Lipid Clinic is an Efficacious Model of Preventive Medicine

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Background. A lipid clinic is a specialized center for the diagnosis and treatment of patients with impaired lipid metabolism.

Aim. To characterize patients accessing lipid clinic and assess the efficiency of treatment in a specialized medical center.

Material and methods. A retrospective analysis of the surviving medical records of outpatients who visited the lipid clinic of the National Research Center for Therapy and Preventive Medicine (Moscow, Russia) in 2011-2019 (n=675) was carried out. Cardiovascular risk (CVR) and target lipoproteins levels were evaluated in accordance with actual guidelines for the diagnostics and correction of dyslipidemias.

Results. The mediana of lipid clinic patients age was 57 [46;65] years. Female persons attend lipid clinic more often (61.5%). 48.5% of patients had low density lipoprotein cholesterol (LDL-c) >4.9 mmol/L, 7.7% had triglycerides level >5.5 mmol/L. Most of the patients were diagnosed with type IIa hyperlipidemia (44,1%) or type IIb (28,0%). Inherited impaired lipid metabolism was diagnosed in 27.7% individuals. 12.7% of the patients had familial hypercholesterolemia, 57.4% – had secondary causes of impaired lipid metabolism. More than half of the patients (52.4%) had low or moderate CVR, 28.1% had a very high CVR. High or very high CVR individuals revisited the lipid clinic more often than people with lower risk (68.2% vs. 35.4%). Revisiting patients (25.4%) reached LDL-c targets more often (33.3% of very high CVR patients; 45.5% of moderate-risk people) than in ordinary outpatient practice. High-intensity statin therapy was recommended for 32% of patients, and combined lipid-lowering therapy – for 14.8%. Among very high CVR individuals, combined lipid-lowering therapy was prescribed for 38.5%. Given the lipid-lowering therapy prescribed in the lipid clinic, LDL-c<1.8 mmol/L and <1.5 mmol/L will be achieved at 40.7% and 32.9% of patients with very high CVR.

Conclusion. Lipid clinic is an important part of the medical care system for long-term follow-up of patients with impaired lipid metabolism, and it is more efficient in achieving target values of lipids and correcting risk factors in comparison with the primary medical service.

Keywords: lipid clinics, hyperlipidemia, statins, outpatient practice, preventive medicine.

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Introduction

Lipid metabolism disorders (LMDs) are a wide group of heterogeneous diseases and conditions, both genetically determined and acquired, pathogenetically interrelated through lipid and lipoprotein metabolism abnormalities. In addition to hereditary LMDs (dyslipidemias, glycolipidoses) [1], there are a number of secondary LMDs that develop as a result of malnutrition, obesity, or liver (non-alcoholic fatty liver disease, cholestasis), kidney (chronic kidney disease, nephrotic syndrome), endocrine (diabetes, hypothyroidism) or autoimmune disorders [2]. LMDs play a key role in the pathogenesis of atherosclerosis [3], contributing to the development of liver or pancreatic problems, such as hypertriglyceridemia-induced acute pancreatitis [4], or cosmetic problems, such as xanthoma or xanthelasma [3]. Atherosclerosis, in turn, is the leading cause of coronary heart disease and strokes, which are among the major contributors to mortality worldwide [5].

Keeping lipoprotein levels under control is an essential part of primary and secondary prevention of cardiovascular diseases (CVDs) of atherosclerotic

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origin [6]. However, despite the current recommendations, the target LP values are often not achieved in routine clinical practice. According to the 2016 retrospective outpatient chart register REKVAZA, no patients classified as high risk or extremely high risk had reached the low density lipoprotein cholesterol (LDL-C) goals [7]. Evaluation of outpatients as part of ARGO study showed that total cholesterol (TC) <4 mmol/L was achieved only in 2.04-7.38% of cases, depending on the combination of pre-existing CVDs, with the majority of the examined individuals identified as extremely high cardiovascular risk (CVR) [8]. According to EUROASPIRE V survey, only 29% of patients reach LDL-C levels of <1.8 mmol/L six months after hospitalization for a coronary event [9].

