Mehman N. Mamedov

TREATMENT OF DYSLIPIDAEMIA:
from recommendations to clinical practice

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Treatment of dyslipidaemia: from recommendations to clinical practice

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Although water is as clear as a pearl
To overdrink it means to suffer harm.

Nizami Ganjavi

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List of abbreviations

ACC	American College of Cardiology
ACS	Acute coronary syndrome
AHA	American Heart Association
ALT	Alanine aminotransferase
Apo A1	Apolipoprotein A1
Apo B	Apolipoprotein B
AST	Aspartate aminotransferase
BMI	Body mass index
CAD	Coronary artery disease
CI	Confidence interval
CKD	Chronic kidney disease
CPK	Creatine phosphokinase
CV	Cardiovascular
CVD	Cardiovascular disease
EAS	European Atherosclerosis Society
ESC	European Society of Cardiology
FCH	Familial combined hyperlipidaemia
FH	Familial hypercholesterolaemia
GFR	Glomerular filtration rate
HDL	High-density lipoprotein
HF	Heart failure
HIV	Human immunodeficiency virus
HL	Hepatic lipase
HMG-CoA reductase	3-hydroxy-3-methyl-glutaryl coenzyme A reductase

IDL	Intermediate density lipoproteins
LCAT	Lecithin-cholesterol acyltransferase
LDL	Low-density lipoprotein
LPL	Lipoprotein lipase
MI	Myocardial infarction
PAD	Peripheral arterial disease
PPAR alpha	Peroxisome proliferator-activated receptors alpha
RR	Relative risk
TG	Triglyceride
VLDL	Very-low-density lipoprotein
WHO	World Health Organization

Introduction

It is known that disorders of lipid metabolism are one of the most important risk factors in the development of cardiovascular disease associated with atherosclerosis. This concept, first proposed 100 years ago, has been demonstrated in many experimental and prospective clinical trials. The American Horus study has found signs of atherosclerosis in the remains of 4 ancient populations. However, at the turn of the 21st Century, atherosclerosis is considered as a non-infectious pandemic.

According to scientific studies an increase in low density lipoprotein cholesterol by 10% contributes to the development of cardiovascular events by 20%. To date, low-density lipoprotein cholesterol is considered to be the most atherogenic particle. On the other hand, some studies have demonstrated that not hypercholesterolaemia but the ratio of atherogenic and antiatherogenic particles plays an important role in the development of cardiovascular events. In particular, the international INTERHEART study involving 30,000 patients with myocardial infarction from 52 countries showed that among 9 risk factors, the ratio of apolipoproteins A1 and B (atherogenic index) was the most powerful risk factor. Thus, speaking of lipid abnormalities, it is more accurate to identify dyslipidaemia not hypercholesterolaemia, which is a violation of the atherogenic and antiatherogenic particles ratio. Hypertriglyceridaemia and low high-density lipoprotein cholesterol are also independent risk factors for atherosclerosis.

Views on the treatment of dyslipidaemia have radically changed over the past 25 years. If during the 1980's the basic principles for the treatment of lipid abnormalities were diet and low-dose monotherapy without statins, then at the beginning of the 21st century, we often hear theses about aggressive lipid-lowering therapy with high doses of statins and their combination with other lipid-lowering medicines.

Certainly, changing the lifestyle and diet remain one of the basic principles for treatment of lipid disorders. The Finnish North Carelia prospective study has shown that a reduction of butter consumption by 70% over 30 years led to a decrease in total cholesterol of 50%.

There are 5 groups of lipid-lowering drugs available for clinicians. Some of them mostly lower triglycerides and increase high-density lipoprotein cholesterol, and some predominantly lower levels of total and low-density lipoprotein cholesterol. Of course, statins are the most widely prescribed lipid-lowering drugs, as it has been proven that lowering low-density lipoprotein cholesterol from 24% to 60% contributes to a reduction in cardiovascular mortality.

Lipidology is the youngest and, it could be argued, the most dynamically developing trend in cardiology. There have been established international recommendations and guidelines for the treatment of lipid abnormalities in recent years. In particular, there were standards for target lipid levels, the use of different doses of lipid-lowering drugs, their safety and monitoring, and treatment regimens for different categories of patients. However, views on the tactic of treatment of hypercholesterolaemia and other lipid disorders are rapidly changing. Recent U.S. recommendations for treatment of hypercholesterolaemia have caused a great resonance and have been accepted as ambiguous, as they are in some ways contrary to established opinions. However, all experts agree that patients with high cardiovascular complications should have adequate prolonged lipid-lowering therapy.

This book analyzes the problem of lipid abnormalities, theoretical knowledge of atherosclerosis and lipidology, practical recommendations and strategies in diagnosing dyslipidaemia, and selection of lipid-lowering therapy depending on the specific clinical case. There are separately presented issues on monitoring the effectiveness and safety of different modes of lipid-lowering therapy.

This book is intended for use in general practice, and is intended to be helpful to cardiologists, general practitioners, endocrinologists, neurologists, vascular surgeons, rheumatologists, and medical students.

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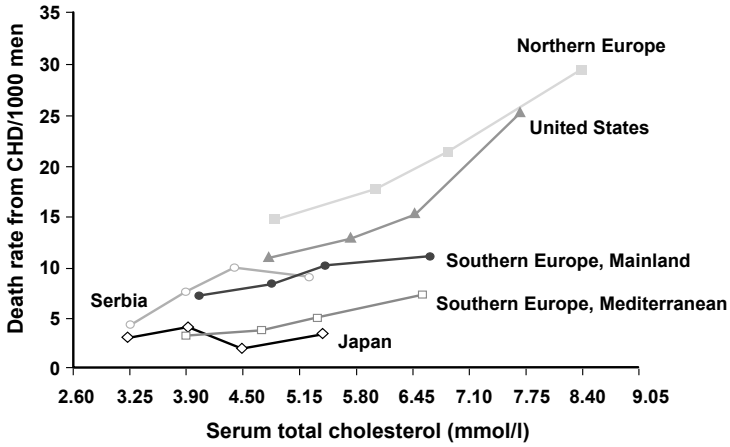
Chapter 1

DYSLIPIDAEMIA IS AN IMPORTANT RISK FACTOR FOR ATHEROSCLEROSIS

In p cardiovascular ractical medicine, the concept of disorder of lipid metabolism is often associated with elevated levels of total cholesterol in the blood. This phenomenon is referred to as hyperlipidaemia or hypercholesterolaemia. However, the term dyslipidaemia more precisely characterizes disorders of lipid metabolism, which implies a violation of the ratio of atherogenic (i.e. contributing to the development of atherosclerosis) and antiatherogenic particles in favour of increasing the first. What is atherosclerosis? Why have people started to talk about it more often, and every year the fight with it becomes more aggressive?

In the 1980's, we received the results of the first longstanding (prospective) studies that tracked the causal link between cardiovascular disease (CVD) (coronary artery disease (CAD), myocardial infarction (MI)) and risk factors. It was found that in the development of CVD, associated with atherosclerosis, more than 200 risk factors are involved [1]. Among them, the most important were three modifiable factors: smoking, hypertension and hypercholesterolaemia. Verschuren et al. in their Seven Countries Study showed that regardless of nationality and race in all populations from 7 different countries an increase in plasma cholesterol was associated with an increase in cardiovascular (CV) death (Figure 1). In general, in clinical practice the prevailing number of CAD patients have mild to moderate hypercholesterolaemia [2]. Later, in another international cross-sectional



Adapted from Verschuren et al., 1995

Fig. 1. Relationship of serum cholesterol to mortality (Seven Countries Study)

study, a significant association was demonstrated showing the ratio of atherogenic and antiatherogenic particles with an acute coronary event. Thus, the INTERHEART study, led by Salim Yusuf from Canada, involving 30,000 patients admitted to intensive cardiology care from 52 countries, investigated the relationship of acute coronary syndrome (ACS) and 9 risk factors (dyslipidaemia, smoking, hypertension, obesity, type 2 diabetes, stress/depression, alcohol abuse, insufficient intake of fruits and vegetables, and physical inactivity) [3]. It was found that, regardless of nationality, socio-ethnic environment, and gender, dyslipidaemia had the leading position in the development of acute MI (Table 1). Interestingly, dyslipidaemia was evaluated by the ratio of the concentration of apolipoprotein (apo) B and apo A1.

Atherosclerosis is a disease of blood vessels (arteries) which is characterized by their compaction and luminal stenosis. It should be noted that atherosclerotic vascular disease is a chronic and indolent (lengthy) process [4]. According to different authors, there is a 10–15 year period between the appearance of fatty streaks in the lumen of the artery and the first clinical signs of atherosclerosis, except for some forms of familial hypercholesterolaemia (FH) [5].

Table 1. **The risk of acute myocardial infarction in patients with a combination of risk factors: results of the INTERHEART study 52 countries**
(15,152 experimental vs. 14,820 control groups)

Risk factors, causing 91% of the risk of myocardial infarction	
	RR (99% CI)
Dyslipidaemia (apo B/apo A1)	3.25 (2.81 to 3.76)
Smoking	2.87 (2.58 to 3.19)
Depression/Stress	2.67 (2.21 to 3.22)
Diabetes	2.37 (2.07 to 2.71)
Hypertension	1.91 (1.74 to 2.10)
Abdominal obesity	1.62 (1.45 to 1.80)
Alcohol consumption	0.91 (0.82 to 1.02)
Physical activity	0.86 (0.76 to 0.97)
Consumption of fruits/vegetables	0.70 (0.62 to 0.79)

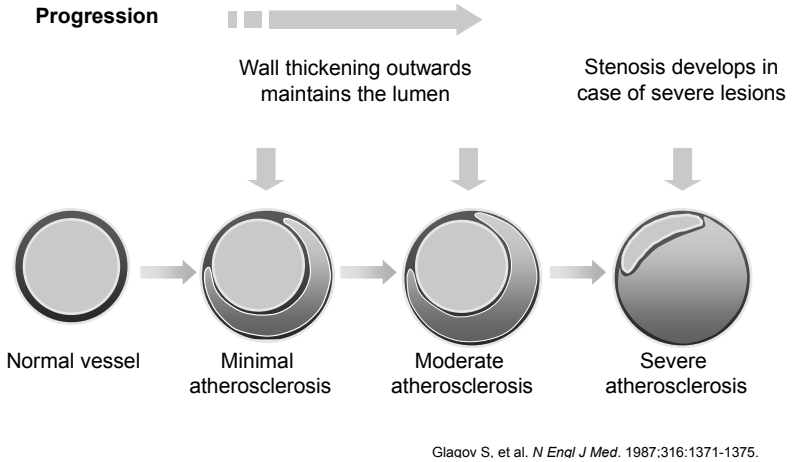


Fig. 2. Progression of atherosclerosis: a hypothesis of Glagov remodeling

Consequently, atherosclerotic plaque formation process can be divided into several stages (Figure 2):

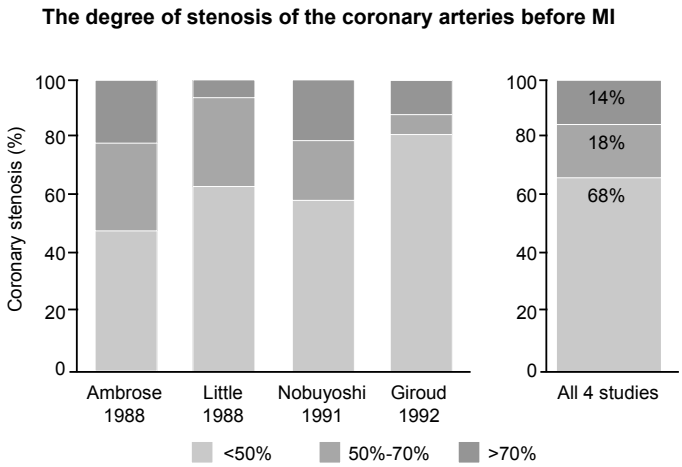
Stage I — delay and accumulation of lipids in the intima of vessels is the beginning of the process. In the context of intimal thickening (migration of smooth muscle cells), there is retention of low-density

lipoproteins (LDL) for a long time, whereby the components of lipoproteins are oxidized.

Stage II — oxidation of lipids is a structural and functional impairment of these particles, and they cannot act as construction and energy substrates. They irritate nearby cells; the modified lipoproteins are perceived as a foreign substance, and defence mechanisms are triggered, namely an inflammatory process is activated. There is migration of monocytes to the endothelium, and after penetration into the intima they are transformed into macrophages. Macrophages, absorbing oxidized lipoproteins, are transformed into foam cells. The accumulation of foam cells and lymphocytes is the initial step of the atherosclerotic process. Morphologically, this formation looks like a lipid stain.

Stage III — plaque formation that is when a lipid spot turns into atheroma. As a result of the secretory activity of macrophages and foam cells, the membrane, which separates the intima from the media (middle layer), dissolves. There is an active migration of medial smooth muscle cells. Absorbing foam cells, they secrete collagen.

Thus, a fibrous cap of atherosclerotic plaques appears, wherein the core consists of an accumulation of oxidized lipids and macrophages. The progression of this process in the intima of arteries leads to the



Falk E, et al. *Circulation*. 1995;92:657-671.

Fig. 3. Under what degree of stenosis does myocardial infarction develop?

formation of lipid plaques which obstruct normal blood flow to vital organs — heart, brain, kidneys and lower limbs.

