Title of Project. Russian research program evaluating the extent of underdiagnosed and undertreated of familial hypercholesterolaemia in the working-age population.

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Abstract

Purpose. Actual prevalence of familial hypercholesterolaemia (FH) in the Russian Federation is unknown, hence the main aim of the present study is to evaluate the extent to which FH is underdiagnosed and undertreated in the Russian Federation.

Scope. During 2014-2016 one core and 14 local centers included 640 patients with total cholesterol ≥ 7.5 mmol/L, or low-density lipoprotein cholesterol (LDL-C) ≥ 4.9 mmol/L.

Methods. The Russian FH Registry (RuFH) is a multicenter, national registry that is enrolling patients diagnosed with FH from outpatient practices. The patients evaluation consists of clinical status and risk factors profile assessment, blood sampling, ultrasound exam of heart and carotids, and Achilles tendon, adequacy of lipid-lowering therapy.

Results. As an expected outcome, this program raised awareness and increased appropriate assessment and treatment of FH patients.

Key Words: Familial Hypercholesterolemia; Registry; Atherosclerosis; Prevention.

Purpose. *Study Objectives*

The main aim of the present study is to evaluate the extent to which FH is underdiagnosed and undertreated in the Russian Federation for global reduction of cardiovascular risk in the country. The RuFH initiative has several key objectives: 1) to estimate the prevalence of FH patients and to determine the number of heterozygous and homozygous forms in the Russian Federation, 2) to evaluate the distribution of Lp(a) in individuals diagnosed with definite and probable FH, 3) to reveal the severity of carotid atherosclerosis, aortic valve stenosis and coronary heart disease in Russian patients with FH, 4) to determine *PCSK9 concentration in patients with severe hypercholesterolemia*, 5) to compare the clinical significance of the Dutch Lipid Clinic Network criteria and the Simon Broome Registry criteria for diagnosing FH in Russian adults, 6) to assess the prognosis of individuals with FH. The main outcome measure is the increase in the number of FH patients treated appropriately according to current lipid-lowering strategies and the reduction in risk of ASCVD associated with FH.

We see the opportunity for further innovative research work in this area with the establishment of the standardized electronic medical tool. The focus of the Program is aimed at cardiologists, endocrinologists, primary care providers (internists, general practitioners from the outpatients units (policlinics)), public health practitioners, healthcare providers, patients in the Russian Federation.

Scope

Background and Context.

The contribution of cardiovascular diseases (CVD) to total mortality of the Russian population is 57%; they dominate among the causes of hospitalization and disability. In 2012, the mortality rate associated with CVD in Russia was 729.3 cases per 100,000[1], whereas in the developed European countries it is 3 to 4 times lower.[2] Coronary heart disease (CHD) is the leading cause of cardiovascular mortality (397 cases per 100,000, or 53%), followed by cerebrovascular disease (233 cases per 100,000, or 31%).[3] In 2011, among Russians the mean absolute decrease in CVD mortality for men amounted -39.7 cases per 100,000; among women - -24.9 cases per 100,000 as compared to 2002.[4] Although significant progress has been made over the past decades, life expectancy in Russia is 8 to 11 years shorter than in the European Union. The economic costs associated with CVD in Russia are about 1 trillion rubles annually ($30 billion). The following seven risk factors are shown to contribute to premature death in Russia: hypertension (35.5%), hypercholesterolemia (23%), smoking

(17.1%), insufficient intake of fruits and vegetables (12.9%), obesity (12.5%), excessive alcohol consumption (11.9%), and physical inactivity (9%).

The results of a large Moscow Screening Project with participation of 52,075 individuals has shown that the median for total cholesterol (TC) in men over 30 and women over 35 years significantly exceeds the level of 5.0 mmol/L, defined as optimal for the population of healthy people.[5] In a study performed in the Western Administrative District of Moscow, of the 2,400 persons who had attended outpatient clinics due to any health related matters, the level of TC above 7.5 mmol/L was detected in 12.2% (n = 291) and LDL-C level above 4.9 mmol/L was observed in 10%. Among the study participants, there were patients with CHD (36%), as well as individuals at various cardiovascular risk according to the SCORE chart.[6]

Settings, Participants, Incidence, Prevalence

Despite combined efforts of the Government and medicine community during last 5 years (the national project Health, the newly built Primary and Regional Vascular Centers all over the country), CVD mortality remains high. The proposed high FH prevalence that is underestimated could largely impact CVD epidemiology. We stipulate that in the Russian Federation the actual number of such patients aware of their disease is unknown, and could be estimated at about 1%.