Lipid Clinics (LCs) are intended to serve as a tool of preventive medicine for the effective management of patients with LMDs and/or non-achievement of the LP goals. Since 2011, the National Medical Research Center for Internal Medicine and Preventive Care (NMRC TPM) of the Ministry of Health of Russia has been running a Lipid Clinic to provide consultations and long-term management of patients. The referral to the Lipid Clinic of the NMIC TPM is based on the following criteria: LDL-C >4.9 mmol/L; triglycerides (TG) >5.5 mmol/L; intolerance to statins; lipid-lowering therapy (LLT) in patients with contraindications to statins/ezetimibe; indications for multidrug LLT; suspected hereditary dyslipidemia; early development and/or rapid progression of atherosclerosis in a patient or their close family; failure to achieve the lipid goals despite an ongoing LLT.

This study aimed to analyze the pool of patients presenting to the Lipid Clinic, and to evaluate the efficacy of treatment in a specialized lipid center setting.

Material and methods

A retrospective analysis was performed on the outpatient medical records of patients who had visited the Lipid Clinic of the National Medical Research Center for Internal Medicine and Preventive Care between 2011 and 2019. The study included data from 675 patients.

The diagnosis was made in line with the ICD-10 classification or in accordance with the Fredrickson's classification adopted by the World Health Organization as the international standard nomenclature for hyperlipidemias (HLPs) [10]. The CVR scores and LP goals were assessed according to 2016 ESC/EAS guidelines and 2017 Russian guidelines for the diagnosis and correction of dyslipidemias [6,11].

Of all lipid metabolism parameters, total cholesterol, LDL-C, high density lipoprotein cholesterol (HDL-C), triglyceride, and lipoprotein (a) levels were measured. The diagnosis of hyperlipoproteinemia (a) was based on lipoprotein (a) levels >30 mg/dL.

The patients' histories of ongoing or previous CVDs and sequellae were analyzed. Peripheral atherosclerosis was defined as the presence of atherosclerotic plaques in the extracranial brachiocephalic arteries, renal arteries, or arteries of the lower extremities identified by duplex ultrasound or angiography. Atherosclerosis was considered significant if an atherosclerotic plaque narrowed an artery lumen by ⩾50%, with or without signs of plaque instability.

The patients of Lipid Clinic were assessed for the following secondary HLP causes: unhealthy diet (including excessive alcohol consumption), metabolic changes such as excess body weight, obesity, non-alcoholic fatty liver disease, type 1 or 2 diabetes, hypothyroidism (thyroid-stimulating hormone >10 μIU/ml), polycystic ovary syndrome, chronic kidney disease (GFR <60 ml/min/1.73m^2), cholestatic syndrome, and HLP-inducing medications. Alcohol consumption was assessed based on data from medical records compared against the validated AUDIT questionnaire [12]. A score of ⩾8 indicated hazardous drinking behaviour.

To assess the intensity of statin therapy, the doses of various statins were converted to an equivalent dose of atorvastatin.

The results were processed using the Statistica 8.0 software package (Statsoft Inc., USA). Data were assumed to be normally distributed if the Shapiro-Wilk's test was >0.05. Since most of the compared variables showed non-normal distributions, the data are presented as median values (25-75 percentiles).

Results and discussion

Clinical characteristics of the patients included in the study are presented in Table. 1.

The majority of patients presenting to the Lipid Clinic were middle aged (median: 57 years) and predominantly female. 48.5% of patients had severe hypercholesterolemia (LDL-C >4.9 mmol/L), while extremely high TG levels (>5.5 mmol/L) were detected in 7.7% of patients, which alone may be suggestive of hereditary dyslipidemia.

An early onset of atherosclerosis in working-age individuals is usually associated with hereditary LMDs. Specialized lipid centers are the best diagnostic tool for hereditary LMDs [13]. A review of performance of a lipid center at the District Cardiology Center in Surgut showed that 36.2% out of 900 patients consulted per year were diagnosed with primary hypercholesterolemia, and 28.4% had mixed HLP [14].

In our LC, the majority of patients were diagnosed with type IIa (44.1%) or IIb (28.0%) hyperlipidemia. Hereditary LMDs were diagnosed in 22.7% of patients. Among these, the most common diagnosis was familial hypercholesterolemia (FH; 55.8%), which is the most common hereditary LMD [15,16]. It is important to know that FH was diagnosed in every eighth patient. The percentage of isolated hypertriglyceridemia and combined hereditary HLP was 4.9% and 4.7%, respectively. One patient was diagnosed with familial hypobetalipoproteinemia confirmed by genetic testing (a mutation in the APOB gene). A cascade screening revealed familial hypobetalipoproteinemia in the son and father of the proband [17].