A meta-analysis of several studies has showed that 68% of patients develop MI when the vessel lumen stenosis is less than 50%, which confirms the hypothesis, proposed by M. Davies, of plaque instability (Figure 3). Unstable plaque has a large lipid core and a thin fragile fibrous cap, which can easily break under tension. Due to rupture of this fibrous cap in the artery lumen, a thrombus is formed, leading to acute disruption of blood supply to these organs and, depending on the localization, leads to the development of MI, stroke and limb ischaemia [6].

Thus, the quantitative and qualitative disorder of lipid metabolism plays an important role in the formation of atherosclerotic plaques, contributing to the development of CV complications.

Chapter 2

BASICS OF LIPID AND LIPOPROTEIN METABOLISM

Lipid metabolism is a complex interaction of multiple substances, which include lipids, lipoproteins, apolipoproteins, enzymes (lipoprotein lipase (LPL)), and lipoprotein receptors [7]. Detailed analysis of biochemical processes are unlikely to be needed by a practitioner. However, it is important to know some regularities of lipid metabolism.

Lipids

Cholesterol is the main but not the only indicator of a level of lipids. These include triglycerides (TG) and phospholipids. In the human body, each of these parameters has an important function [1, 7].

Triglycerides

These are esters of fatty acids and glycerol (sugar alcohol), and a part of various lipoproteins, dominating in chylomicrons and very-low-density lipoproteins (VLDL). TG are synthesized in the liver and adipose tissue. In the small intestine TG are formed by absorption from food and esterification of monoglycerides. TG are a good source of energy. After a fatty meal, the concentration of TG in the blood rises quickly, but normally returns to baseline after 10–12 hours. In some groups of patients (Type 2 diabetes, metabolic syndrome), the concentration of TG does not return to normal for a long time (2–3 hours).

This phenomenon in the world literature is known as «postprandial lipidemia» [8].

Fatty acids

Fatty acids get into the body with food or are synthesized from the breakdown products of carbohydrates. Part of the fatty acids is constantly formed in adipose tissue as a result of TG lipolysis. Fatty acids used by the body as an energy source, which is generated during their oxidation. During the basic metabolism, the oxidation of fatty acids occurs in the myocardium, liver and diaphragm, and in skeletal muscle during physical exercise. Fatty acids play an important role in lipid metabolism, driving cholesterol and glycerine esterification. There are saturated (prevalent in animal fats), monounsaturated and polyunsaturated (vegetable oil and fish oil) fatty acids [7].

Phospholipids

Phospholipids are glycerol esters containing fatty and phosphoric acids. Their main source is liver. Phospholipids are important structural components of cell membranes and accompanied by cholesterol. In practical terms, the level of phospholipids in the blood is not defined, because they have no effect on the risk of CAD.

Cholesterol

Cholesterol refers to the group of steroids and is synthesized mainly in the liver and the distal portion of the intestine. One third of cholesterol gets to the body through food. Cholesterol performs important biochemical functions in the human body, namely, it is necessary for the synthesis of steroid hormones and bile formation. Its oxidation product under the influence of sunlight is converted in the skin into vitamin D3. It is a part of all cell membranes in the body. Cholesterol can be free and esterified. Free cholesterol is metabolically active, while cholesteryl esters are its transported and deposited forms. Esterified cholesterol can be found in the adrenal cortex, plasma, atherosclerotic plaques, whereas free cholesterol is a part of cell membranes. Some biological (age, sex, race, seasons) and behavioral (diet, alcohol, smoking, physical activity) factors affect the level of cholesterol in the blood [1].

Lipoproteins

All lipids are released into the blood in the form of macromolecular complexes, lipoproteins, which consist of a mixture of proteins, phospholipids, free and esterified cholesterol, and TG [4]. Proteins that make up the lipoproteins are called apolipoproteins. Due to highly specific interactions between apolipoproteins and proteins — receptors on the cell membrane — the binding of lipoproteins with cells occurs. Structurally, the external hydrophilic layer of lipoproteins is formed by molecules of apolipoproteins, phospholipids, and free cholesterol; and their inner layer (hydrophobic core) consists of cholesteryl esters and TG. Depending on the density, size and composition of inbound lipids and apolipoproteins, lipoproteins are classified into 5 classes: chylomicrons, VLDL, intermediate density lipoproteins (IDL), LDL, high-density lipoprotein (HDL) [7].

Chylomicrons

Chylomicrons are the largest and lightest particles. Chylomicrons are synthesized in the epithelial cells of the small intestine from lipids of exogenous (food) origin. They mostly contain TG and, in smaller quantities, phospholipids, cholesterol, and proteins. Their main function is to carry TG from food. The maximum concentration in the blood is extant within 3–6 hours after ingestion. Isolated hyperchylomicronemia is rare and usually indicates a hereditary defect of LPL. Hyperchylomicronemia is not a biochemical marker of atherosclerosis, but the concomitan hypertriglyceridaemia (HTG) and can trigger the development of acute pancreatitis.

Very-low-density lipoproteins

VLDL are synthesized in the liver. They are also called pre-beta-lipoprotein, similar to chylomicrons, contain less TG, and serve to transport endogenous TG. Therefore, their high content in plasma is shown as HTG.

Intermediate density lipoproteins

IDL contain in their composition more cholesteryl esters than VLDL. Normally, a part of IDL is captured by the liver receptors, and another

part is hydrolyzed and converted into LDL. Increased levels of IDL in the blood are manifested as hypercholesterolaemia and HTG. In clinical practice, an isolated increase in IDL is quite rare.

Low-density lipoproteins

LDL (beta lipoproteins) mainly consist of cholesteryl esters, i.e. they are the main carriers of endogenous cholesterol. Elevated levels of LDL in plasma are clearly associated with the development of coronary, carotid (carotid artery), and peripheral atherosclerosis. However, in order for LDL to obtain atherogenic properties, they should undergo a modification, based mostly on the process of lipid peroxidation. Given the important role of LDL in the formation of atherosclerotic plaque, LDL cholesterol is the primary target for lipid-lowering therapy.

High-density lipoproteins

HDL (alpha lipoproteins) are antiatherogenic particles that carry out reverse cholesterol transport from the vascular wall and macrophages into the liver where cholesterol is excreted as a part of bile acids. There is an inverse correlation between levels of VLDL and HDL. Moreover, the level of HDL cholesterol in plasma is inversely related to the development of atherosclerosis: the lower the level of HDL, the higher the likelihood of developing atherosclerosis.

Figure 4 shows the contribution of each class of lipoproteins in the total level of cholesterol and TG in the blood, which demonstrates their potential in the development of atherosclerotic vascular disease.

Besides the above, there is another type of lipoprotein called lipoprotein A, which is not defined in practical terms. Lipoproteins A are atherogenic particles, similar to LDL and treated as an independent biochemical marker of atherosclerosis [8]. Along with lipoproteins, there are other elements involved in the metabolism of lipids:

1. Enzymes — hepatic and extrahepatic LPL, lecithin cholesterol acyltransferase, 3-hydroxy-3-methyl-glutaryl coenzyme A reductase (HMG-CoA reductase);
2. LDL receptors and receptors for chylomicron remnants;
3. Proteins that carry lipids, for example, the protein responsible for transfer of cholesteryl esters [7].

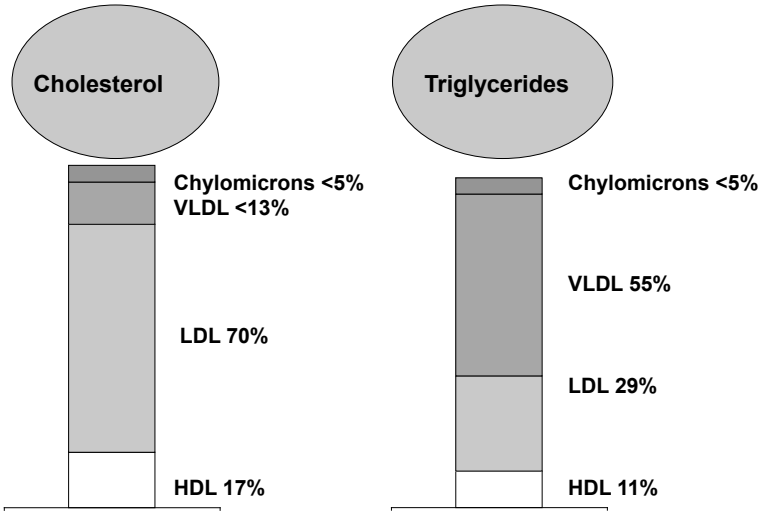


Fig. 4. The contribution of each class of lipoproteins in levels of total cholesterol and triglycerides

A brief outline of lipid metabolism

Food fats provide up to 50% of the energy for the body. Dietary fat (TG, cholesterol and phospholipids) is absorbed in the intestine by enzymatic hydrolysis (Figure 5). The absorption process occurs with the participation of bile. In intestinal cells, there is a resynthesis of lipids and an assembly of large TG-rich protein-lipid complexes — chylomicrons — which enter the bloodstream via the lymph. Under the influence of extrahepatic LPL, chylomicrons in plasma turn into remnants which are then captured by the liver receptors. VLDL carry endogenous TG from the liver into the plasma, where they undergo, like chylomicrons, partial cleavage to remnants — IDL. IDL are either captured by LDL receptors or, under the influence of hepatic LPL, turn into atherogenic LDL particles. Antiatherogenic particles have complex origins: the lipid component consists of free cholesterol and phospholipids, released in VLDL and chylomicron lipolysis, or free cholesterol coming from peripheral cells.

Thus, lipoprotein metabolism is a dynamic process that involves transfer of lipids and apolipoproteins between different classes of

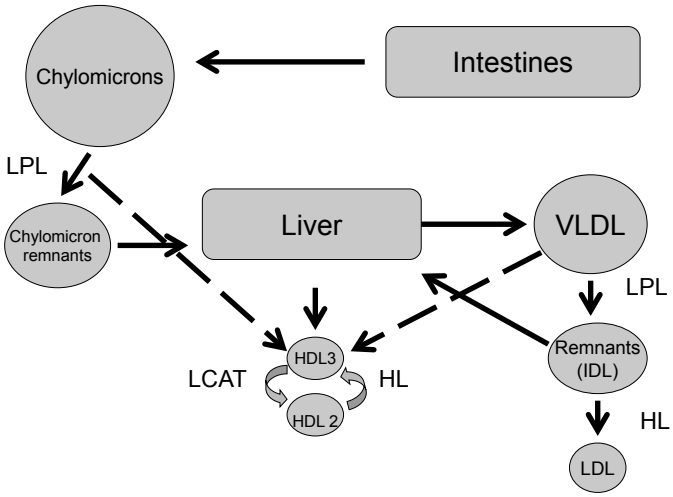


Fig. 5. Simplified diagram of lipoprotein metabolism

lipoproteins, in which enzymes are actively involved. These interactions lead to a receptor-mediated entry of cholesterol into the cell and its removal from the cell [5].

Chapter 3

PRIMARY HYPERLIPIDAEMIA: SOMATIC SYMPTOMS AND THE RISK OF CORONARY ARTERY DISEASE

Primary or familial hyperlipidaemia is caused by the presence of certain genetic defects which lead to a deficiency of enzymes, apolipoproteins and receptors. It can be of either monogenic or polygenic character [9, 10]. And it is characterized by a severe degree of lipid metabolism disorder and external appearance of somatic symptoms (arcus senilis, lipemia retinalis, tuberose and tendon xanthomas on the extensor surfaces of the hands, elbows and knees, Achilles tendon, eruptive xanthomas, scattered throughout the body, and xanthelasma on the eyelids).

The most common inherited disorders of lipid metabolism are: FH, polygenic hypercholesterolaemia, familial combined hyperlipidaemia (FCH), familial HTG, type III hyperlipidaemia, hypoalphalipoproteinaemia [10, 11].

Familial hypercholesterolaemia

This monogenic disease is not related to sex and manifested in any case upon receipt of the defective gene (Table 2). The disease is a mutation of the gene coding the synthesis of LDL receptors. There are homozygous and heterozygous forms of the disease. In the first form, receptors are almost completely non-functional, and cholesterol levels are 4–5 times higher than normal; in heterozygous form, approximately half of the receptors function, and cholesterol levels

Table 2. **Familial hypercholesterolaemia**

	Familial combined hyperlipidaemia	**Familial hypercholesterolaemia**
Somatic symptoms	Arcus senilis	Arcus senilis, tendinous xanthomas
Associated symptoms	Obesity, impaired glucose tolerance, hyperuricemia, HDL deficiency	No
Defect	↑ Hepatic synthesis of apo B-100 as part of VLDL	Damage in the structure of the LDL receptor or apo B-100 receptor
Frequency amongpopulation	1:50	1:500
Frequency among patients with CAD	15%	1–3%
Risk of CAD	Moderate	High

exceed normal by 2 times, respectively. Patients with the homozygous form have at an early age clinical signs of atherosclerosis. Many of them die before they reach the age of 30 years. Patients with heterozygous form of hypercholesterolaemia develop CAD at the age of 40–50 years. At a patient's examination, attention is drawn to the tuberous (lumpy) and tendon xanthomas, which are located on extensor surfaces of the back of the hand, elbow and knee joints, buttocks and Achilles tendons. Preliminary diagnosis is based on detection of xanthomas, high cholesterol levels, and family history — the early development of CAD in the immediate family. The final diagnosis is confirmed after genetic analysis, which is carried out in specialized clinics, where a patient also gets an appropriate therapy with statin, plasmapheresis or immunoadsorption of LDL. The prognosis for a timely started and regular therapy in most cases is favourable.