The estimated number of patients with FH in Russia is at least 300,000 with the heterozygous form and approximately 140-280 with the homozygous form. It must be emphasized that FH is mostly not diagnosed in Russia and as the result the true number of patients with FH who are not receiving adequate treatment is unknown. Currently, estimates of the incidence of the disease in Russia are based on the results of epidemiological studies conducted in other countries. Thus, the available statistics is merely the result of extrapolation of foreign studies.

Study population and design

Approval of study protocol from the Local Ethics Committees was obtained in all participating centers. All patients gave a signed informed consent form.

The RuFH is a prospective, population-based, multicenter study. Subjects of both sexes above the age of 18 with TC ≥7.5 mmol/L or LDL-C ≥4.9 mmol/L were included in the Program. Those with secondary causes of hypercholesterolemia, such as untreated diabetes mellitus (HbA1c >8%) or hypothyroidism (thyroid-stimulating hormone >1.5 upper normal limit), renal failure (creatinine clearance <30 ml/min), holestatic liver diseases, including

biliary cirrhosis, tumors with an active process in the last 5 years were excluded from the study.

During the first phase of the Program, a database of individuals with TC levels ≥7.5 mmol/L (290 md/dL) and/or LDL-C ≥4.9 mmol/L (190 mg/dL) was set up from a random sample of the Moscow adult population, including 18,000 people. The INVITRO Research Laboratory has provided the data of consecutive individuals who agreed to participate in the Program and who had lipid panel measurement during one randomly taken month in 2013. Levels of TC ≥7.5 mmol/L (290 md/dL) were observed in 1505 individuals (8%). The potentially eligible participants suspected for FH were sent a notification letter describing high cholesterol level, atherosclerosis risk status and need for additional screening. Through 2014 to 2016, the potential participants were invited to the Russian Cardiology Research and Production Center through Email.

The second phase of the Program started in 2015 and included Federal Medical Centers in Saint Petersburg, Chelyabinsk, Novosibirsk, and Kazan. The cities are selected based on the availability of 1) health facilities with trained health personnel, necessary equipment and analysis methods and 2) technological facilities of the INVITRO laboratory. Of note, during study progress several additional regional medical centers joined the Project **(Table 1)**. According to the standard protocol, regional participating centers enrolled and examined 240 patients.

Data Sources/Collection

The Web-based RuFH registry was developed as a part of Electronic Medical System (EMS), located at the official portal of Russian National Atherosclerosis Society – www.noatero.ru

Access to the EMS is provided through encrypted Web-protocol (SSL) with logins and passwords that were securely given to the admitted regional medical centers as they were consecutively connected to the system. The current preference is to use high complexity engine-generated passwords and to provide one login-password pair per center (for the responsible investigator). All participating centers are able to fill personal forms for the patients with suspected FH that are examined within those centers. The Web form contains all the required information about clinical, demographic data, medical history, current diagnostic, treatment and management information, the list of the fields is identical to the approved hard-copy Patient Registration Form that was sent to the centers. Every medical site is able to view some statistical data regarding this particular site. However, the full statistics is available exclusively from the Core Center – Russian Cardiology Research and Production Center.

The development of the EMS was started in April, 2014, and finished in November, 2014. During December, 2014, the investigators of the Core Center were trained to operate with web-forms. In January, 2015, the Core Center was connected to the EMS and web-based registration of the patients was initiated. During February all hard-copied archived of FH patients examined in the Core Center were entered to the web form. Since March, 2015, all actions regarding patient registration were performed using the web form and the hard-copied form simultaneously. Also in March the tutorial video explaining operation with the EMS was created and made open-accessed for all participants (URL: https://noatero.ru/ru/registr-rosghs). Since March the process of regional centers connection was initiated. Up to date (Feb. 11, 2016), 10 more centers are connected, and the data regarding 643 patients is stored in the Web database. **Table 1 represents the list of the participating centers and Fig. 1** reflects their contribution to the patient enrollment. The majority of patients currently registered are from Moscow (RCRPC, Core Center), Novosibirsk, Saint-Petersburg and Chelyabinsk centers.

Table 1. The list of participating centers and dates of their connection to the EMS.

