessed the effectiveness of both primary and secondary CVD prevention in more than 18 European countries, demonstrated a significant gap between the current clinical guidelines (2019) and actual clinical practice — on average, only 33% of patients achieved target LDL values. Among patients with very high cardiovascular risk (CVR) while receiving lipid-lowering therapy, only 17% and 22% of patients achieved LDL values of <1,4 mmol/L within primary and secondary prevention, respectively [1].

There are following possible problems leading to inadequate control of dyslipidemia: 1) inaccurate stratification of CVR, mainly within primary prevention; 2) no continuity in the management of patients with lipid metabolism disorders; 3) low adherence of patients to lipid-lowering therapy; 4) limited availability of apheresis and subsidized pharmaceutical provision programs for the three main lines of lipid-lowering drugs, especially within primary prevention.

Patients with lipid metabolism disorders represent an extremely heterogeneous group, for the management of which competent risk stratification is required. Over the past decades, serious advances have been made in the treatment of patients with high and very high CVR due to the introduction of high-tech medical care and secondary prevention measures. Nevertheless, according to Rose's prevention paradox, at the population level, most cardiovascular events occur in patients with moderate and low risk. In this regard, working with these cohorts of patients has the greatest potential for reaching long-term targets. All this emphasizes the need to improve the system for managing lipid metabolism disorders with the development of criteria for referral to lipid centers.

Management of care for patients with familial hypercholesterolemia

Within the primary prevention, the greatest difficulty is the identification of patients with a heterozygous familial hypercholesterolemia (FH). Despite the progress achieved in genetic testing in addition to novel treatment technologies, the prevalence of detection and adequate management of patients with FH remains low, especially given

the prevalence of heterozygous FH (1:200-1:250) in the population [2]. The development of nationwide clinical and genetic screening programs contributes to early detection and adequate management through assessment of cascade screening data, lifestyle changes, and timely pharmacological intervention. So, created in 1994 in the Netherlands, and in 2009 in Italy, the National Screening Program for FH have demonstrated effectiveness in CVR management in this category of patients [3, 4].

Since 2015, the project of the European Atherosclerosis Society (EAS) EAS FH Studies Collaboration has been successfully implementing, the purpose of which was to identify and treat patients with FH [5]. The Russian National Atherosclerosis Society participates in this initiative, as a part of which the register RENESSANS was maintained. The maintenance of such a register made it possible to draw attention to this problem and significantly increase the proportion of patients with FH. Currently, the EAS registry numbers >62 thousand patients from 62 countries, among which 41 thousand patients are persons with a definite or probable FH according to clinical and/or genetic criteria. Up-to-date information on the register is available on EAS website: <https://www.eas-society.org/>.

One of the key issues concerning patients with FH in Russia is the possibility of providing expensive classes of lipid-lowering drugs and apheresis. It should be noted that most of them receive therapy as part of the primary cardiovascular prevention. In this regard, the Almazov National Medical Research Center, with the support of Russian Society of Cardiology (RSC), initiated a register creation for patients with suspected FH (Dutch Lipid Clinic Network score 6 or more) [6], within which genetic testing is provided. This register, covering a number of Russian regions, is considered as a possible tool for choosing patients for subsidized pharmaceutical provision with lipid-lowering therapy, including based on positive genetic testing results.

Practical aspects of managing care for patients with lipid metabolism disorders. EAS and RSC project — Lipid Clinics Network

EAS initiated the **Lipid Clinics Network project**, the aim of which was to introduce common European standards for the diagnosis and treatment of lipid metabolism disorders, as well as to ensure the continuity of managing these patients at the local, regional and federal levels. In accordance with this, a possible organization chart of lipid service has been developed and a mechanism of bidirectional interaction at the regional and local levels has been worked out (Figure 1). Federal and regional centers carry out clinical, research and educational functions with a different competency.



Figure 1. Organization chart of the lipid service.

Abbreviation: HTHC — high-tech healthcare.

There are following criteria for referral to regional and federal lipid centers:

- severe hypercholesterolemia (total cholesterol level $>8,0$ mmol/L and/or LDL $>5,0$ mmol/L, and/or triglycerides >10 mmol/L), requiring determination of optimal patient management (indications for high-dose and/or combination therapy with lipid-lowering drugs, including monoclonal antibodies);
- cardiovascular events/CVDs under the age of 50, including revascularization due to atherosclerosis (timely, aggressive secondary prevention is required);
- difficulties in selecting lipid-lowering therapy (intolerance, side effects, concomitant diseases).

At the same time, it is necessary to differentiate the groups of patients needing consultation in lipid centers to optimize diagnosis and treatment, and the dynamic follow-up groups, which, due to the severity of disease course, require observation within a specialized center. Such separation of patients will provide the timely in-depth examination without an unreasonable increase in the number of lipid centers.

To introduce European standards into actual clinical practice, together with key European atherosclerosis experts, work is performed to develop an algorithm to create a decision support system that will be used for assessing the risk and determining management tactics in accordance with the latest guidelines on lipid metabolism disorders.