Polygenic hypercholesterolaemia

This kind of familial hyperlipidaemia is widely spread, and, in contrast to the FH, is characterized by a moderate increase in the concentration of cholesterol. The therapy involves dietary considerations and prescription of a statin.

Familial combined hyperlipidaemia

This can present in different variants (phenotypes). It is believed that the hereditary defect is associated with an increased production of apo B-100. The disease, in contrast to polygenic hypercholesterolaemia, rarely begins in childhood or it may appear as an isolated HTG. FCH occurs quite commonly in the population. The therapy depends on hyperlipidaemia phenotype.

Familial hypertriglyceridaemia

This is evident when there is an increase in the concentration of TG in the range of 2.3–5.6 mmol/l and, in some cases, may reach 11.3 mmol/l (Table 3). Familial HTG in some families is accompanied by the development of CAD, in others not. Severe isolated HTG is dangerous due to development of acute pancreatitis. The nature of genetic mutation is not known, although there is an assumption about the presence of a defect in the apolipoproteins C–II gene.

Table 3. **Familial hypertriglyceridaemia**

	Familial hypertriglyceridaemia	**Severe hypertriglyceridaemia**
Somatic symptoms	None	Lipemia retinalis, eruptive xanthomas
Associated symptoms	Obesity, impaired glucose tolerance, hyperuricemia, HDL deficiency	Same + pancreatitis, paresthesia, emotional instability
Defect	↑ Hepatic triglyceride synthesis	↑ Hepatic triglyceride synthesis, slow catabolism of chylomicrons and VLDL
Frequency among population	1:50	1:1000
Frequency among patients with CAD	15%	1:500
Risk of CAD	Low	Low

Hypoalphalipoproteinfemia

This is characterized by a decrease in HDL. The genetic defect is not known. Hypoalphalipoproteinaemia is a rare disease that leads to

an early development of coronary atherosclerosis, and sometimes, corneal opacity. Due to violations of the reverse cholesterol transport, the latter is intensively deposited in the reticuloendothelial tissue, and is evident as enlarged tonsils, hepatosplenomegaly, neuropathy, amyloidosis. The therapy for hypoalphalipoproteinaemia is limited and not very effective.

Chapter 4

SECONDARY HYPERLIPIDAEMIA: WHICH DISEASES AND DRUGS CAUSE DISORDERS OF LIPID METABOLISM?

Some diseases, hormonal disorders, and medication intake may be accompanied by disorders of lipid metabolism. This type of problem is classified as a secondary hyperlipidaemia. Unlike primary hyperlipidaemia, this lipid metabolism disorder has mild or moderate severity, and somatic symptoms are generally not detected. However, the on-going disorder of lipid metabolism may induce the development of atherosclerosis [12].

Diseases that cause secondary disorders of lipid metabolism are divided into several groups (Table 4):

1. Endocrine and metabolic diseases (hypothyroidism, pituitary hypofunction, diabetes, gout, obesity, alcohol abuse, acute intermittent porphyria);
2. Kidney diseases (nephrotic syndrome, chronic renal failure);
3. Acute diseases (burns, infections);
4. Liver diseases (primary biliary cirrhosis, biliary atresia);
5. Other disorders (anorexia nervosa, systemic lupus erythematosus).

The fact that lipid levels increase during pregnancy often causes anxiety in young women. Changes in the concentration of cholesterol and TG levels are associated with an increase in VLDL, LDL and HDL, caused mainly by an increase in oestrogen levels. Usually, after delivery these lipid indicators return to normal. In women with familial

Table 4. **Causes of secondary hyperlipidaemia: somatic diseases**

Endocrine and metabolic disorders • Hypothyroidism • Pituitary hypofunction • Diabetes mellitus • Acute intermittent porphyria • Pregnancy	**Kidney diseases** • Nephrotic syndrome • Chronic renal failure
Storage disease • Gaucher Disease • Dextrinosis • Tay-Sachs disease	**Liver diseases** • Biliary atresia
Other diseases • Anorexia nervosa • Systemic lupus erythematosus	**Acute diseases** • Burns • Infections • Myocardial infarction?

hyperlipidaemia, during pregnancy lipid concentrations always increase quite significantly.

Prolonged intake of certain drugs also causes secondary hyperlipidaemia (Figure 6). These include some antihypertensives (thiazides, oksodolin, nonselective beta-blockers — propranolol), immunosuppressants (cyclosporine, FK506, prednisolone), and sex steroids (hormone replacement therapy, which includes drugs of estrogen and progesterone in different ratios). Barbiturates and cimetidine also have similar effects. The changes in the lipid levels on a background of drug usage are mild: TG increase by 15–30% and cholesterol — by 6–10%. The abolition of these drugs usually leads to normalization of the lipid profile. Moderate and heavy alcohol consumption also causes secondary hyperlipidaemia (HTG). An increase in HDL cholesterol is observed more often [13].

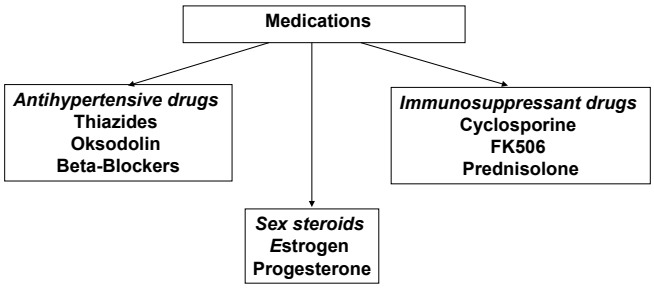


Fig. 6. Secondary causes of hyperlipidemia: medications

Chapter 5

PHENOTYPES OF HYPERLIPIDAEMIA: IMPORTANCE IN EVERYDAY PRACTICE

Lipidology, as a clinical discipline, appeared in 1967, when Levy and Fox Fredrickson first introduced the classification of hyperlipidaemia. Later, experts from the *World Health Organization* (*WHO*) modified this classification. Except for hypoalphalipoproteinaemia, the WHO classification organizes all types of disorders of lipid metabolism on 6 different phenotypes. It does not divide the causes of the violations as genetically predetermined or secondary. A type of hyperlipidaemia in a patient may change from one to another under the influence of medication treatment and lifestyle changes [14]. Despite these shortcomings, this system is very convenient in practical medicine; it allows a rational approach to the diagnosis and treatment of hyperlipidaemia. To determine the phenotype it is necessary to measure the fasting levels of patient's TG, total cholesterol and LDL cholesterol. In some cases it is necessary to determine the level of chylomicrons, as well as conduct electrophoresis (for example, for determining type III hyperlipidaemia). Below, there are main features for types of hyperlipidaemia (Table 5, 6).

Phenotype I is characterized by an isolated increase in chylomicrons. Cholesterol and TG levels can be moderately elevated or normal. This phenotype of hyperlipidaemia is rare and usually not associated with the development of atherosclerosis. Occasionally, its signs are found in systemic lupus erythematosus.

Table 5. **Classification of hyperlipidaemia (phenotypes)**

Type	Plasma cholesterol	Triglycerides	Lipoprotein disturbances	Atherogenicity
I	Increased	Increased or normal	Excess of chylomicrons	Non-atherogenic
II a	Increased	Normal	Excess of LDL	High
II b	Increased	Increased	excess of LDL and VLDL	High
III	Increased	Increased	Excess of remnants	High
IV	Often normal	Increased	Excess of VLDL	Moderate
V	Increased	Increased	Excess of chylomicrons and VLDL	Low

Table 6. **Etiology of lipoprotein phenotypes**

Type	Primary causes	Secondary causes
I	Lipoprotein lipase deficiency	Systemic lupus erythematosus
II a	Familial hypercholesterolemia	Hypothyroidism
II b	Combined familial hyperlipidemia	Diabetes, nephrotic syndrome, anorexia nervosa
III	Type III familial hyperlipidaemia	Hypothyroidism, diabetes, obesity
IV	Familial combined hypertriglyceridaemia	Diabetes, chronic kidney disease
V	Familial hypertriglyceridaemia Lack of apo C-II	Alcohol, diuretics, beta blockers, contraceptive pills

Phenotype IIa is characterized by increased levels of LDL and total cholesterol, while TG levels stay normal. This phenotype is quite common in the population and is closely associated with the development of atherosclerosis, particularly CAD. In heritable disorders of lipid metabolism, phenotype IIa is diagnosed in patients with familial and polygenic hypercholesterolaemia. Disorders of lipid metabolism in hypothyroidism also exhibit similar changes.

Phenotype IIb is characterised by increased levels of LDL cholesterol and VLDL cholesterol. Individuals with phenotype IIb have combined hyperlipidaemia. This type of hyperlipidaemia is also widely spread and has a high atherogenic potential. In cases of primary hyperlipidaemia, phenotype IIb is observed more frequently in patients with FCH. Often,

combined hyperlipidaemia is a manifestation of secondary disorders of lipid metabolism in diabetes, nephrotic syndrome, and anorexia nervosa.

Phenotype III is manifested by increased levels of IDL, and, as a result, cholesterol and TG levels. It is a rare type of disorders of lipid metabolism. If phenotype III is suspected then an essential help in the diagnosis is an electrophoresis of the blood serum in agar gel (appearance of broad beta-line). People with phenotype III, which include hypothyroidism, diabetes and obesity, are at high risk of developing atherosclerosis.

Phenotype IV is characterized by increased levels of VLDL, and presence of HTG. It occurs in 40% of patients with disorders of lipid metabolism, and might be a reflection of familial HTG. In combination with low levels of HDL cholesterol, this phenotype is highly atherogenic. In some cases, patients with diabetes and chronic kidney disease have this type of hyperlipidaemia.

Phenotype V is rare. It is characterized by a simultaneous increase in the levels of chylomicrons and VLDL, presence of HTG, and a moderate increase of blood cholesterol. Usually there is no clear link between the phenotype V and development of atherosclerosis. However, evident HTG which accompanies this phenotype is dangerous due to development of acute pancreatitis. Moderate and excessive alcohol use, thiazide diuretics, non-selective beta-blockers and some contraceptive pills cause similar to phenotype V disorders of lipid metabolism.

Unfortunately general practitioners do not use phenotypic classification of lipid disorders, although this approach greatly facilitates the strategy of selection of lipid-lowering therapy.

Chapter 6

NON-PHARMACOLOGICAL WAYS OF TREATING DISORDERS OF LIPID METABOLISM: WHAT CAN WE EXPECT?

At the end of the 20th century, several prospective studies were conducted on the relation of CVD and diet of a population in different countries [15]. In particular, the Seven Countries Study has showed that there is a significant association between mortality from CAD and fat consumption. Compared with Japan, where the population's diet is dominated by plant products and fish, in the countries of Northern Europe and the U.S. death rate was 15 times higher, because the population of these countries consume large quantities of foods containing saturated fats and cholesterol [2]. Then there was a question: «Why does a German doctor get ill more often and live less long when compared with a Greek fisherman?» It was found that the population of the Mediterranean countries consume a lot of fish, seafood and regularly drink wine. Later, this type of food was labelled, «the Mediterranean diet» and was considered optimal for the prevention of CAD.

Non-pharmacological therapy (such as lifestyle modification or behaviour change) involves the administration of antiatherosclerotic diet, management of excessive body weight, increase of physical activity and smoking cessation [16]. Basic requirements for lipid-lowering diet are the following:

— Reduce of fat intake to 30% of total calories consumed (2000 calories);

— Reduce of cholesterol consumption to less than 300 mg/day;

— The ratio of polyunsaturated to saturated fats should be 1.5;

— Increase of soluble fibre consumption to 10–25 g/day, plant sterols/stanols to 2 g/day.

Patients should be encouraged to include in the diet more marine fish, fruits and vegetables that are rich in natural antioxidants and vitamins.

Cholesterol is mainly found in animal products (including offal), high-fat dairy products and sea products which should be considered when compiling of the daily diet. Limiting the consumption of dietary cholesterol and saturated fats can reduce cholesterol in the blood by 10–12%.

Saturated fatty acids contained in animal fats increase level of LDL cholesterol. Replacement of saturated fatty acids by poly-and monounsaturated leads to a decrease in LDL cholesterol and does not have any effect on the level of HDL cholesterol. Complete replacement of natural fats by margarine, especially by hard ones is not recommended, as the hydrogenation of polyunsaturated fats leads to the formation of trans-fatty forms of acids, which can also increase the level of LDL cholesterol. It is recommended to consume liquid vegetable fats and/or soft margarines (in jars). In the preparation of soft margarines, the transesterification method is used — mechanical mixing of liquid and solid vegetable fats without affecting their biological structure. The source of monounsaturated fatty acids are olive, rapeseed, peanut, sunflower, and corn oils. Source of polyunsaturated fatty acids are sunflower, corn, cottonseed, soybean and linseed oils. Fish oils (sea and ocean mackerel, sardines, salmon, herring, etc.) refer to ω-3 polyunsaturated fatty acids. In the GISSI-Prevenzione trial, patients with myocardial infarction had used 1 g of ω-3 polyunsaturated fatty acids for 12 months which resulted in a reduction of all-cause mortality by 28%.