Center ID	Center name	City	Date of connection
1	Russian Cardiology Research and Production Center	Moscow	Jan. 2015
2	Research Institute of Internal Medicine	Novosibirsk	Mar. 2015
3	Saint-Petersburg State University	Saint-Petersburg	Mar. 2015
4	Military Medical Academy	Saint-Petersburg	Mar. 2015
5	Chelyabinsk State Medical Academy	Chelyabinsk	Apr. 2015
6	Samara State Medical University	Samara	Apr. 2015
7	Ural State Medical University	Ekaterinburg	Apr. 2015
8	Interregional Clinical and Diagnostic Center	Kazan’	Jun. 2015
9	Therapy Center of Karelia	Petrozavodsk	Jul. 2015
10	Regional Clinical Consultative and Diagnostic Centre	Stavropol’	Oct. 6, 2015
11	Central Military Clinical Hospital	Moscow	Oct. 13, 2015

12	Sakhalin Regional Hospital	Yuzhno-Sakhalinsk	Oct. 25, 2015
13	Laboratory of Clinical Lipidology	Moscow	Oct. 31, 2015
14	City Polyclinic №15	Samara	Nov. 11, 2015
15	Regional Clinical Center of Diagnostics and Cardiac Surgery	Surgut	Jan. 12, 2016

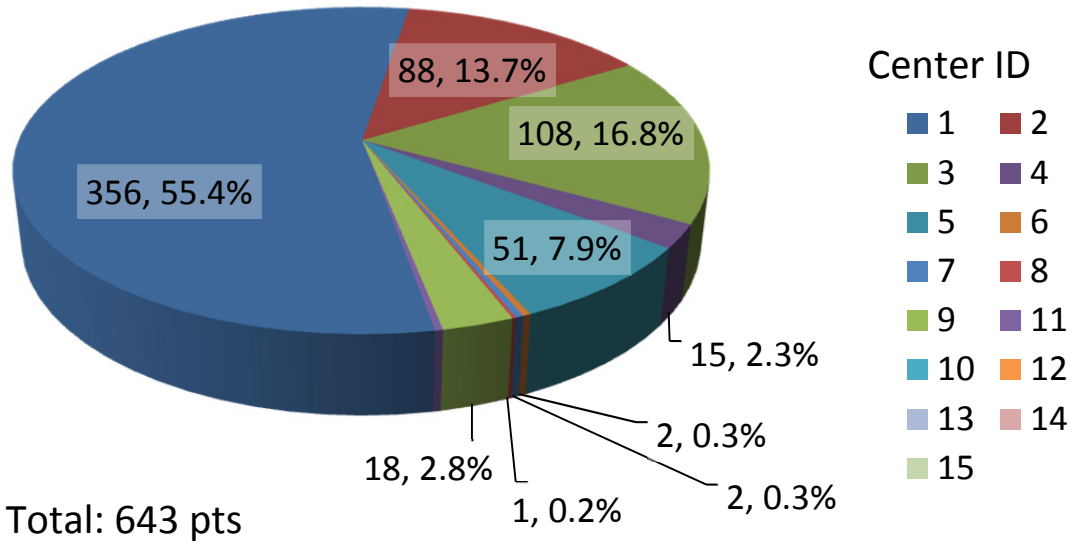

Fig. 1. Contribution of the centers to the patient enrollment.

Interventions, Measures, Limitations

At a screening visit, all participants signed an informed consent form. As a next step, patients completed specifically designed questionnaires which include contact details, information on atherosclerosis risk factors, history of cardiovascular diseases, current diet and medical therapy with a detailed description of the lipid-lowering drugs. All laboratory and instrumental methods are presented in **Fig. 2**. Clinical diagnosis of FH was established Dutch Lipid Clinic Network and Simon Broome Criteria. Patients with FH were provided with information about screening first-degree relatives, and additional educational materials about FH.