An elevated plasma lipoprotein (a) level is another independent risk factor for the development of CVD [18]. Hyperlipoproteinemia (a) was detected in 57 (8.4%) patients of our Lipid Clinic. Of these, an isolated increase in lipoprotein (a) >30 mg/dL, without any other LMDs, was revealed in 2 patients. By contrast, 19 (33.3%) patients had a combination of hyperlipoproteinemia (a) with other hereditary dyslipidemias. The percentage of individuals with hyperlipoproteinemia (a) among patients with FH was 16.3%, which, probably due to the lack of relevant data in some patients, was 3 times less than would be expected according to the RENAISSANCE register reporting increased lipoprotein (a) levels in 42% from a total of 1208 patients with heterozygous FH [19]. Patients with FH typically have more frequent elevations in lipoprotein (a) than the average frequency in the population [20].

The median age of Lipid Clinic patients with hereditary LMDs was 49 years, indicating a rather late arrival of LMD patients to a specialized center. Early identification of hereditary LMDs is extremely important, leading to early initiation of appropriate LLT, preventing the risk of developing or progression of CVD, acute pancreatitis, and enabling cascade screening in patients' families [3].

Table 1. Clinical characteristics of Lipid Clinic patients in 2011-2019 (n=675)

Parameter	Value
Male gender, n (%)	260 (38.5)
Age, years	57 [46; 65]
LP levels before LLT initiation	
TC, mmol/L	7.6 [6.5; 9.0]
LDL-C, mmol/L	5.1 [4.1; 6.3]
HDL-C, mmol/L	1.3 [1.1; 1.7]
Triglycerides, mmol/L	1.6 [1.1; 2.6]
Distribution according to type of dyslipidemia	
No diagnosis, n (%)	29 (4.3)
Hyperlipoproteinemia (a), n (%)	2 (0.3)
HLP IIa, n (%)	29 8 (44, 1)
HLP IIb, n (%)	189 (28.0)
Combined HLP, n (%)	32 (4.7)
FH, n (%)	86 (12.7)
Isolated hypertriglyceridemia, n (%)	33 (4.9)
Familial hypobetalipoproteinemia, n (%)	1 (0.1)
No LMDs, xanthelasmosis, n (%)	3 (0.4)
No LMDs, lipomatosis, n (%)	2 (0.3)
Diseases and conditions underlying secondary HLPs	
Excess body weight, n (%)	194 (28, 7)
Obesity, n (%)	
grade 1	100 (14.8)
grade 2	22 (3.3)
grade 3	7 (1.0)
Unhealthy diet, n (%)	50 (7.4)
Excessive alcohol consumption, n (%)	6 (0.9)
Fatty hepatosis, n (%)	96 (14.2)
Steatohepatitis, n (%)	23 (3.4)
Cholestasis, n (%)	6 (0, 9)
Hypothyroidism, n (%)	1 (0.1)
Polycystic ovary syndrome, n (%)	4 (0.6)
LMD-inducing medications, n (%)	4 (0.6)
Diseases causing high or extremely high CVR	
Coronary heart disease, n (%)	11 8 (17, 5)
Myocardial infarction, n (%)	68 (10.1)
Acute cerebrovascular accident or transient ischemic attack, n (%)	17 (2.5)
Significant peripheral atherosclerosis, n (%)	79 (11.7)
Diabetes mellitus, n (%)	53 (7.9)
Chronic kidney disease, n (%)	30 (4.4)

Data are presented as median values (25; 75 percentile) unless otherwise specified

LP – lipoproteins, LLT – lipid-lowering therapy, HLP – hyperlipidemia, TC – total cholesterol, LDL-C – low-density lipoprotein cholesterol, HDL-C – high-density lipoprotein cholesterol, FH – familial hypercholesterolemia, LMD – lipid metabolism disorder, CVD – cardiovascular risk

Much attention is also paid by the Lipid Clinic to the ruling out of secondary HLPs, which occurred much more commonly than, or concomitant with primary HLPs. Similar to primary LMDs, secondary LMDs can increase the risk of cardiovascular events, depending on the length of exposure to elevated LDL-C or TG levels. Identification and subsequent elimination or treatment of a secondary LMD cause can result in dose reduction or even cessation of LLT. In some cases, secondary LMDs could provide the key to the patient's underlying disease [2]. At our Lipid Clinic, 57.4% of patients had at least one secondary cause for LMD, with 16.9% having 2 or more of them. Some patients had as much as four concomitant secondary causes for LMD. One of the most common secondary LMD causes, increased body weight, has been reported in almost half (47.8%) of Lipid Clinic patients. Thus, 35% from a total of 238 patients with dyslipidemia followed up in a study at a UK-based Lipid Clinic, were obese [21]. Similar findings are reported by an Italian Lipid Clinic: the majority (69.0%) of 1657 patients in the study were overweight (49.8%) or obese (19.2%) [22]. Another cause of secondary HLP observed at our Lipid Clinic (18.5% of patients) were verified liver diseases.