It is not recommended to dramatically reduce the overall amount of fat below the recommended limits, and replace them with carbohydrates is inappropriate. This is accompanied by a decrease in both LDL and HDL cholesterol, but their ratio does not reduce. Moreover, an excessive consumption of carbohydrates contributes to an increase in TG.

Water soluble fibre (dietary fibre) reduces the concentration of cholesterol by 10–12%. The sources of fibre are fruits (apple, pear, grapefruit, orange, banana, strawberry, raspberry, and etc.), vegetables (green peas, cauliflower, green beans), and legumes (lentils, peas and beans). Adding 15 g of pectins (gelling agents) contained in vegetables (beets, carrots) and fruits (apple, plum, peach, black currant) reduces cholesterol levels by 15%. In recent literature, there are data on the role of phytosterols and phytostanols in lowering cholesterol levels, as they reduce the absorption of cholesterol in the human intestine. Stanols and sterols are cholesterol-like substances and perform in plant cell membranes the same function as that of cholesterol in animal cells. Their main sources are nuts, grains, seeds, and vegetable oils, and their consumption in a dose of 2–3 g/day reduces the total cholesterol level to 10% [17, 18].

It is recommended to reduce the body weight to the optimum value [19]. To determine the optimal weight, the body mass index (BMI) is widely used (BMI = weight (kg) / height $(m)^2$). The normal BMI range is 18.5–24.9 kg/m^2. Currently, the evaluation of abdominal obesity is measured by waist circumference. Normally, the waist circumference should not exceed 94 cm for men and 80 cm for women. Physical activity involves performing regular physical activity, preferably aerobic. Duration of daily activities should be 30–40 minutes, at least 3–5 times a week. The intensity of physical activity should be as such to achieve the heart rate up to 60–75% of the maximum allowed for certain age group (for age group 20–39 years — 110–140 beats/min, 40–59 — 100–125 beats/min, 60–69 — 95–105 beats/min). Ideal speed for the reduction of body weight loss is 400–800 g per week [20, 21].

The new recommendations of the *American College of Cardiology* (ACC) and the *American Heart Association* (AHA) for the treatment of overweight and obesity demonstrated that small but steady weight loss of 3% to 5% leads to a clinically significant improvement in health in the form of reducing the levels of TG, blood glucose, haemoglobin A1c, and the risk of developing type 2 diabetes. Greater reduction in body weight contributes to a decrease in blood pressure, normalization of LDL and HDL cholesterol, as well as to a reduction in the quantity of drugs to control blood pressure, glucose and lipids. To get the desired results, those with overweight and obesity should participate in

comprehensive programmes to change their lives for at least 6 months. To do this, participants must adhere to the strategy of a low calorie diet and increased physical activity. There are recommended comprehensive measures of high intensity (for example, ≥14 sessions in 6 months) on weight loss in individual or group training sessions [22].

There is often discussed question on the effects of alcohol on the lipid profile and the possibility of its prescription for the management of disorders of lipid metabolism [23]. It was shown that moderate doses of alcohol may favourably affect blood lipids. Of course, a lot of this depends on the patient's level of intelligence and relationship to their health. If a doctor is sure that a patient will strictly follow his/her prescription, then he/she may recommend the patient to consume alcohol in the following doses: vodka, or brandy, or whiskey — 45–50 ml/day, table red wine — 150 ml/day. Of these drinks, the wine is preferred because studies have shown that in countries where the population consume mostly red wine, CVD mortality is lower than in countries where preference is given to spirits or beer.

Which results will we have by prescribing a complex of non-pharmaceutical measures, including antiatherosclerotic diet, management of excessive body weight, and an increase in physical activity? Our studies show that the systematic implementation of these measures, depending on the initial levels of lipids, leads to lower levels of total cholesterol by 10–12%, LDL cholesterol by 13–15%, and TG by 15–30%. In some cases, these changes help avoid prescribing of lipid-lowering drugs. And with moderate to severe lipid disorders, compliance with non-pharmaceutical measures allows to reduce doses of drugs.

Planned non-pharmacological intervention at the state level can reduce cholesterol and the risk of CV complications [24]. The North Karelia Project (Finnish national study) can serve as an example [25]. It is known that the diet of Nordic people is dominated by food with high content of animal fats, which is one of the important causes of the high mortality from CVD. Over 35 years of observations (1972–2007 years) in 6 regions of the country, the consumption of animal fats (i.e. butter) had decreased from 70% to 10% (Figure 7). Reduction in intake of butter was associated with a significant decrease in total cholesterol levels from 7 mmol/l to 5.3 mmol/l (Figure 8).

Thus, lifestyle changes are one of the basic methods for treating disorders of lipid metabolism. It is necessary to develop and implement specific measures where the principles for lifestyle changes are effectively applied in real clinical practice.

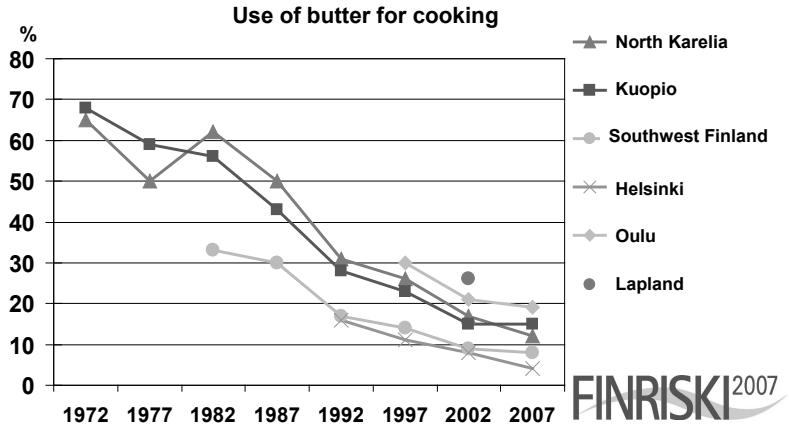


Fig. 7. North Karelia project: diet and lifestyle changes

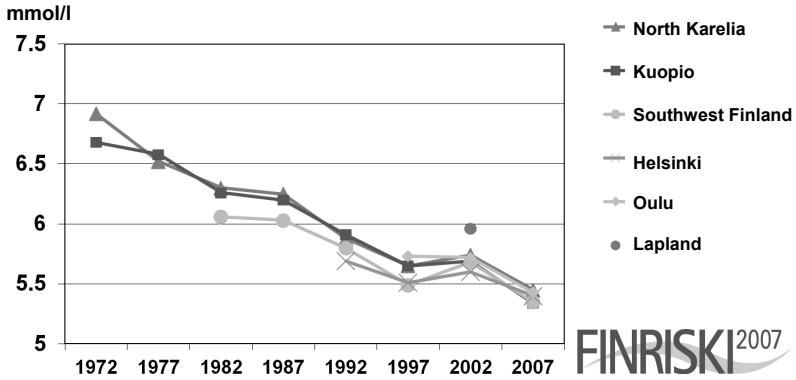


Fig. 8. Serum cholesterol in men aged 30–59 years

Chapter 7

PHARMACOLOGICAL TREATMENT OF DISORDERS OF LIPID METABOLISM: CHARACTERISTICS OF THE MAIN DRUG GROUPS

Over the past 30 years, the quantity of lipid-lowering drugs has increased due to new classes and generic statins, and this helps effectively reduce lipid levels in a broad segment of population. Today, there are five classes of lipid-lowering medications: bile acid sequestrants, nicotinic acid derivatives, cholesterol absorption inhibitors, fibrates, and statins (inhibitors of cholesterol synthesis) [4, 5]. These classes are different not only by the mechanism of action, but also by the effect on the basic parameters of the lipid profile (Table 7).

Table 7. **Effects of lipid-modifying therapies on lipids**

Therapy	TC	LDL	HDL	TG	Patient tolerability
Bile acid sequestrants	Down 20%	Down 15–30%	Up 3–5%	Neutral or up	Poor
Nicotinic acid	Down 25%	Down 25%	Up 15–30%	Down 20–50%	Poor to reasonable
Fibrates	Down 15%	Down 5–20%	Up 20%	Down 20–50%	Good
Cholesterol absorption inhibitors	Down 10%	Down 18%	Up 1–2%	Down 8%	Good
Statins	Down 22–40%	Down 27–55%	Up 6–12%	Down 10–30%	Good

Adapted from Yeshurun D, Gotto AM. Southern Med J 1995;88(4):379–391, Knopp RH. N Engl J Med 1999;341:498–511, Gupta EK, Ito MK. Heart Dis 2002;4:399–409

Bile acid sequestrants

Bile acid sequestrants (ion-exchange resins) have been used as lipid-lowering medications for more than 30 years. Ion exchange resins bind bile acids in the lumen of the small intestine and increase their excretion in the faeces. Due to reduction in absorption of bile acids from the intestine, more receptors are synthesized in the liver to meet the shortfall of cholesterol, and this leads to the reduction of cholesterol content in blood plasma. For the first time, thanks to clinical studies using resins, it was shown that lowering the levels of cholesterol reduces coronary events. In a 7–10 year prospective study in men aged 35–59 years with a total cholesterol level >7 mmol/l, the application of resin (cholestyramine) was resulted in a decrease in mortality from CAD and/or nonfatal MI by 19%, the risk of angina by 20 %, and reduction in the incidence of positive exercise test by 25%.

The most common types of resins are cholestyramine and colestipol. Cholestyramine is administered at a dose of 8–24 g/day, colestipol — 5–30 g/day in a powdered form which is dissolved in a liquid (tea, kissel). At these doses, sequestrants reduce levels of total and LDL cholesterol by 15–30% and increase the level of HDL cholesterol by 5%. Sequestrants are contraindicated in type III familial hyperlipidaemia, when levels of TG >5.6 mmol/l. Bile acid sequestrants are classified as safe drugs because they are not absorbed from the intestine into the blood. However, they cause constipation, bloating, dyspepsia, and unpleasant taste sensations, which is often the reason for not being considered. Due to appearance of more effective hypolipidemic agents, bile acid sequestrants are not currently used in monotherapy and mainly used as additional tools to the main treatment for severe hypercholesterolaemia, for example, FH [26]. In most countries, the resins are rarely used [27].

Nicotinic acid derivatives

Nicotinic acid (niacin) belongs to the group of vitamins B, but at higher doses (3–5 g/day) it has lipid-lowering effect. Nicotinic acid reduces the speed of lipolysis in adipose tissue, thereby the delivery of free fatty acids into the liver is reduced. Moreover, the synthesis and

secretion of VLDL and LDL is also lowered. Nicotinic acid decreases the speed of destruction of apo A1 in the liver, which is associated with an increase in reverse cholesterol transport from tissues to the liver. These mechanisms provide a decrease in TG by 20–40%, LDL cholesterol by 10–20%, and an increase in HDL cholesterol by 15–30%. In the 5 year Coronary Drug Project study of secondary CVD prevention, nicotinic acid helped to lower the development of MI by 27% and stroke by 24%, which ultimately significantly reduced the overall mortality by 11% [28].

Application of nicotinic acid is often accompanied by some side effects, like sharp facial and upper body blushing with feelings of heat and tides. This reaction is due to active release of prostaglandins under the influence of nicotinic acid. Side effects could be significantly weakened by prescribing 0.5 g of aspirin a half an hour prior to receiving the nicotinic acid and its gradual dose titration. It is recommended to take nicotinic acid during a meal. The other possible side effect is an abdominal pain, which is mentioned by up to 5% of patients and may be associated with exacerbation of gastritis. However, the most formidable, but rare complication is the development of liver failure. 5–10% of patients with diabetes and gout have a possibility of aggravation of underlying disease. In recent years, prolonged form of nicotinic acid (niacin, etc) is widely used. Due to slow release, the prolonged form of nicotinic acid has fewer side effects [29, 30].

Cholesterol absorption inhibitors in the intestine

At the end of the 20th century, a new drug with a local mechanism of action appeared on the market, namely, the selective blocking of dietary and bile cholesterol absorption in the small intestine, which in turn leads to a reduced transport of cholesterol from the intestine to the liver [31]. A lipid-lowering effect of ezetimibe appears after 2 weeks of treatment; it is well tolerated and does not affect the absorption of fat-soluble vitamins. Ezetimibe has a mild lipid-lowering effect, which is manifested in a reduction of total cholesterol by 10%, LDL cholesterol by 18%, TG by 8%, and in an increase of HDL cholesterol by 1–2%. However, the drug is used as an additional tool for

normalization of lipid metabolism. In particular, the combination of 20 mg of simvastatin and 10 mg of ezetimibe lowers cholesterol by 46%, which corresponds to that of 80 mg of simvastatin alone. Co-administration of 10 mg of ezetimibe and 10 mg of atorvastatin leads to a decrease in cholesterol by 53%.

Fibrates (Fibric acid derivatives)

Fibrates were introduced into clinical practice in the 70's of the 20th century. The first representative of this group was clofibrate, and then there were synthesized gemfibrozil, bezafibrate, ciprofibrate and fenofibrate [32]. Currently, only fenofibrate is available in pharmacies. Fibric acid derivatives act as synthetic ligands (signal transmitters) between nuclear peroxisome proliferator-activated receptors alpha (PPAR alpha) and certain regions of genes, and this directly affects their activity. PPAR alpha are localized in the liver, muscles, kidney and heart, where they stimulate the catabolism of lipids. Under the influence of fibrates (PPAR alpha agonists), there are changes in activity of certain target genes, which leads to:

1. An increase in the activity of lipases — enzymes that break down TG in lipoproteins rich in TG;
2. An increase in the activity of the acetyl-coenzyme A synthetase, which accelerates the intracellular transport of cholesterol and reduces the levels of free fatty acids;
3. Direct impact on the genes of apo A, thereby increasing the concentration of apo A, the major proteins of HDL.