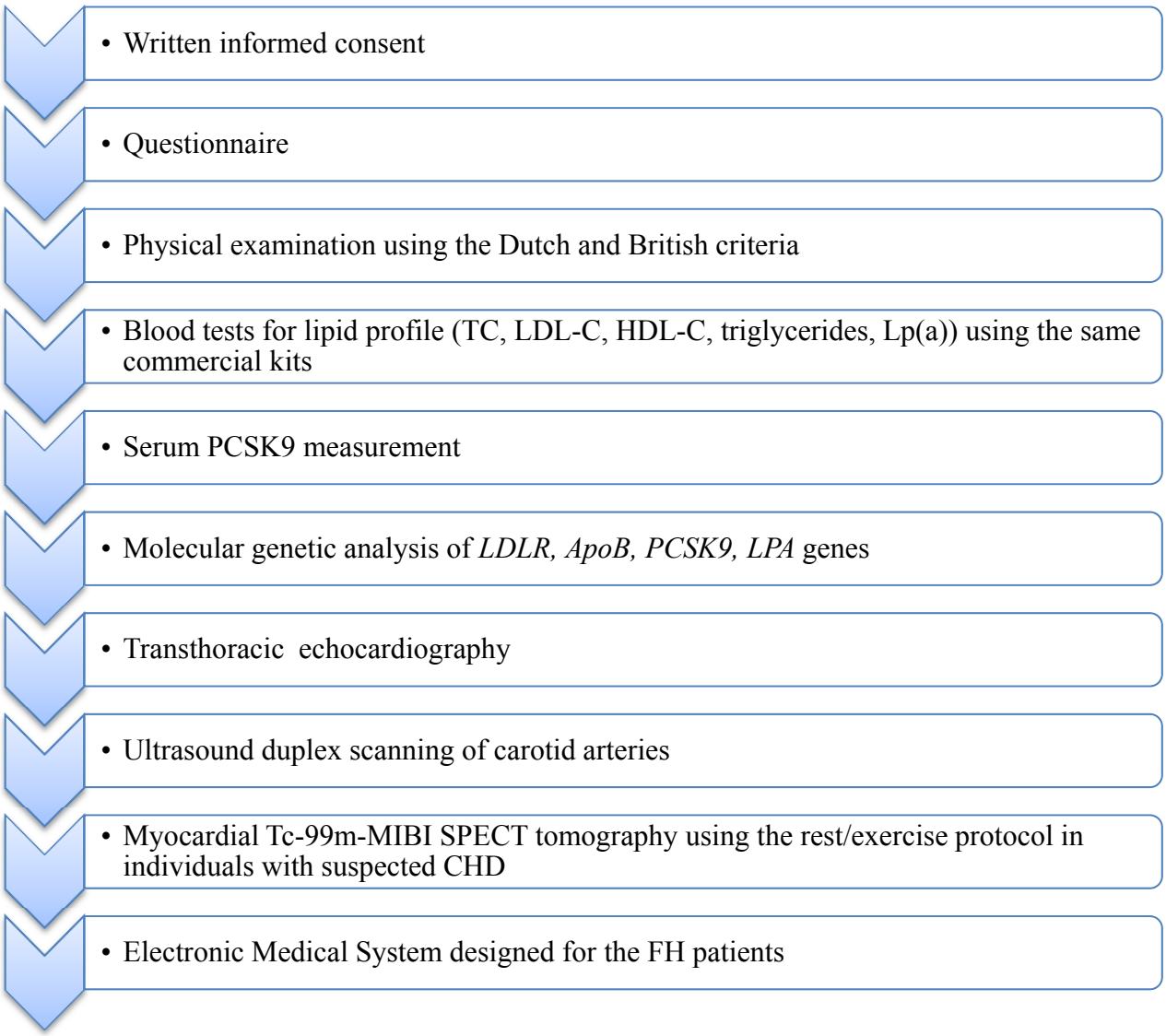

Figure 2. Screening visit assessments.

Blood specimens were collected and serum after centrifugation as well as EDTA plasma were archived at -70C. The genetic sub-study of FH-causing mutations is intended to include 60 individuals with established (8 scores or more, n = 30), and probable (6-8 scores, n = 30), FH diagnosis according to the Dutch criteria.

Lp(a) concentration was determined by enzyme-linked immunosorbent assay using monospecific polyclonal sheep anti-human-apo(a) antibodies as previously reported[7]. PCSK9 levels were measured by enzyme-linked immunosorbent assay with commercially available kit (RnD Systems, USA).

The Russian Cardiology Research and Production Center is the academic coordinating center which provides the Program oversee and feedback. The independent Executive

Scientific Committee includes representatives from the RNAS from other centers. The study is not designed to evaluate any specific treatment or other intervention, and therefore a calculation for the statistical power of the study has not been performed. Standard statistical analysis of the data was performed using the STATISTICA software (StatSoft Inc., Russia).