It is necessary to conduct specialized training events for therapists, cardiologists, endocrinologists and dermatologists, as well as active telemedicine consultations in difficult cases of lipid metabolism disorders, including with the involvement of international experts. So, in February 2020, on the basis of Almazov National Medical Research Center, the first online consultation with professor A. L. Katanpapo was held. Three participating regions brought up difficult clinical cases for discussion, during which a council of experts adjusted the management tactics for 6 patients with severe combined genetic dyslipidemias.

Currently, a mechanism of bidirectional interaction the Almazov National Medical Research Center with regional lipid centers in the Rostov and Samara Oblasts, the Chuvash Republic and Nizhny Novgorod has been worked out with provision of genetic testing for patients with suspected severe hereditary lipid metabolism disorders with increased LDL levels and hypertriglyceridemia, hyperlipoproteinemia (a).

Successful experience of regional lipid centers Republic of Karelia

In order to identify patients with severe dyslipidemia and the selection of personalized lipid-lowering therapy in the Republic of Karelia, a Lipid Center was created on the basis of Laboratory of Clinical Epidemiology of Petrozavodsk State University Medical Institute.

There are following tasks of the lipid center:

- Provision of qualified consultative, diagnostic, therapeutic and prophylactic care for outpatients with severe lipid metabolism disorders and/or early aggressive atherosclerosis, and/or intolerance to lipid-lowering drugs;
- Standardization of treatment and diagnostic approaches in the management of cardiovascular patients with atherosclerosis and patients with high and very high risk of their development, including the introduction of novel methods of examination and treatment into practice;
- Conducting research and educational events dedicated to diagnostics, effective methods of primary and secondary prevention and invasive treatment of dyslipidemia;
- Development of guidelines on creating education programs for patients with dyslipidemia and their relatives;
- Determination of indications for high-tech treatment methods (proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors), follow-up of patients receiving this therapy;
- Selection of patients with severe dyslipidemia for referral to specialized federal lipid centers for consulting on treatment and rehabilitation.

The following indications for referring patients to a consultation in Lipid Center have been determined:

- Severe dyslipidemia before starting lipid-lowering therapy (total cholesterol $>7,8$ mmol, LDL $>4,9$ mmol/L) after ruling out secondary causes of hyperlipidemia;
- Severe hypertriglyceridemia (>10 mmol/L), resistant to therapy;
- Tendons xanthomatosis at any age, arcus senilis in persons under 45;
- Early onset of coronary artery disease (CAD) or stroke (up to 40 years);
- Patients resistant to statin therapy, with statin intolerance, and those who did not achieve the target lipid profile levels with standard lipid-lowering therapy.

Funding of subsidized pharmaceutical provision for patients in need of PCSK9 inhibitor therapy is carried out within the departmental special-purpose program approved by the order of the Ministry of Health of the Republic of Karelia dated December 24, 2015 № 2504 "Prevention of disability of the population of the Republic of Karelia". The program is reviewed annually — new subprograms are added and the drug list of is updated.

Through the subprograms "Cardiac rehabilitation" and "Individual measures aimed at providing people with drugs for life threatening chronic diseases (conditions)", PCSK9 inhibitors are purchased for patients with FH and aggressive atherosclerosis.

During the Lipid Center's work, a register of FH patients was created ($n=277$; mean age, 48 years). The prevalence of FH in Karelia was determined (1:300). Patients are genotyped and new mutations determine the FH development have been identified. In addition, selection and management of patients receiving PCSK9 inhibitor therapy is underway. Currently, 31 patients (men, 61%; age, 39-74) receive treatment with drugs of this group: 15 people — alirocumab, 16 people — evolocumab. A protocol for patient management using PCSK9 inhibitors was developed; reminders for primary care physicians and for patients receiving these drugs were created.

Krasnodar Krai

In the Krasnodar Krai, two lipid offices have been created — on the basis of Research Institute (RI) of Regional Clinical Hospital (RCH) № 1 and RCH № 2, supporting with the Therapy Department № 1 of the Kuban State Medical University.

The lipid office on the basis of RI-RCH № 1 began to work in March 2017, where patients with suspected FH, as well as patients with very high CVR, are referred for consultative and diagnostic assistance.

In 2019, an office for patients with lipid metabolism disorders began working on the basis of RCH № 2. The office functions as a subdivision of outpatient cardiology department of the ambulatory clinic for specialized course outpatient treatment of RCH № 2. Organized in 1989 as an experimental project, for more than 30 years, this polyclinic provides high-quality outpatient care for patients in the Krasnodar city and Krasnodar Krai, working in conjunction with a diagnostic center. Its peculiarity is the possibility of conducting not only one-time consultations, but also performing diagnostic and therapeutic interventions within repeated visits of patients, during which a diagnostic search and selection/adjustment of therapy is carried out.

Since both hospitals are the main medical institutions of the Krasnodar Krai, patients in lipid offices receive comprehensive laboratory examination and vascular screening — from non-invasive techniques (ultrasound, exercise stress tests) to computed tomography angiography and coronary angiography. If necessary, hospitalization in specialized departments for surgery is possible. The organization of lipid rooms based on hospitals with a powerful diagnostic potential and the availability of X-ray endovascular diagnostics is the best solution.