Clinically, this leads to a moderate reduction in LDL cholesterol by 25% (even with isolated hypercholesterolaemia), a significant decrease in TG levels by 50% and an increase in HDL cholesterol levels by 25%. Along with this, there is a decrease in activity of the inflammatory markers, improvement of insulin sensitivity in the liver and skeletal muscles, and reduction in the levels of fibrinogen and uric acid in blood.

There is a sufficient quantity of data on the efficacy of fibrates in terms of primary and secondary prevention of CV events [33]. In two studies (the Clofibrate Study (*WHO*) and the Helsinki Heart Study) for primary prevention of CVD, the use of fibrates (clofibrate and

gemfibrozil, respectively) led to a reduce in LDL cholesterol by 11%, TG by 35%, and an increase in HDL cholesterol by 11%, which was combined with a decrease in a risk of MI by 25% and all coronary events by 20–34%. However, in both studies, the overall mortality rate almost did not change. Several studies have investigated the efficacy and safety of fibrates for secondary prevention of CVD. In particular, in the 5 year VA-HIT study in men with mild hyperlipidaemia, gemfibrozil helped reduce coronary events by 22%. The DAIS study assessed the effect of fenofibrate on angiographically documented stenosis, and development of clinical signs of CAD in patients with type 2 deabetes in a period of 2–5 years. It turned out that in the group received micronized fenofibrate, the minimal lumen diameter (diameter at the site of stenosis) decreased during the treatment period to a much lesser extent than in the placebo group (difference 40%).

The total number of acute coronary episodes in the fenofibrate group was significantly lower (by 23%) than in the placebo group. The FIELD study, completed in late 2005, was dedicated to investigate the efficacy of fenofibrate in patients with type 2 diabetes and mild hyperlipidaemia. Fenofibrate helped reduce CV events by 11% (without statin administration — by 19%) and non-fatal MI by 24% compared to placebo. Interestingly, the need for laser treatment of diabetic retinopathy decreased by 30% and significantly slowed the progression of albuminuria and nephropathy [34]

In general, treatment with fibrates is most effective in patients with HTG and low HDL cholesterol, with obesity and metabolic syndrome [35].

Fibrates are well tolerated, but 5–10% of patients may have some side effects such as abdominal pain, constipation, diarrhoea, bloating, as well as rashes, itching, headaches, insomnia. These effects tend not to be too bad and do not require discontinuation of the therapy. Fibrates are contraindicated: in children under 12 years; pregnant and breast-feeding women; elderly patients with severely impaired cognitive function; patients with active inflammatory and severe chronic liver diseases; increased liver enzymes (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)) by 2 times above the upper limit of normal; severe myopathies; increased creatine phosphokinase (CPK) levels by 5 times above the upper limit of normal;

symptomatic gallstone disease; and impaired renal function (creatinine >300 mmol/l) [32].

Statins (inhibitors of enzyme HMG-CoA reductase)

Statins are the key drugs in the treatment of hyperlipidaemia [4, 5]. W. Roberts, an american scientist, determined the value of statins in the treatment of atherosclerosis is as high as it was of penicillin for infectious diseases. The following drugs from the group of statins are: lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin and rosuvastatin. First statins (lovastatin, simvastatin and pravastatin) were isolated from the culture of penicillin mushrooms and fungi Aspergillus terrens; fluvastatin, atorvastatin, and rosuvastatin are synthetic drugs. The half-life of statins with an exception of atorvastatin is less than 2 hours. The half-life of atorvastatin exceeds 12 hours, and that can probably explain its more intense effect on lowering total and LDL cholesterol.

The main mechanism of action of statins is a moderate reduction of cholesterol in the liver cells due to a reversible suppression of the key enzyme in cholesterol synthesis — HMG-CoA reductase, and this leads to an increase in the number of LDL receptors and acceleration of their excretion from the blood (Figure 9). Depending on the dose and chemical structure, statins reduce levels of total cholesterol by 22–48% and LDL cholesterol by 27–60% [26]. It was shown that doubling the dose of statins contributes to further reduction in cholesterol levels by 6%. In the literature this is called a rule of six (Figure 10). Dose-dependent effects of main statins are presented in Table 8. Depending on the initial concentration, on the background of statin therapy, TG are reduced by 10–30%, whereas the level of HDL cholesterol is increased by 6–12%. It has been shown in experimental studies that statins help stabilize atherosclerotic plaque by reducing the amount of lipid core, strengthening its shell (anti-inflammatory effect), and improving local endothelial function. It is believed that the pleiotropic effects of statins occur at reduced LDL cholesterol by 25% [36].

In the 90's of the 20 century, there were held the first large-scale clinical studies on the effect of statins on different endpoints,

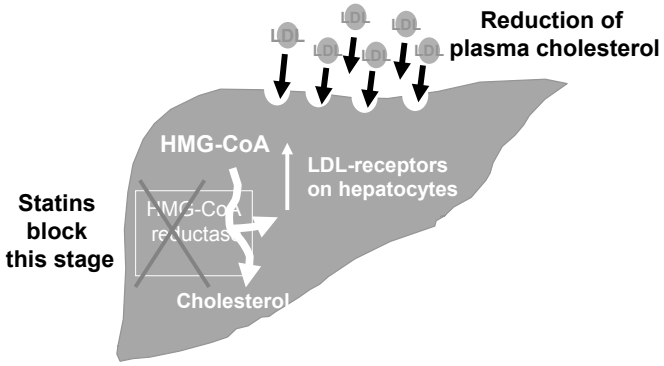
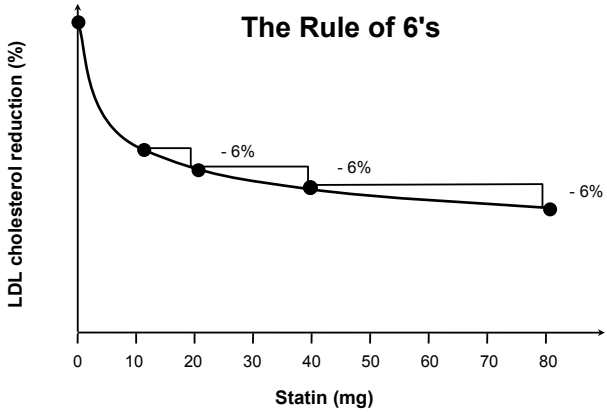


Fig. 9. Mechanisms of statin action



Adapted from Knopp RH et al *N Engl J Med* 1999;341:498–509; Stein E *Am J Cardiol* 2002;89(suppl):50C–57C.

Fig. 10. Statin dose relationship and reduction degree of LDL cholesterol

characterizing CVD and mortality due to atherosclerosis. Meta-analysis of five large prospective studies (4S, WOSCOPS, CARE, LIPID, AF/TexCAPS) showed that the use of statins in patients with moderate and severe hypercholesterolaemia leads to a significant decrease in CV and all-cause mortality. [33].

With the advent of statins, lots of studies were conducted on evaluation of their efficacy at various stages of the CV continuum:

1. Patients with hypertension without CAD;
2. Patients with type 2 diabetes and without CAD;

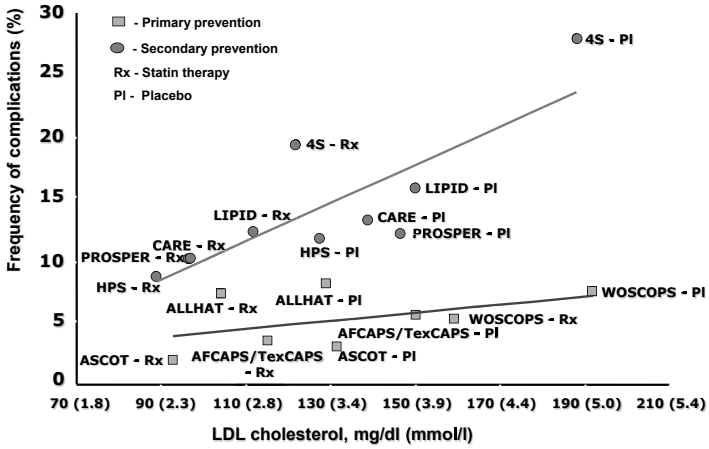
Table 8. **Comparative efficacy of statins to lower cholesterol**

Dose of medication						% reduction	
Atorva statin	**Simva statin**	**Lova statin**	**Prava statin**	**Fluva statin**	**Rosuva statin**	**Total choles-terol**	**LDL choles-terol**
–	10	20	20	40	–	22	27
10	20	40	40	80	5	27	36
20	40	80			10	32	42
40	80				20	37	48
80					40	42	54
					80	48	60

3. Patients with ACS;
4. Patients with exertional angina and after MI;
5. Patients after stroke [37].

The ASCOT study examined the effect of atorvastatin in patients with hypertension and moderate hyperlipidaemia (total cholesterol <6.5 mmol/l and TG <4.5 mmol/l), and without CAD. The study found that systemic administration of 10 mg of atorvastatin daily for 3.5 years resulted in reduction of non-fatal MI and mortality from CAD by 36%, with a decline in cases of stroke by 27% [33, 37]. It is known that two-thirds of patients with type 2 diabetes die from CVD, including MI and stroke. According to a British research on diabetes (UKPDS), LDL cholesterol is the strongest predictor of CAD risk in diabetic patients, since an increase in the level of LDL cholesterol by 1 mmol/l increases the risk of CAD by 57%. Two studies (HPS, simvastatin 40 mg, and CARDS, atorvastatin 10 mg) examined the efficacy of statins in the prevention of CV complications in diabetic patients with mild hypercholesterolaemia [33, 38]. Most patients (>70%) had multiple risk factors, and one third of patients were diagnosed with microvascular complications (retinopathy, microalbuminuria). The atorvastatin therapy of 10 mg in 80% of patients achieved target LDL cholesterol levels, which was associated with reduced risk of CV events by 37%, stroke by 48%, and a decrease in overall mortality by 27%. The HPS study showed a decrease in severe vascular complications by 22%, stroke by 24%, and in the need for revascularization (coronary angioplasty and coronary artery bypass grafting) by 17%. How to prevent the

risk of CV complications in people with exertional angina and/or post-MI? The Greek GREACE study, investigated the relationship of LDL target levels with the development of fatal and non-fatal cases of CV events (MI, stroke) [39]. It was found that in patients with moderate hypercholesterolaemia and CAD to achieve target levels of LDL cholesterol was on average enough to take 24 mg/day of atorvastatin. As a result, the 3-year atorvatstatin therapy (compared with the control group, in which statins were not used) helped reduce the risk of non-fatal MI by 59% and mortality from CAD by 47%, which ultimately reduced all-cause mortality by 43%. According to international recommendations, if statins had not previously been used, they should be prescribed at the early period of hospitalization for ACS. Two studies (MIRACL and PROVE-IT) have studied the efficacy of high-dose atorvastatin in patients with ACS. It was demonstrated that 80 mg of atorvastatin compared with placebo and 40 mg of pravastatin reduces the risk of fatal and non-fatal MI by 16%. One important aspect of evaluating the efficacy of lipid-lowering therapy is its effect on angiographically documented stenoses and development of clinical symptoms of CAD. According to intravascular ultrasound (the REVERSAL study), 80 mg of atorvastatin stops atherosclerosis and can significantly reduce the size of plaques after 18 months of therapy [33, 39]. It was shown that early clinical effects of statins in patients with ACS are associated with effects on inflammatory processes, occurring in the atherosclerotic plaque, and revealed in considerable reduction of C-reactive protein level. Also, statins are effective in primary and secondary prevention of stroke. Meta-analysis of 5 studies (4S, ASCOT, HPS, GREACE, CARDS) suggests that in patients with CAD or high coronary risk, systematic statin administration reduces the risk of stroke by 27–50%. According to the SPARCL study on the efficacy of lipid-lowering therapy in 4,731 patients with stroke or transient ischaemic attack with carotid atherosclerosis, but without sings of CAD, 80 mg atorvastatin reduces the risk of recurrent ischemic stroke by 25% compared with placebo [40]. Thus, a review of studies with hard endpoints convincingly shows that statins are the drugs of choice for both primary and secondary prevention of CV events (Figure 11).



Adapted from Ballantyne CM *et al*. *Am J Cardiol* 1998;**82**:3Q–12Q.

Fig. 11. Relationship between decrease in LDL cholesterol and frequency of cardiovascular complications

In general, statins are well tolerated. However, their intake can be accompanied by side effects in the form of abdominal pain, bloating, constipation. Elevated levels of liver enzymes (ALT, AST by more than 3 times and CPK by more than 10 times) are observed in 0.5–1.5% of patients taking statins. Increase in liver enzyme activity is dose dependent. According to the TNT study, 80 mg/day of atorvastatin, compared with 10 mg/day, was associated with statistically significant increase in liver enzymes [41].