Results (Principal Findings, Outcomes)

Clinical and chemistry characteristics of the study patients are presented in Table 2. A total of 643 patients (66% female, mean age 53.15 years) were recruited in 1 main and several district cardiology clinics. All patients had primary hypercholesterolemia. Hypertension is diagnosed in 54%, family history of premature CVD in 32%, current smoking is in 13%, diabetes mellitus is in 6%. IHD was diagnosed in 18% of participants.

More than 15% of patients have definite FH in accordance with Dutch and Simon Broome criteria (Fig. 4, 5). Mean total cholesterol - 9.2±2.0 mmol/L, LDL cholesterol - 6.3±1.7 mmol/L, Lp(a) - 37±44 mg/dL, PCSK-9 - 382±148 mg/dL. We found positive correlation of PSCK9 level with Lp(a) - r= 0.201, p=0.0030; LDL-C - r= 0.17, p=0.0095; TC - r=0.174; p=0.0108; TG - r=0.216, p=0.00014.

Only 24% were on treatment with hypolipidemic drugs. Titration of statins and achieving of target LDL-C were uncontrolled by patients at study initiation.

Duplex scan of carotid arteries was performed in 498 patients: atherosclerotic plaques were revealed in 432 (87%) subjects, only 17 (3.4%) of them had neurology signs due to stenosis >50%. Median carotid intima-media thickness is 0.70 (interquartile range 0.57-0.89) mm. Aortic valve stenosis was diagnosed on echocardiography in 13 (2.1%) patients of 638.

In accordance with Dutch criteria, definite heFH was diagnosed in 42 of 356 (11.8%) patients included in Core Centre. After that we calculated prevalence of definite FH in Russian Federation from total number of initially selected 18,000 subjects from population. It was approximately 1:100. If we excluded first-degree relatives invited to participate in register, we can assume that the true prevalence of definite FH in Russia is close to 1:200-250.

Table 2. Characteristics of 643 patients registered in the Electronic Medical System.

Variable		Value
Age, years		55 (47-61)
Males		217 (33.7%)
Body mass index, kg/m^2		26.8 (24.1-29.7)
Waist, cm		83 (75-92)
Heart rate, beats/min		70 (66-75)
Systolic blood pressure, mm Hg		128 (120-135)
Diastolic blood pressure, mm Hg		80 (75-80)
Achilles tendon thickening		76 (11.8%)
Achilles tendon thickening in relatives		25 (3.9%)
Maximal total cholesterol in history, mmol/l		8.6 (8.0-9.7)
Hypercholesterolemia in relatives	Yes	279 (43.4%)
	No	53 (8.2%)
	Unknown	311 (48.4%)
Patients that learned first time about personal hypercholesterolemia		106 (16.5%)
Hypolipidemic therapy	No therapy	489 (76.0%)
	Statins	127 (19.8%)
	Statins+ezetimibe	16 (2.5%)
	Other hypolipidemic therapy without statins	11 (1.7%)
Current blood tests	Total cholesterol, mmol/l	8.2 (7.7-9.0)
	LDL-C, mmol/l	5.9 (5.5-6.8)
	HDL-C, mmol/l	1.4 (1.2-1.7)
	Triglycerides, mmol/l	1.7 (1.2-2.4)
	C-reactive protein, mg/l	1.3 (0.6-3.7)
	Glucose, mmol/l	5.5 (5.0-5.8)
	Lipoprotein(a), mg/dl	19.4 (7.7-49.2)

	PCSK9, mg/dl	359.0 (288.8-447.7)
Comorbidities	Arterial hypertension	345 (53.7%)
	Smokers (including past smokers)	206 (32.0%)
	MI/Stroke/cardiac death in1st degree relatives before 60 years	206 (32.0%)
	Type 2 diabetes	40 (6.2%)
	Ischemic Heart Disease	118 (18.4%)
	MI	47 (7.3%)
	PCI	33 (5.1%)
	CABG	15 (2.3%)
	Peripheral arteries atherosclerosis	45 (7.0%)
	Ischemic stroke	13 (2.0%)
Heart failure class (NYHA):	I	24 (3.7%)
	II	29 (4.5%)
	III	3 (0.5%)
	IV	1 (0.2%)

Quantitative data is represented as median (1st-3rd quartile).