Among all patients managed at the Lipid Clinic, 42 patients (6.2%) reported having side effects while on statins. Similar to previous studies, the most common event was muscle pain, alone (26.2%) or accompanied by creatine phosphokinase elevations (11.9%). In the EUROASPIRE V study, muscle pain was the main symptom in 62% of patients who reported statin intolerance [9]. Alanine aminotransferase (ALT) elevations were reported in 12 patients (28.6%). The percentage of patients reporting right upper quadrant abdominal pain was 11.9%. 7.1% of patients complained of indigestion. The contribution of all other symptoms was minimal and their causal relationship with statins could not be confirmed. During a clinic visit, 7 (0.84%) patients reported side effects while on ezetimibe, and 2 patients experienced them on fenofibrate.

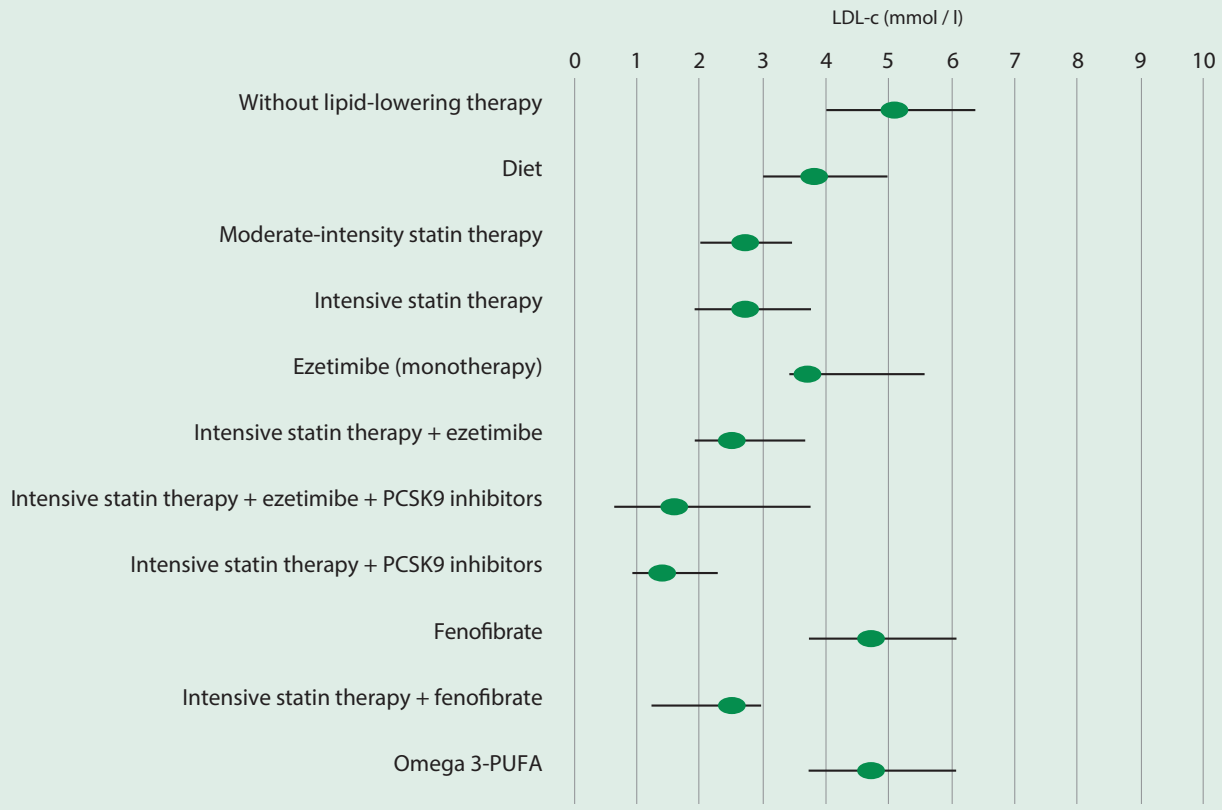
More than 50% of patients managed at the Lipid Clinic were those at low (24.7%) to moderate (27.7%) CVR. Similar findings were reported in a study reviewing the performance of four UK-based Lipid Clinics: 87% of patients referred to the LCs had no CVDs of atherosclerotic origin [23]. These findings may be indicative of patients' motivation to pursue a healthy lifestyle and to adhere to primary prevention. At our Lipid Clinic, the percentages of patients classified as high and extremely high CVR were 19.1% and 28.4%, respectively. Among patients at extremely high CVR, 59.4% had coronary heart disease, 25% had diabetes mellitus, and 18.2% had multifocal atherosclerosis. Follow-up of 1000 patients in a Greece-based Lipid Clinic showed the percentage of extremely high CVR patients of 48%, of which 44% had diabetes. Of those, 21% had diabetes concomitant with coronary heart disease, and 23% had diabetes with acute cerebrovascular accident [24].