During statin treatment, there are rarely observed (0.1–0.5%) myopathy and myalgia, which symptoms are pain and weakness in the muscles, but not an increase in CPK. The most dangerous complication of statin therapy is rhabdomyolysis or muscle breakdown with the possible damage of the renal tubules. It is a severe, life-threatening disease with a very high level of CPK (10 or more times higher than normal) and creatinine in blood. Patients' urine becomes brown and myoglobin is determined by urinalysis. This complication is extremely rare — 0.1% of case over 1 million prescriptions [42]. Risk of rhabdomyolysis is increased when statins are prescribed at the same time with fibrates, cytostatics, and macrolides (antibiotics). There is a wide discussion about the use of statins in patients with renal insufficiency.

In patients with glomerular filtration rate ≥30 ml/min/1.73 m^2, statins can be used in both small and high doses, whereas in hemodialysis patients (or glomerular filtration rate <30 ml/min/1.73 m^2), doses of some statins should be reduced by 2 times [43].

Recently, there has been some evidence of other side effects of statins. In particular, in the JUPITER Trial, daily dose of 20 mg of rosuvastatin in patients with high CV risk resulted in a statistically significant increase in glycated HbA1c compared with a control group (n = 270 versus n = 216, p = 0.01). Similar effects have been observed when using other statins [44]. There is also discussion in the literature about an effect of statins on erectile function. The obtained data are mixed, and studies were conducted involving a small number of patients and of relatively short duration. It is likely that we are talking about high doses of statins. This question is the subject to further research.

Thus, lipid-lowering drugs can be conditionally divided into two groups: main and auxiliary. The main group is predominant with statins which mainly decrease cholesterol levels and fibrates which mainly decrease TG and increase HDL cholesterol levels. Recently, derivatives of nicotinic acid have been increasingly used in a combination with statins. Cholesterol absorption inhibitors were originally designed for combined use with statins, but there are some publications about their successful use in combination with fibrates. In general, to achieve target lipid levels is increasingly discussed an aggressive lipid-lowering therapy (high-dose statins or their combination with other lipid-lowering drugs) (Figure 12).

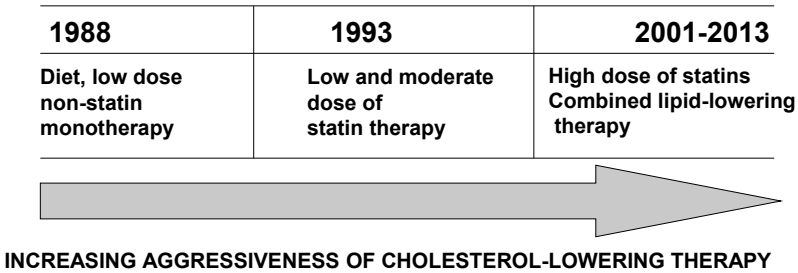


Fig. 12. Evolution of Lipid Management Guidelines: National Cholesterol Education Program

Prospects for the use of other lipid-lowering drugs

For the treatment of atherosclerosis, there have been tested a number of tools, which included antioxidants: vitamins E, A, C, probucol; preparations containing omega-3 fatty acids (maksepa, eiconol); hormone replacement drugs (estrogens); number of dietary supplements and food (garlic). Currently, according to large-scale clinical studies, the expected benefits of the majority of these tools are not obtained [45, 46]. However, in some cases, the application of some of these means is justified. Omega-3 fatty acids are administered at high doses for the treatment of severe HTG (phenotype V). A new group of drugs — protein inhibitor — cholesteryl ester transfer (torcetrapib), contributing to an increase in HDL cholesterol level, is not widely used. There are wide discussions regarding efficacy and safety of drugs with fixed-dose of two lipid-lowering drugs, in particular, statins and fenofibrate [47].

Extracorporeal methods of treatment

In cases where lipid-lowering drug therapy is not effective and/or can not be applied, there is an option to use invasive ways of treatment for disorders of lipid metabolism. These include: plasmapheresis and LDL apheresis. LDL apheresis is a number of extracorporeal treatments: cascade plasma filtration, heparin deposition, plasma- and hemosorption on ion-exchange or immune-sorbents. LDL apheresis is indicated for patients with homozygous and severe heterozygous forms of type IIa familial hyperlipidaemia, patients resistant to drug lipid-lowering therapy, and patients with severe hyperlipidaemia, who underwent coronary revascularization surgery or angioplasty to prevent formation of restenoses associated with the re-formation of lipid plaques [48].

Chapter 8

MANAGEMENT OF DYSLIPIDAEMIAS IN DIFFERENT CLINICAL SETTINGS

Selection of a lipid-lowering treatment strategy consists of several stages and depends on the clinical condition of a patient [6, 26]. The following are general provisions for the selection of a lipid-lowering therapy:

— Assessment of overall CV risk;

— Patients' motivation to reduce CV risk;

— Identification of target LDL cholesterol levels;

— Calculation of the required percentage of LDL cholesterol reduction to achieve target levels;

— Drug selection;

— Dose selection to achieve the result;

— If monotherapy is not effective, to use a combination of drugs.

In the leading countries of the world (USA, Australia and European countries), doctors when choosing a treatment strategy take into account an individual risk indicator of CV complications, which is determined by the following systems: Framingham and Pooled Cohort Equations in the U.S., and Systemic Coronary Risk Estimation (SCORE) in European countries, including Russia [6, 49]. The total indicator is calculated based on the following data: age, sex, smoking status, levels of blood pressure and total cholesterol. At the presence of additional risk factors, including HTG and/or low HDL cholesterol, it is necessary to use the SCORE system. These systems are used in patients with risk factors for primary prevention of CVD. Typically, in patients

without CAD, but with the presence of three or more risk factors and total cholesterol level at 5–6.5 mmol/l (or LDL cholesterol at 2.5–3 mmol/l), treatment begins with lifestyle changes. The appropriateness of a drug therapy is decided on the basis of not reaching the target cholesterol levels for 2–3 months. At the level of total cholesterol >6.5 mmol/l, drug therapy is prescribed without a probationary period.

In patients with CAD and its equivalents in all cases along with a diet, it is recommended to receive lipid-lowering therapy. TG levels in the range of 1.7–2.3 mmol/l are an indication for dietotherapy, and at levels of 2.3–5.5 mmol/l after 2–3 months, lipid-lowering therapy is prescribed. In patients with CAD and its equivalents in conjunction with normal lipid levels, it is necessary to reduce cholesterol levels by 30–40%.

A practical approach to achieve target LDL cholesterol levels

To determine the dose of a drug, the percentage reduction in LDL cholesterol levels, needed to achieve the desired result, should be appointed. Table 9 shows the calculation of the necessary percent depending on the baseline and target LDL cholesterol levels.

Table 9. **Percentage reduction in LDL cholesterol levels to achieve target values?**

Baseline of LDL cholesterol, mmol/l	**% rediction to achieve target levels**		
	< 1.8 mmol/l	**<2.5 mmol/l**	**<3.0 mmol/l**
>6.2	>70	>60	>55
5.2–6.2	65–70	50–60	40–55
4.4–5.2	60–65	40–50	30–45
3.9–4.4	55–60	35–40	25–30
3.4–3.9	45–55	25–35	10–25
2.9–3.4	35–45	10–25	<10
2.3–2.9	22–35	<10	–
1.8–2.3	<22	–	–

According to the European guidelines, selection of drug therapy for hypercholesterolaemia is presented in Table 10.

Table 10. **Recommendations for the pharmacological treatment of hypercholesterolaemia**

Recommendations	Class of recommendation	Level of evidence
Prescribe statin up to the highest recommended dose, or highest tolerable dose to reach the target level.	I	A
In the case of statin intolerance, bile acid sequestrants or nicotinic acid should be considered.	IIa	B
A cholesterol absorption inhibitor, alone or in combination with bile acid sequestrants or nicotinic acid, may also be considered in the case of statin intolerance.	IIb	C
If target level is not reached, statin combination with a cholesterol absorption inhibitor or bile acid sequestrant or nicotinic acid may be considered.	IIb	C

Medicines for the treatment of hypertriglyceridaemia

As indicated above, HTG also leads to the development of CVD. According to the recommendations, it is necessary before treatment to exclude causes of secondary HTG. It is known that the lifestyle changes can significantly reduce HTG.

In Table 11, there are European recommendations for treatment of HTG.

Table 11. Recommendations for drug treatment of HTG

Recommendations	Class of recommendation	Level of evidence
In particular high risk patients (TG >2.3 mmol/l), lowering of HTG by using the following drugs:		
is recommended: fibrates	I	B
should be considered: nicotinic acid	IIa	B
nicotinic acid + laropiprant	IIa	C
n-3 fatty acids	IIa	B
statin + nicotinic acid*	IIa	A

Recommendations	Class of recommendation	Level of evidence
statin + fibrate*	IIa	C
may be considered: combinations with n-3 fatty acids**	IIb	B

* — Evidence for additional lipid-lowering, compared with monotherapy
** — The evidence for prevention of CVD using combination therapy is in general limited.

Drugs affecting the level of HDL cholesterol

Since low levels of HDL cholesterol is an independent risk factor for early development of CVD, its increase can be considered as a secondary additional objective in patients with dyslipidaemia. Table 12 presents the main European recommendations to increase levels of HDL cholesterol.

Table 12. **Recommendations if drug treatment of low HDL cholesterol is considered**

Recommendations	Class of recommendation	Level of evidence
Nicotinic acid is currently the most efficient drug to raise HDL cholesterol and should be considered.	IIa	A
Statins and fibrates raise HDL cholesterol with similar magnitude and these drugs may be considered.	IIb	B
The efficacy of fibrates to increase HDL cholesterol may be attenuated in people with type 2 diabetes.	IIb	B

Chapter 9

COMBINATION LIPID–LOWERING THERAPY: INDICATIONS, EFFICACY, SIDE EFFECTS AND CONTRAINDICATIONS

In practice, combined dyslipidaemia is often found, so it is important to prescribe combination therapy of the treatment for disorders of lipid metabolism.

In general, combined lipid-lowering therapy is prescribed in the following cases [6]:

- Treatment of familial hyperlipidaemia;
- Management of unwanted effects of one drug treatment;
- To enhance the action of a drug for refractory hyperlipidaemia;
- To reduce the cost of treatment through the use of low doses of two drugs, rather than a high-dose of one (in Russia this option is not justified);
- To achieve the target levels of cholesterol when it was not previously atchieved.

A combination of a statin and cholesterol absorption inhibitor is considered to be one of the most effective and safe for lowering total and LDL cholesterol, and it is used in IIa and IIb types of hyperlipidaemia [31]. In recent years, a combination of statins with fibrates has been widely discussed. Several studies have shown that the combination of statins with fenofibrate is safer than the combination of statins with other fibrate — gemfibrozil [50]. This concept formed the basis of a project to create a combined drug with fixed-doses of

simvastatin and fenofibrate. The combination of these drugs can be applied at types IIa, IIb and III hyperlipidaemia.

Due to the relevance of simultaneous management of hypercholesterolaemia and low levels of HDL cholesterol, a combination of statins with nicotinic acid derivatives can be used in patients with types IIa and IIb hyperlipidaemia. But the side effects of the latter in the forms of vasodilation and hot flushes may reduce patients' adherence to the therapy [30].

For the management of distinct HTG (types IV and V hyperlipidaemia) are shown combinations of fibrates with nicotinic acid derivatives or with fish oil. Fish oil (omega-3 fatty acids) may also be used in a combination with statins in patients with type IIa and IIb hyperlipidaemia [45, 46].

Contraindications to a combination lipid-lowering therapy are the following conditions [6]:

- Individual intolerance (severe skin reactions and diseases of the gastrointestinal tract);
- Active and severe chronic liver disease (ALT/AST is 2 times above the upper limit of normal);
- Myopathy with increased CPK by more than ten above the upper limit of normal;
- Renal failure (creatinine >300 micromol/l or >3 mg/dl).

Chapter 10

MONITORING OF LIPIDS AND ENZYMES IN PATIENTS ON LIPID–LOWERING THERAPY

In order to control the effectiveness and safety of lipid-lowering therapy, monitoring of lipid levels and blood enzymes is recommended.

Table 13 shows detection rate of lipid profile and monitoring of liver (ALT, AST) and muscles (CPK) enzymes when selecting a therapy [6].

Table 13. **Summary of recommendations for monitoring lipids and enzymes in patients on lipid-lowering therapy**

Testing lipids
How often should lipids be tested? • Before starting lipid-lowering drug treatment, at least two measurements should be made, with an interval of 1–12 weeks, with the exception of conditions where immediate drug treatment is suggested such as in ACS.
How often should patient's lipids be tested after starting lipid-lowering treatment? • 8 (±4) weeks after starting drug treatment. • 8 (±4) weeks after adjustments to treatment until within the target range.
How often should cholesterol or lipids be tested once a patient has reached target or optimal cholesterol? • Annually (unless there are adherence problems or another specific reason for more frequent reviews).
Monitoring liver and muscle enzymes
How often should liver enzymes (ALT) be routinely measured in patients taking lipid-lowering drugs? • Before treatment • 8 weeks after starting drug treatment or after any dose increase • Annually thereafter if liver enzymes are <3×upper limit of normal.