Indications for referral to lipid office are:

- Total cholesterol >8 mmol/L;
- LDL cholesterol $>4,9$ mmol/L;
- Lipoprotein (a) >30 mg/dL;
- Triglycerides >10 mmol/L;
- Failure to achieve target LDL-C levels using highest tolerated doses of statins;

- Combination of atherosclerotic CVD with diabetes, as well as the rapid progression of atherosclerosis, despite therapy with highest tolerated doses of lipid-lowering drugs.

Participation in the all-Russian register allows to create a database of patients with FH, which makes it easier to enroll patients in regional and federal programs of subsidized pharmaceutical provision (PCSK9 inhibitors). Another function of these offices is to select patients with severe hypercholesterolemia to participate in international clinical trials with promising lipid-lowering molecules. Specialists of lipid offices are also employees of the Therapy Department of the Kuban State Medical University and carry out educational activities among residents and cardiologists of the Krasnodar Krai.

Nizhny Novgorod Oblast

Taking into account the great urgency of cardiovascular morbidity, in March 2019, a regional lipid center was created on the basis of Nizhny Novgorod City Clinical Hospital № 5, according to the order of the Ministry of Health of Nizhny Novgorod Oblast № 315-131/19P/od dated March 1, 2019.

There are following indications for referral to the lipid center: hyperlipidemia (total cholesterol >7,5 mmol/L, or LDL >4,9 mmol/L, or triglycerides >10 mmol/L), requiring a high-dose and/or combination therapy with lipid-lowering drugs; early CVDs, including revascularization (<55 years of age), requiring aggressive secondary prevention; suspected intolerance to lipid-lowering therapy due to side effects or its insufficient effectiveness; patients of difficult clinical situations to consider a lipid-lowering therapy.

Patients are referred to the lipid center with above indications from outpatient clinics: from primary prevention offices, from general practitioners, cardiologists, endocrinologists. Also, the patients are referred to the lipid center by internal selection (counseling service of city cardiology dispensary specialists, as well as among patients discharged from the primary vascular centers and cardiology departments of Nizhny Novgorod CCH № 5, who, if indicated, are referred by hospital-based physician) and self-referral. Today, the referral ways to the lipid center are now distributed as follows: internal selection — 78,1%, external referral — 15,1%, self-referral — 6,8%.

Due to the small proportion of patients referred by external medical centers, one of the priority areas of the lipid center today is the widespread dissemination of information on its functioning and specifics of referring patients with lipid metabolism disorders. During 2020, 372 patients were consulted (small number of consultations are associated with the COVID-19 pandemic and related restrictions). More than 40 patients with FH and 1 patient with severe familial hypertriglyceridemia are followed up.

Currently, 73 patients with LDL >4,9 mmol/L are regularly followed up in the regional lipid center, of which 38 (52,1%) receive PCSK9 inhibitor therapy. The main funding sources to receive PCSK9 inhibitors are compulsory medical insurance funds (resource of diagnostic related groups) (n=20; 52,6%) and federal benefits (n=18; 47,4%).

All patients have prior CVD, including CAD (86,3%) and/or peripheral arterial atherosclerotic diseases (45,2%). In more than half of the patients, CAD developed at a young age (women, <60; men, 55). Most patients had prior recurrent cardiovascular events and a history of revascularization. As a result, all followed up patients have very high or extremely high CVR (63,1% and 36,9%, respectively). At the same time, in the subgroup of patients receiving PCSK9 inhibitors, the proportion of individuals with extremely high is naturally higher and amounts to 55,3%.

A significant proportion of patients in the lipid center have a hereditary predisposition to lipid metabolism disorders. Sixteen (21,9%) patients had relatives with a certain FH. More than one third of patients (35,6%) had a family history of CVD. According to the Dutch Lipid Clinic Network (DLCN), the FH was established in 26 (35,6%) patients, probable — 15 (20,5%), possible — 14 (19,1%) patients. As a result, 55 patients out of 73 (75,3%), with varying degrees of probability, could have FH. The limited genetic testing potential makes it difficult to make an accurate diagnosis and makes it difficult to predict treatment strategy. Treatment of patients with PCSK9 inhibitors showed high efficiency in achieving target LDL levels (although it was used in the most severe patients, among whom more than half had extremely high CVR). During treatment, the LDL decreased to ≤1,0 mmol/l in 23 (60,5%) patients, ≤1,4 mmol/l in 27 (71,1%), ≤1,8 mmol/l in 33 (86,8%).

Perspectives

The creation of a network of lipid centers will make it possible to effectively implement the strategy for managing lipid metabolism disorders both in high-risk groups and at the population level. The introduction of uniform standards for managing dyslipidemia will ensure a high-quality care for each patient, and the network structure will ensure the availability of consultations by leading specialists in difficult cases. The ideology of this project implies a further expansion of the structure and its openness; all data on joining the project is available on the RSC website (available at: https://scardio.ru/proekty/sovместnye_proekty_s_amdzen/proekt_evropeyskogo_obschestva_po_aterosklerozu_lipid_clinics_network/).

Relationships and Activities: none.

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