Patients at high or extremely high CVR were more likely to return for follow-up visits (68.2% vs. 35.4% among individuals at low and moderate risk), which may indicate the need for long-term follow-up of patients in these high-risk groups and step-by-step adjustment of an appropriate LLT, and longer times to achieve the LP goals, as well as better adherence to therapy among high-risk individuals.

Baseline LP levels and clinical response to varying intensity treatments were analyzed (Figure 1, Table 2). Baseline (pre-LLT) LDL-C levels (5.1 [4.1; 6.3] mmol/L) were consistent with data reported by other LCs. Thus, in one of the Italian LCs, mean pre-LLT levels of LDL-C were 4.8±1.0 mmol/L in females vs. 4.3±1.3 mmol/L in males [22]. The median LDL-C level in non-treated FH patients was 7.6 [6.5;8.6] mmol/L, which is slightly higher than the data from patient registers for FH. Mean LDL-C level is reported to be 6.6 mmol/L [19] in the RENAISSANCE register and 6.2 mmol/L in the US national register [25]. This may be due to differences in diagnostic approaches (at our Lipid Clinic, the diagnosis of FH is based on a ⩾6 score according to Dutch DLCN criteria [3]).

Overall, the extent of LP reduction on different LLT regimens was consistent with the literature data [3]. Long-term case follow-up at a specialized center is considered to improve LLT efficacy. In the Alliance study, a 34.3% decrease in LDL-C was observed among 958 CHD patients on atorvastatin (mean dose 40.5 mg) followed-up at a US-based specialized center, vs. only 23.3% in the control group receiving LLT outside the LCs, suggesting lesser efficacy of LLT in an outpatient setting [26].

Analysis of patient data from LC confirmed the modern concept: in most cases, efficient LP reduction required the use of combination LLT [3]. As illustrated



LDL-c – low density lipoprotein cholesterol, PUFA – polyunsaturated fatty acids

Figure 1. Low-density lipoprotein cholesterol levels during different types of therapy

in Figure 1, only the administration of combination LLT including PCSK 9 inhibitors made it possible to achieve the LDL-C goals essential for the treatment of extremely high CVR patients.

In addition to drug therapy effects on LP, the effect of drug-free modalities was assessed, including diet, which led to an 18.6% reduction in LDL-C, and as much as 29.1% reduction in TG levels. Interestingly, a triglyceride lowering diet appeared to yield better results than a lipid-lowering diet did in regard to elevated LDL-C levels. The efficient diet-driven reduction in lipoprotein levels supports recommending it to all patients, regardless of the use or amount of LLT. The efficacy of last correction of therapy has not been

Table 2. Changes in lipoprotein levels during different polypidemic therapy

		Change, Δ%			
		LDL-C		Triglycerides	
Lipid-lowering measures	n (%)	Expected	LC	Expected	LC
Diet	35 (5.2)	-10 [3]	-18.6	⩾-10 [3]	-29.1
Moderate-intensity statin therapy	60 (8.9)	-(30-50) [3]	-38.3	-14 [33]	-22.5
High-intensity statin therapy	54 (8.0)	≈(-50) [30]	-47.2	-17 [32]	-18.1
Ezetimibe alone	7 (1.0)	-(15-22) [3]	-43.4	(-9,3) -0 [34]	-5.8
Moderate-intensity statin therapy + Ezetimibe	12 (1.8)	≈(-54) [31]	-54.1	≈(-30) [31]	-20.8
High-intensity statin therapy + Ezetimibe	10 (1.5)	≈(-65) [30]	-58.5	-(34-40) [31]	-30.0
High-intensity statin therapy + Ezetimibe + PCSK 9 inhibitors	3 (0.4)	≈(-85) [30]	-74.4		-46.6
High-intensity statin therapy + PCSK 9 inhibitors	6 (0.9)	≈(-75) [30]	-76.5		-14.0
Fenofibrate	8 (1.2)	-(5-20) [30]	-19.1	-(20-50) [30]	-56.1