What if liver enzymes become raised in a person taking lipid-lowering drugs? If <3×upper limit of normal: • Continue therapy • Recheck liver enzymes in 4–6 weeks If values rise to ≥3×upper limit of normal: • Stop statin or reduce dose, recheck liver enzymes within 4–6 weeks • Cautious reintroduction of therapy may be considered after ALT has returned to normal.
How often should CPK be measured in patients taking lipid-lowering drugs? Pre-treatment • Before starting treatment • If baseline CPK level >5×upper limit of normal, do not start drug therapy; recheck Monitoring • Routine monitoring of CPK is not necessary • Check CPK if patient develops myalgia Increase alertness regarding myopathy and CPK elevation in patiens at risk such as: elderly patients, concomitant interfering therapy, multiple medications, liver or renal disease.
What if CPK becomes raised in a person taking lipid-lowering drugs? If >5×upper limit of normal: • Stop treatment, check renul function and monitor CPK every 2 weeks • Consider the possibility of transient CPK elevation for other reasons such as muscle exertion • Consider secondary causes of myopathy if CPK remains elevated If ≤5×upper limit of normal: • If no muscle symptoms, continue statin (patients should be alerted to report symptoms; consider futher checks of CPK) • If muscle symptoms, monitor symptoms and CPK regularly.

Requirements for safety monitoring with a combination of two or more lipid-lowering drugs compared with monotherapy are stricter, because the risk of adverse events increases [51].

For safety control, levels of ALT, AST, CPK, creatinine, and full blood count are initially determined. Repeated monitoring of these parameters is assigned 4–6 weeks after the beginning of treatment.

Chapter 11

THERAPY FOR DISORDERS OF LIPID METABOLISM IN VARIOUS CLINICAL SITUATIONS

In European guidelines, there is a detailed strategy for management of disorders of lipid metabolism in some groups of patients [6]. They include people with familial dyslipidaemia, elderly patients, people with metabolic syndrome and diabetes, with heart failure (HF) and valvular disease, autoimmune diseases, kidney disease, peripheral arterial disease (PAD), stroke, transplantation, and human immunodeficiency virus (HIV). It must be emphasized that recommended therapy is determined on the basis of clinical trials.

Familial hyperlipidaemia

It is known that the blood lipid levels are largely determined by genetic factors. Expressed forms of lipid disorders manifest as familial hyperlipidaemia. If a form of familial hyperlipidaemia has been suspected, it is necessary to consult in a specialist lipid clinic. Table 14 presents a summary on diagnosis and treatment of familial hyperlipidaemia [6].

Table 14. **Diagnostic criteria for the clinical diagnosis of heterozygous FH**

	Criteria	Score
Family history	First-degree relative known with premature CAD* and/or first-degree relative with LDL cholesterol >95th centile	1

	Criteria	Score
	First-degree relative with tendon xanthomata and/or children < 18 with LDL cholesterol >95th centile	2
Clinical history	Patient has premature CAD*	2
	Patient has premature cerebral/peripheral vascular disease	1
Physical examination	Tendon xanthomata	6
	Arcus cornealis below the age of 45 years	4
LDL cholesterol, mmol/l	>8.5	8
	6.5–8.4	5
	5.0–6.4	3
	4.0–4.9	1
Definite FH		Score > 8
Probable FH		Score 6–8
Possible FH		Score 3–5
No diagnosis		Score < 3

* Premature CAD: male before 55, women before 60 years of age.

Table 15 presents the main recommendations for the treatment of patients with familial hyperlipidaemia.

Table 15. **Recommendations for detection and treatment of patients with FH**

Recommendations	Class of recommendation	Level of evidence
FH is suspected in patients with CVD aged <50 years among men or <60 years among women, in subjects with relatives with premature CVD or in subjects with known FH in the family.	I	C
It is recommended to confirm the diagnosis with clinical criteria or whenever the resources are available with DNA analysis.	I	C
Family screening is indicated when a patient with FH is diagnosed.	I	C

Recommendations	Class of recommen-dation	Level of evidence
Children of parents with FH are recommended: • to be diagnosed as early as possible • to be educated to adopt a proper diet • to receive pharmacological treatment in late childhood or in adolescence.	I	C
Children with HoFH need special attention already from the first year of life.	I	C
Target levels of LDL cholesterol are <2.5 mmol/l or in the presence of CVD are <1.8 mmol/l. If targets cannot be reached, maximal reduction of LDL cholesterol should be considered using appropriate drug combination in tolerated doses.	IIa	C

Management of patients with familial hyperlipidaemia not only involves consulting on healthy lifestyles and appointment of lipid-lowering therapy, but also faster examination to identify atherothrombotic disease.

Recommendations for women

An impact of lipid-lowering therapy is equal in men and women [52].

- Statin treatment is recommended for primary prevention of CAD in high risk women.
- Statins are recommended for secondary prevention in women with the same indications and targets as in men.
- Lipid-lowering drugs should not be given when pregnancy is planned, during pregnancy or during the breast feeding period.

Elderly patients

In elderly patients in high risk group, assignment of lipid-lowering drugs has a beneficial effect with a reduction in CV morbidity and mortality (Table 16).

Table16. **Recommendations for treatment of dyslipidaemia in the elderly**

Recommendations	Class of recommen-dation	Level of evidence
Treatment with statins is recommended for elderly patients with established CVD in the same way as for younger patients.	I	B
Since elderly people often have comorbidities and have altered pharmacokinetics, it is recommended to start lipid-lowering medication at a low dose and then titrate with caution to achieve target lipid levels which are the same as in the younger subjects.	I	C
Statin therapy may be considered in elderly subjects free of CVD, particularly in the presence of at least one other CV risk factor besides age.	IIb	B

Metabolic syndrome and diabetes

Patients with metabolic syndrome and especially type 2 diabetes have higher CVD risk than the rest of population. Disorders of lipid metabolism precede type 2 diabetes for several years, and are commonly found in patients with abdominal obesity, metabolic syndrome, and type 2 diabetes [53, 54].

— Dyslipidaemia in metabolic syndrome includes an increase in TG (postprandial and fasting), apo B, and LDL, and a decrease in HDL and apo A1;

— Non-HDL cholesterol or apo B are good indirect markers of lipoprotein containing TG, and are the secondary targets of therapy (non-HDL cholesterol <3.3 mmol/l);

— Increased waist circumference and increased TG are good indicators for identifying high-risk patients with metabolic syndrome;

— Atherogenic dyslipidaemia is one of the major risk factors for CVD in patients with type 2 diabetes.

Table 17 shows the European recommendations for determining a treatment strategy for disorders of lipid metabolism in patients with type 2 diabetes.

Table 17. **Recommendations for treatment of dyslipidaemia in diabetes**

Recommendations	Class of recommendation	Level of evidence
In all patients with type 1 diabetes and in the presence of microalbuminuria and renal disease, LDL cholesterol lowering with statins as the first choice is recommended irrespective of the basal LDL cholesterol concentration.	I	C
In patients with type 2 diabetes and CVD or CKD, and in those without CVD who are over the age of 40 years with one or more other CVD risk factors or markers of target organ damage, the recommended goal for LDL cholesterol is <1.8 mmol/l and secondary goal for non-HDL cholesterol is <2.6 mmol/l and for apo B <80 mg/dl.	I	B
In all people with type 2 diabetes LDL cholesterol <2.5mmol/l is the primary target. Non-HDL cholesterol <3.3 mmol/l and apo B <100 mg/dl are the secondary targets.	I	B

Heart failure and valvular disease

Although data of some studies suggest that statins may reduce the appearance of HF in patients with CAD, there was no evidence of beneficial effects of this therapy in patients with HF and valvular disease [55, 56] (Table 18).

Table 18. **Recommendations for treatment of dyslipidaemia in HF or valvular disease**

Recommendations	**Class of recommendation**	**Level of evidence**
n-3 polyunsaturated fatty acids may be considered to be added to optimal treatment in patients with HF (New York Heart Association classification II–IV).	IIb	B

Recommendations	Class of recom-mendation	Level of evidence
Cholesterol-lowering therapy with statins is not indicated in patients with moderate to severe HF (New York Heart Association classification III–IV).	III	A
Lipid-lowering treatment is not indicated in patients with valvular disease without CAD.	III	B

Autoimmune diseases

Autoimmune diseases are characterized by extensive atherosclerotic lesions and, thus, a higher level of morbidity and mortality in comparison with the rest of population (Table 19).

Table 19. **Recommendations for treatment of dyslipidaemia in autoimmune diseases**

Recommendations	Class of recom-mendation	Level of evidence
As yet there is no indication for the preventive use of lipid-lowering drugs only on the basis of the presence of autoimmune diseases.	III	C

Kidney disease

Decreased glomerular filtration rate is associated with an increased risk of CVD independent of other risk factors [57–59]. Dyslipidaemia in kidney disease is usually accompanied by an increase in TG and a decrease in HDL cholesterol, while the values of total and LDL cholesterol are less pronounced (Table 20).

Table 20. **Recommendations for lipid lowering drugs in patients with moderate to severe CKD (stages 2–4, glomerular filtration rate 15–89 ml/min/1.73 m^2)**

Recommendations	Class of recommendation	Level of evidence
CKD is acknowledged as a CAD risk equivalent; in these patients LDL cholesterol reduction is recommended as the primary target of therapy.	I	A
LDL cholesterol lowering reduces CVD risk in CKD subjects and should be considered.	IIa	B
Statins should be considered to slow the rate of kidney function loss modestly and thus protect against the development of end-stage renal disease requiring dialysis.	IIa	C
Since statins have a beneficial effect on pathological proteinuria (>300 mg/day) they should be considered in patients with stage 2–4 CKD.	IIa	B
In moderate to severe CKD statins as monotherapy or in combination with other drugs should be considered to achieve LDL cholesterol <1.8 mmol/l.	IIa	C

Transplant patients

Lipid disorders are common in patients undergoing transplantation of an organ, and contribute to the development of both atherosclerosis and transplant vasculopathy, giving rise to most vascular diseases [60, 61]. Table 21 provides recommendations for management of lipid disorders in patients after trasnplantation in terms of evidence-based medicine.

Table 21. **Recommendations for treatment of dyslipidaemia in transplant patients**

Recommendations	**Class of recommendation**	**Level of evidence**
Global CV risk management strategies are a priority in transplant patients.	I	C

Recommendations	Class of recommendation	Level of evidence
Statins should be considered as the first-line agents in transplant patients. Initiation should be at low doses with careful up-titration and with caution regarding potential drug–drug interactions, particularly for those on ciclosporin.	IIa	B
In patients who are intolerant of statins, alternative or additional therapy may be considered: ezetimibe for those where high LDL cholesterol is the principal abnormality; fibrates or nicotinic acid for those where hypetriglyceridaemia and/or low HDL cholesterol is the principal abnormality.	IIa	C

Peripheral arterial disease

Presence of PAD in a patient is an independent risk factor for MI and CVD death [61]. Risk with the presence of PAD is equivalent to risk with CAD, so these patients have the same treatment strategies (Table 22).

Table 22. **Recommendations for lipid-lowering drugs in patients with PAD**

Recommendations	Class of recommendation	Level of evidence
PAD is a high risk condition, and lipid-lowering therapy (mostly statins) is recommended in these patients.	I	A
Statin therapy is recommended to reduce the progression of carotid atherosclerosis.	I	A
Statin therapy is recommended to prevent the progression of aortic aneurysm.	I	C

Cerebral stroke

The relationship between dyslipidaemia and CVD including ischemic stroke and transient ischaemic attack has been well studied.

Lipid-lowering therapy has a beneficial effect on reducing the frequency of non-haemorrhagic stroke and recurrence [62]. Below are the recommendations for the management of disorders of lipid metabolism for primary and secondary prevention of stroke (Table 23).

Table 23. **Recommendations for lipid-lowering drugs for primary and secondary prevention of stroke**

Recommendations	Class of recommendation	Level of evidence
Statin therapy to reach established treatment goals is recommended in patients at high global risk.	I	A
Statin therapy is recommended in patients with other manifestations of CVD.	I	A
Statin therapy is recommended in patients with a history of non-cardioembolic ischaemic stroke or transient ischaemic attack.	I	A

HIV patients

Highly active antiretroviral therapy causes an increase in LDL cholesterol and TG, which doubles the risk for CVD [63].

There is no data on the efficacy of statins, ezetimibe, niacin, and fibrates in patients with HIV.

Lipid-lowering drugs (mostly statins) are prescribed to patients with HIV in the presence of dyslipidaemia to achieve the standard target values of blood lipids (class of recommendation IIa, level of evidence C).

Chapter 12

HOW TO IMPROVE PATIENTS' ADHERENCE TO LIFESTYLE CHANGES AND DRUG THERAPY?

One of the important issues of therapy for disorders of lipid metabolism is a commitment to lipid-lowering therapy. In real practice, in most cases, there are problems with performing of long-term lipid-lowering therapy. Leading international experts suggest several ways to improve adherence to long-term lifestyle changes and lipid-lowering pharmacotherapy [6].

Hints to help adherence to lifestyle changes

Develop a good alliance with the patient.

Make sure that the patient understands how lifestyles affect CV disease and use this to gain commitment to the change in behaviour.

- Explore potential barriers to the change.
- Design with the patient a lifestyle change plan that is realistic and encouraging.
- Reinforce the patient's efforts to change.
- Involve other experts wherever needed and possible.
- Arrange a schedule of follow-up visits.