The results of the current registry data analysis are shown in **Figs. 3-6**.

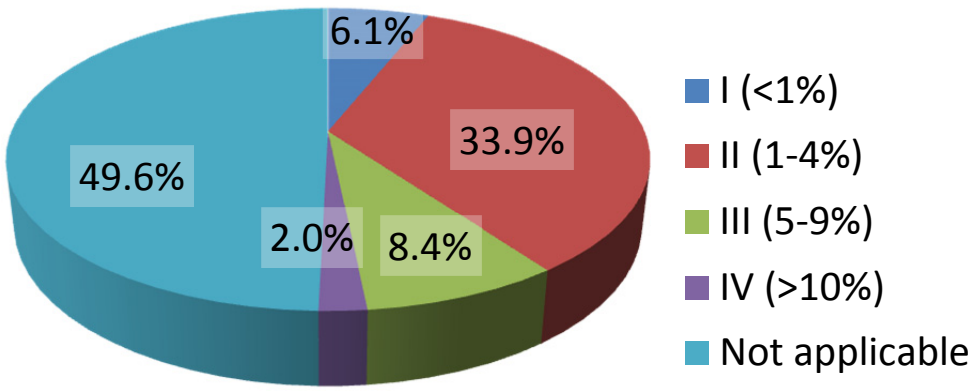

Fig. 3. SCORE risk category (n=643).

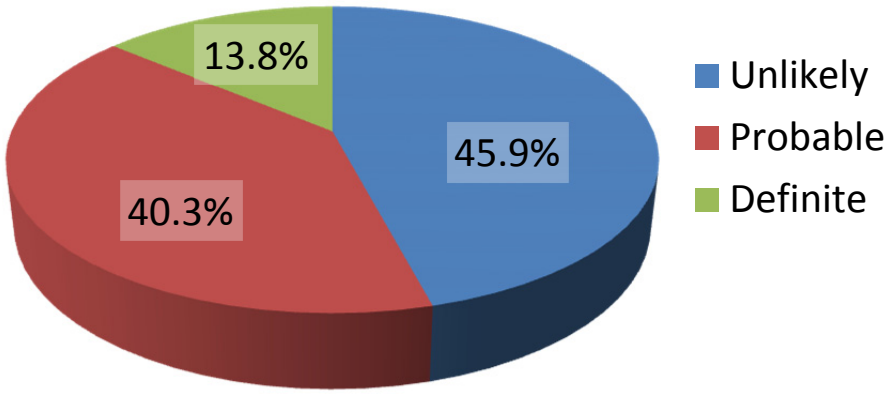

Fig. 4. FH probability according to the Simone Broom criteria (n=643).

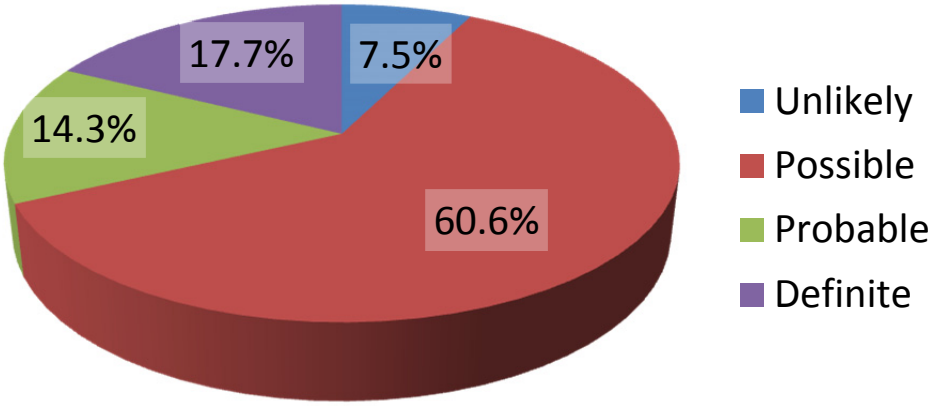

Fig. 5. FH probability according to the Dutch Lipid Clinic Network Criteria (n=589).

Note: Criteria calculations are not possible yet in 54 patients (no LDL-C data).