LDL-C – low density lipoprotein cholesterol, LC – Lipid Clinic

assessed in all patients, but even so the LP goals appeared to reached more often in the Lipid Clinic setting than in routine outpatient practice [7,8]. This is also consistent with the findings of the Italian LC that evaluated patients referred to the LC by general practitioners: only 20% of high CVR patients on statins had LDL-C levels of <2.6 mmol/L [22]. In the International Cholesterol management Practice Study (ICLPS), only 32.1% of extremely high CVR patients on LLT reached LDL-C levels of <1.8 mmol/L [27].

Overall, among patients managed at our Lipid Clinic, 17.9% of high CVR patients and 18.8% of extremely high CVR patients achieved the LDL-C goals of <2.5 and <1.8 mmol/L, respectively. At the same time, patients who visited the LC repeatedly reached the LDL-C goals more often, which can be explained by the use of more intensive LLT due to the possibility to monitor the LP values over time, as well as the increased adherence to therapy with long term follow-up. Among the extremely high CVR patients on follow-up LC visits, 33.3% reached LDL-C levels of <1.8 mmol/L vs. 15.7% at the first visit, and levels of <1.5 mmol/L was reached by 19.6% vs. 5,9%; among high CVR patients, 33.3% vs. 9.5% reached the target levels of <2.5 mmol/L; among moderate CVR patients, 45.5% vs. 27.3% reached the target LDL-C level <3.0 mmol/L; and among low CVR patients, 66.7% vs. 41.7% reached the LDL-C goal of <3.5 mmol/L, respectively. Gavish D. et al. report more frequent achievement of LP goals (LDL-C <2.5 mmol/L) with repeated LC visits in patients needing secondary prevention of CVD (57% vs. 22% at the first visit) [28].

It should be noted that among FH patients who visited the LC repeatedly, 24% of patients reached the target levels of <2.5 mmol/L vs. 4% before the first LC visit, and 13.3% of patients reached LDL-C levels of <1.8 mmol/L vs. 0 patients, respectively. Prior to the first LC visit, no patient with familial hypertriglyceridemia or combined hyperlipidemia had target TG levels of <1.7 mmol/L but 19.4% of patients had reached it subsequently.

Before presenting to our Lipid Clinic, 12.7% of patients had used high-intensity statin therapy vs. 32% after visiting the LC. It is important to observe that combined LLTs are more often prescribed at specialized lipid centers, which has been confirmed by a number of foreign studies. A database review on 339 patients of UK-based LCs showed that only 8.5% of patients were using combined LLTs at the date of first LC visit, while subsequently the percentage of such patients increased to 48.4% [29]. At our Lipid Clinic, 4.4% of patients received combined LLTs at the first visit vs. 14.8% of patients by the time of a follow-up visit. Among the extremely high CVR individuals, 38.5% received combined LLT vs. 14.1% before the LC visiting. Of all patients with extremely high CVR, 167 had available LDL-C values during the first visit; before the first LC visit, target LDL-C levels of <1.8 mmol/L were reported in 9.0% of patients, and values of <1.5 mmol/L were reported in 4.8% of patients. Based on the expected LDL-C reduction (Table 2) it was estimated that, with the prescribed LLT, the LDL-C goals could be eventually reached by another 31.7% and 28.1% of patients, respectively. The percentage of patients using PCSK 9 inhibitors at the time of our LC's data review was still low due to low access to the drug. It is expected that wider use of combined LLT, including PCSK 9 inhibitors, may increase the percentage of individuals reaching the LDL-C goals.

Conclusions

In the age of personalized medicine, the creation of specialized lipid centers becomes an important and urgent task. The possibility for in-depth examination of patients, including molecular genetic techniques, makes Lipid Clinics a unique tool for diagnosing hereditary LMDs and performing cascade screening in patients' families. Verification of the exact origin of HLP, timely prescription of pathogenetically substantiated, highly efficient LLT, or LLT adjustment in difficult clinical situations make lipid centers more effective in achieving lipoprotein goals and reducing the risk factors as compared to primary health care facilities.

Relationships and Activities: none.

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