Tips to help compliance with multiple drug therapies

- Simplify the dosing regimen if possible by reducing daily doses and concomitant medications.
- Choose cheaper alternatives.
- Provide clear written and oral instructions.
- Undertake a dialogue with the patient regarding adherence.
- Tailor the regimen to the patient's lifestyle and needs.
- Involve the patient as partner in the treatment.
- Use behavioural strategies (reminder systems, cues, self-monitoring, feedback, reinforcement).

Chapter 13

COMPARATIVE ANALYSIS OF NEW AMERICAN AND EUROPEAN RECOMMENDATIONS: CONSENSUS ON THE TREATMENT OF PATIENTS WITH DISORDERS OF LIPID METABOLISM

It is known that international recommendations based on evidence are developed on the basis of three sources:

1. Experimental studies to investigate lipid metabolism and action of new agents;
2. Clinical studies examining the efficacy of non-pharmacological interventions and medications;
3. Epidemiological studies to monitor the prevalence of dyslipidaemia and assessment of CV risk.

In the hierarchy of international recommendations, American recommendations traditionally occupy the first place, followed by recommendations of the *European Society of Cardiology* (ESC). International and national guidelines are adapted.

At the end of 2013, the *ACC* and *AHA* released joint recommendations for the treatment of cholesterol in order to reduce atherosclerosis (2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic CV Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines), which provoked strong debates and criticism in broad scientific community. The reason is radical changes in some

previously adopted strategies for the treatment of hypercholesterolaemia. A short time later the European experts on atherosclerosis released newsletter entitled «New guidelines in USA: 2013 ACC/AHA Guidelines on the Treatment of Blood Cholesterol to Reduce Atherosclerotic CV Risk. How do they compare with the *European Atherosclerosis Society* (EAS)/ ESC guidelines for the management of dyslipidaemia?» [6, 26].

This chapter presents main contradictions between the two recommendations. A consensus is also offered for the treatment of dyslipidaemia, taking into account both positions on monitoring of disorders of lipid metabolism.

What level of CV risk is an indication for medical treatment?

Talking about the contribution of dyslipidaemia treatment in CVD prevention, its role in primary and secondary prevention must be emphasized [64, 65].

Effectiveness of primary prevention, including reducing LDL cholesterol, has been proven in numerous clinical studies. For the purpose of drug therapy prescription in both recommendations, the basic principle is the level of total CV risk.

European and American recommendations emphasize the importance of reducing LDL cholesterol for secondary prevention. To do so, there should be clinical manifestations of atherosclerosis (ACS or history of MI, stable or unstable angina, coronary or other arterial revascularization, cerebral atherosclerosis, and atherosclerosis of peripheral arteries) [6, 26]. In some cases (European recommendations) diabetes is considered as equivalent to CVD and requires therapy regardless of the presence of CVD.

Determination of total CV risk by European SCORE system is based on the following parameters: age, gender, total cholesterol, systolic blood pressure and smoking status. In the *EAS/ESC* recommendations, risk stratification is represented by division into four groups according to the general level of CV risk: very high, high, moderate and low risk. Prevention is recommended in accordance with the general assessment of CV risk.

The Pooled Cohort Equations were developed as an annex to the 2013 ACC/AHA Guideline to determine CV risk. This system allows estimating 10-year risk of CVD complications associated with atherosclerosis (coronary death, nonfatal MI, fatal or nonfatal stroke). This system of CV risk is designed for individuals with LDL cholesterol levels <190 mg/dl. To determine the risk, the following information is necessary: age, sex, race, total cholesterol, HDL cholesterol, systolic blood pressure, use of antihypertensive medications, diabetes status, and smoking status.

The *EAS/ESC* recommendations propose to consider LDL cholesterol-lowering medication for primary prevention when total CV risk is high (5–10%) or very high (>10%), and / or in patients with moderate CV risk and LDL cholesterol levels ≥2.5 mmol/l (100 mg/dl), despite lifestyle change.

The new *ACC/AHA* recommendations suggest statin treatment for primary prevention in patients with 7.5% risk of CV complications of atherosclerosis, regardless of the level of LDL cholesterol. This level corresponds to a 2.5% risk of death from CV causes within 10 years in accordance with the SCORE system. This *ACC/AHA* strategy manifests itself in the form of increasing the number of patients who will be assigned to lifelong treatment with statins from age of 40 years and older. Taking into account the use of statins by most of the population, the probability of side effects from the drugs is quite high.

On which option to be oriented: LDL or non-HDL cholesterol?

In most clinical trials, the level of LDL cholesterol is used as an indicator or marker of lipid-lowering therapy efficacy. Moreover, the target level of LDL cholesterol is primary for a drug therapy strategy. On the other hand, some studies have shown that in certain clinical situations non-HDL cholesterol may be a better marker for evaluating the efficacy of therapy compared with LDL cholesterol, for example, in patients with HTG, diabetes, metabolic syndrome, and etc. This hypothesis is supported by results of a meta-analysis of 14 large clinical trials involving statins, 7 studies with fibrates, and 6 studies with nicotinic acid derivatives.

The new American guidelines argue that there is no evidence to support further use levels of LDL cholesterol and/or non-HDL cholesterol as target levels of lipid-lowering therapy. As an alternative, to reduce CV risk it is suggested to use statin therapy of different intensities. According to American experts non-statin lipid-lowering therapy alone or in addition to statin therapy does not provide acceptable benefits of reducing CV risk in comparison with their potential adverse effects in routine clinical practice.

Thus, the new American guideline does not recommend using levels of LDL and non-HDL cholesterol as indicators or markers to evaluate the efficacy of statin therapy.

Treatment strategy: target levels of lipid or intensity of treatment?

According to two recommendations, strategy of lipid-lowering therapy can be divided into two types:

Strategy № 1 or the European approach

Achievement of target levels (LDL cholesterol <1.8 mmol/l with CVD and <2.5 mmol/l without CVD). Target levels are the most important tool in everyday clinical practice, helping the patient and physician interaction to improve adherence to therapy. Target levels of therapy are widely used in various clinical conditions, such as in hypertension or type 2 diabetes treatments [8].

Strategy № 2 or the new American approach

It is high (≥50%, mainly for secondary prevention) or moderate (30% <50%, mainly for primary prevention) intensity of statin therapy. The final choice of strategy often remains in place for a clinician [7].

In European guidelines compromise options are also applied. It is proposed, for example, to lower LDL cholesterol by 50% from baseline as a target in patients with very high CV risk, if it is not possible to reach the level of LDL cholesterol <1.8 mmol/l (70 mg/dl).

Is it only statins?

The *ACC/AHA* recommendations focus on statin therapy for the prevention of CVD and distinguish four groups of patients requiring statin therapy:

1. People with clinically manifested atherosclerosis;
2. People with a primary increase in LDL cholesterol levels >4.9 mmol/l (190 mg/dl);
3. People with diabetes, aged 40–75 years, with the levels of LDL cholesterol between 1.8–4.9 mmol/l (70–189 mg/dl) without clinical manifestations of atherosclerosis;
4. People without clinical manifestations of atherosclerosis or diabetes, with LDL levels between 1.8–4.9 mmol/l, and the risk of clinical manifestations of atherosclerosis in 10 years ≥7.5% [7].

The *EAS/ESC* recommendations along with statins also include an in-depth discussion of options for medical treatment with other groups of drugs, not just statins. This principle is based on the effect of lipid-lowering drugs on different sections of lipid metabolism. It is known that statins inhibit cholesterol synthesis in the liver and increase the number of LPL receptors. This is the main but not the only pathway for metabolism of cholesterol and other lipids. Experimental and clinical studies have demonstrated that in lipid metabolism, an important role belongs to delivery of exogenous fat into the body and reverse cholesterol absorption in the intestine, etc.

Before and after the widespread use of statin, efficacy of other lipid-lowering drugs in the prevention of CVD has been proven in several clinical studies.

In general, the *EAS/ESC* recommendations suggest a broader approach for the management of dyslipidaemia.

Summary data on similarities and differences for selection of drug therapy

Table 24 summarizes similarities and differences in the use of drug therapy between European and American guidelines on the treatment of dyslipidaemia. According to data, the main differences between

the two recommendations are such indicators as target levels, level of overall risk and selection of tactics for drug therapy.

Table 24. **Data on similarities and differences in the use of drug therapy between European and American recommendations**

	EAS/ESC	AHA/ACC
Secondary prevention	Target LDL cholesterol <1.8 mmol/l, or at least 50% reduction. If target cannot be reached with statin, drug combination may be considered.	High-intensity statin. If 50% reduction is not reached drug combination may be considered.
Statin intolerance in secondary prevention	Reduce statin dose, consider combination therapy.	Moderate or low dose statin, consider combination therapy
Primary preven-tion LDL >4.9 mmol/l	Target LDL cholesterol <2.5 mmol/l. If target cannot be reached maximal reduction of LDL cholesterol, using appropriate drug combinations in tolerated doses.	High-intensity statin therapy, aimed at achieving at least 50% reduction of LDL cholesterol. If 50% reduction cannot be achieved, consider additional therapy.
Primary prevention in diabetes	Diabetes with other risk factors or organ damage: Target LDL cholesterol ≤1.8 mmol/l, or at least 50% reduction. Uncomplicated diabetes: Target LDL <2.5 mmol/L.	Diabetes with high risk: High-intensity statin therapy. Diabetes with low risk: Moderate-intensity statin therapy
Primary prevention High risk	SCORE ≥5% risk of fatal CVD: Target <2.5 mmol/l.	Total risk for CVD event >7.5%: Moderate- to high-intensity statin therapy. Risk 5–7.5% risk of CVD event: Moderate-intensity statin therapy.

Consensus on the treatment of patients with dyslipidaemia

Thus, developers of American and European recommendations bring their scientific arguments and clinical studies. Taking into

account the similarities and contradictions of both recommendations, it is possible to construct a scheme of treatment of disorders of lipid metabolism. This is a kind of consensus between the two recommendations that have two main similarities:

1. The need to reduce LDL cholesterol in the prevention of CVD;
2. Patients at high CV risk should be treated with medicines.

In general, a treatment strategy depends on the type of prevention. For this purpose, patients are divided into two groups:

1st group of patients with risk factors without CVD — primary prevention,

2nd group of patients with risk factors and CVD — secondary prevention.

For primary prevention of CVD, it is necessary, first of all, to determine the level of CV risk. In our case, we recommend using the European SCORE system. Simultaneously, it is recommended to determine levels of fasting lipids. Along with this, it is recommended to define a clinical group category, as each of them has its own characteristics in the selection of treatment. The individual clinical groups include people with the following nosologies: familial dyslipidaemia, elderly patients, patients with metabolic syndrome, diabetes, heart failure, valvular disease, autoimmune diseases, kidney disease, peripheral arterial disease, stroke, transplantation, and human immunodeficiency virus.

To conduct drug therapy for primary CVD prevention, patients are divided into two groups: high or very high cardiovascular risk.

Patients with high CV risk are recommended lifestyle changes and moderate or intensive therapy (often with statins). To assess the effectiveness of therapy, it is necessary to monitor level of CV risk, as well as lipid profile in order to determine the achievement of target levels.

For secondary prevention, it is also necessary to determine the level of lipid parameters and determine the clinical group. Purpose of the treatment is to achieve target levels of LDL cholesterol or decrease its level by 50% (in some cases 30–50%).

Patients with other disorders of lipid profile (for example, HTG, low HDL cholesterol) should also have drug therapy, including using other lipid-lowering drugs (Figure 13).

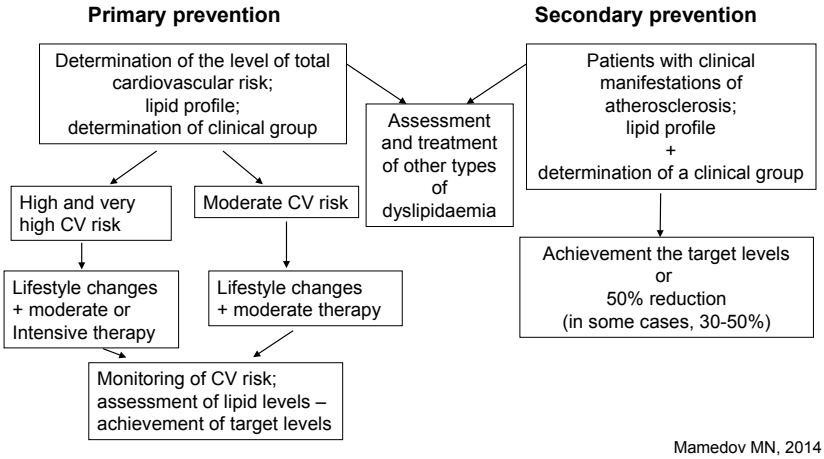


Fig. 13. Consensus on the treatment of patients with dyslipidaemia

We hope that the presented consensus takes into account the advantages and disadvantages of both recommendations and will serve as a practical guide for clinicians.

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Appendix 1

CLASSES OF RECOMMENDATIONS AND LEVELS OF EVIDENCE

Tables 1 and 2 show the classes of recommendations and levels of evidence on which the benefits and efficacy of various interventions are assessed.

Table 1. **Classes of recommendations**

Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.
Class III*	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.

* The use of Class III is not recommended by the *European Society of Cardiology*

Table 2. **Levels of evidence**

A	Data derived from multiple randomized clinical trials or meta-analyses.
B	Data derived from a single randomized clinical trial or large non-randomized studies.
C	Consensus of opinion of experts and/or small studies, retrospective studies, registries.