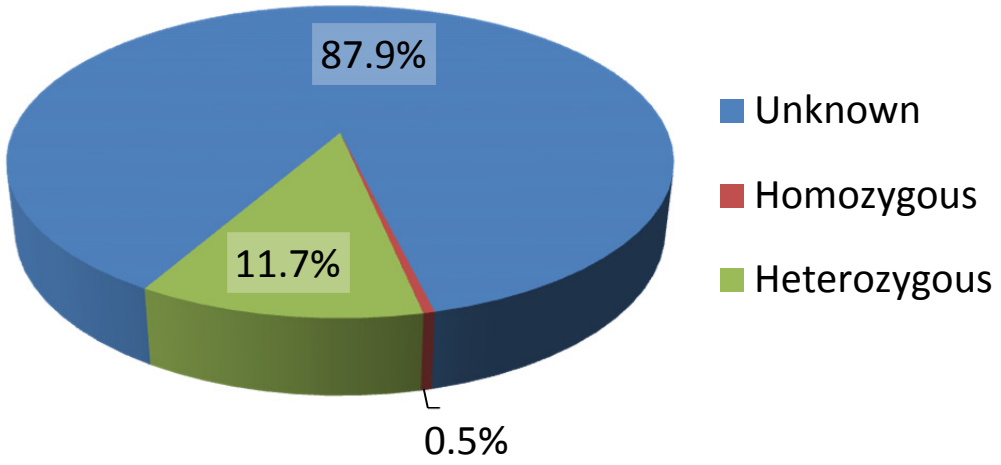

Fig. 6. FH type according to clinical/genetic data (n=643).

Discussion, Conclusions, Significance, Implications

We state the following facts: 1) the prevalence of heterozygous FH in Russia is higher than 1:500 and is approximately 1:250; 2) 85 per cent of patients with severe primary hypercholesterolemia have atherosclerotic plaques in carotid arteries; 3) aortic valve stenosis is diagnosed for the first time was revealed in 2 per cent of study participants; 4) Lp(a) levels above 30 mg/dl was obtained in 38% patients; 5) Dutch clinical criteria for the FH diagnosis are more useful for Russian population; 6) there is positive correlation between PCSK9 concentration and TC, Lp(a), LDL-C and triglycerides levels; 7) efforts on raising awareness of cardiovascular disease in FH were performed among patients, healthcare providers, population and government through educational materials, lipid schools, public relations.

We estimate that as a result of the RuFH initiative the percentage of people aware of their cholesterol level will increase up to 20% from the baseline, those who will receive statins will achieve the guideline-driven targeted LDL-C levels in 30% of cases. The percentage of physicians with an appropriate knowledge in FH will increase by an average of 30-50%.

High-intensity lipid-lowering therapy prescribed to this category of patients on a regular basis will lead to lower rates of cardiovascular deaths. Implementing this treatment strategy over the country will result in a significant decrease of spending.

We believe that the results of this study will for the first time provide the evidence base required by the health care system for changing its policy in the treatment of patients with FH. Establishing cholesterol thresholds depending on age and sex would lead to being able to detect subclinical atherosclerosis earlier. A combination of LDL-C measurement and

genetic analysis will identify the relatives of FH patients. All these efforts should improve the quality of care provided to FH patients in Russia.

Undoubtedly, FH is a socially significant problem that needs the involvement of patient organizations and government support. It should be noted that in the Russian Federation as well as in some other countries homozygous FH is not included in the rare disease list. FH is one of the few genetic diseases that meets the World Health Organization required criteria for the population-based large-scale screening programs aimed for early disease detection and its optimal management started timely. This approach is key for a successful primary prevention of CVD in FH patients within any particular region, the country, and the world. Using the data obtained from Federal State Statistics Service it is planned to assess the impact of this Program on cardiovascular mortality in geographic regions participating in the Program.

Conclusion

Epidemiological data suggest that the high rate of cardiovascular morbidity and mortality in Russia are partly due to an underestimation of the significance of hypercholesterolemia, including the high prevalence of FH. Timely detection of FH helps to initiate treatment not only in the indexed case, but also it motivates conducting a clinical and genetic screening of relatives, thus increasing the number of promptly diagnosed individuals. Until now in Russia there was no single system for FH patients' registration, which makes the present study unique. We propose that the innovative layout of the RuFH will allow to identify the FH prevalence in the Russian population and make a necessary adjustment to the existing diagnostic criteria. We suggest that only combining our efforts will usher in a new era of the battle against the threat of atherosclerotic cardiovascular disease.

Disclosures. None of the authors have financial relationships or conflicts of interest related to this study.

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