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FACULTY OF POSTGRADUATE AND PRE-UNIVERSITY EDUCATION

MANAGEMENT OF LIPID DISORDERS

Methodological matherials for independent study for students

UZHHOROD

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FACULTY OF POSTGRADUATE AND
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Methodical matherials are devoted to issues of etiopathogenesis, symptoms, diagnosis and treatment methods of dyslipidaemia. The authors also tried to highlight different diseases and conditions which may lead to lipid disorders. The methodical matherials are intended for senior year students of higher medical educational institutions.

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Background

Dyslipidemias are conditions in which plasma concentrations of lipids, lipoproteins, or triglycerides are considered elevated based on the patient's total cardiovascular disease risk.

Hypercholesterolemia, an elevation of total cholesterol (TC) and/or LDL-C or non-HDL-C (defined as the subtraction of HDL-C from TC) in the blood, is also often referred to as dyslipidemia, to encompass the fact that it might be accompanied by a decrease in HDL-C, an increase in triglycerides, or qualitative lipid abnormalities. Dyslipidemia is classified as serum TC, LDL-C, triglycerides, apolipoprotein B, or lipoprotein(a) concentrations above the 90th percentile, or HDL-C or apolipoprotein A-I concentrations below the 10th percentile for the general population.

Hypercholesterolemia is an important risk factor for atherosclerotic cardiovascular disease, including cerebrovascular disease, coronary heart disease, and peripheral arterial disease; it is usually symptomatically quiescent until significant atherosclerosis has developed.

The epidemiology of dyslipidemia varies by region, age, sex, and ethnicity and is influenced by genetic and environmental factors. According to a systematic review protocol, the global prevalence of dyslipidemia in adults is estimated to range from 20% to 80%, depending on the definition and criteria used. However, comprehensive and updated data on the epidemiology of dyslipidemia is currently lacking in different populations and settings.

The incidence and mortality of dyslipidemia are challenging to measure directly, as dyslipidemia is usually asymptomatic and often coexists with other risk factors, such as hypertension, diabetes, obesity, and smoking.

Hypercholesterolemia is treated with lifestyle modifications such as dietary changes, exercise, and smoking cessation, as well as pharmacologic intervention with statin therapy and selective use of other lipid-lowering drugs.

Etiology

Dyslipidemia, characterized by aberrations in lipid metabolism, has multifaceted etiologies influenced by genetic, environmental, and lifestyle factors. Understanding these etiologies is crucial for developing targeted interventions and preventive strategies. Dyslipidemia can be classified into 2 types based on the etiology:

- ***Primary dyslipidemia***

This type of dyslipidemia is caused by genetic mutations that affect the metabolism of lipids. Primary dyslipidemia can be inherited as an autosomal dominant, autosomal recessive, or X-linked. Some examples of primary dyslipidemia are familial hypercholesterolemia, familial hypertriglyceridemia, familial combined hyperlipidemia, and familial dysbetalipoproteinemia.

The mechanisms of primary dyslipidemia involve defects in the synthesis, transport, or degradation of lipoproteins, which are the main carriers of lipids in the blood. These defects result in the accumulation or deficiency of lipoproteins and lipids in the blood, increasing the risk of atherosclerosis and cardiovascular disease. For example, familial hypercholesterolemia is caused by mutations in the LDL receptor gene, impairing LDL cholesterol uptake from the blood and leading to high LDL cholesterol levels and premature atherosclerosis.

Familial hypertriglyceridemia is caused by mutations in the LPL gene or the apo C-II gene, which impair the hydrolysis of triglycerides in chylomicrons and very low-density lipoproteins (VLDL), leading to high triglyceride levels and pancreatitis. Familial combined hyperlipidemia is caused by the overproduction of

apo B-containing lipoproteins, such as VLDL and LDL, by the liver, leading to high cholesterol and triglyceride levels and insulin resistance. Familial dysbetalipoproteinemia is caused by mutations in the apo E gene, which impair the clearance of chylomicron and VLDL from the blood, leading to high cholesterol and triglyceride levels and xanthomas.

- ***Secondary dyslipidemia***

This type of dyslipidemia is caused by lifestyle factors or other medical conditions that alter the levels of lipids in the blood. Secondary dyslipidemia is reversible or modifiable by addressing the underlying cause. Some examples of secondary dyslipidemia risk factors include physical inactivity, unhealthy nutrition, obesity, diabetes, hypothyroidism, chronic kidney disease, liver disease, alcohol abuse, smoking, and the use of certain drugs.

- Obesity is associated with increased production of very low-density lipoprotein and decreased liver clearance of chylomicrons, leading to high triglyceride and low high-density lipoprotein cholesterol levels.
- Diabetes mellitus is associated with insulin resistance and hyperglycemia, impairing triglyceride lipolysis and the uptake of LDL cholesterol; this leads to high triglyceride and LDL cholesterol levels and low HDL cholesterol levels.
- Hypothyroidism is associated with decreased expression of LDL receptors and lipoprotein lipase, which impair the clearance of LDL cholesterol and triglycerides from the blood, leading to high LDL cholesterol and triglyceride levels.
- Chronic kidney disease is associated with impaired catabolism of apo B-containing lipoproteins and reduced activity of lipoprotein lipase and hepatic lipase, which impair the clearance of triglycerides and cholesterol from the blood, leading to high triglyceride and LDL cholesterol levels and low HDL cholesterol levels.

- Liver disease is associated with impaired synthesis and secretion of lipoproteins and bile acids, which impair the transport and excretion of cholesterol and triglycerides from the liver, leading to high or low cholesterol and triglyceride levels depending on the type and severity of the liver disease.
- Alcohol abuse is associated with increased synthesis of VLDL and decreased oxidation of fatty acids by the liver, leading to high triglyceride levels.
- Smoking is associated with increased oxidative stress and inflammation, which impair the function and synthesis of HDL cholesterol, leading to low HDL cholesterol levels.
- Use of certain drugs, such as corticosteroids, beta-blockers, oral contraceptives, and antiretroviral agents, can affect the metabolism of lipids and lipoproteins by various mechanisms, leading to high or low cholesterol and triglyceride levels depending on the type and dose of the drug.

Biological role of lipids and lipoproteins

Lipoproteins in plasma transport lipids to tissues for energy utilization, lipid deposition, steroid hormone production, and bile acid formation. Lipoproteins consist of esterified and unesterified cholesterol, TGs, and phospholipids and protein components named apolipoproteins that act as structural components, ligands for cellular receptor binding, and enzyme activators or inhibitors.

There are six major lipoproteins in blood: chylomicrons, very lowdensity lipoprotein (VLDL), intermediate-density lipoprotein (IDL), LDL; Lp(a), and HDL (tab.1).

Table 1. Physical and chemical characteristics of human plasma lipoproteins.

	Density (g/mL)	Diameter (nm)	TGs (%)	Cholesteryl esters (%)	PLs (%)	Cholesterol (%)	Apolipoproteins	
							Major	Others
Chylomicrons	<0.95	80–100	90–95	2–4	2–6	1	ApoB-48	ApoA-I, A-II, A-IV, A-V
VLDL	0.95–1.006	30–80	50–65	8–14	12–16	4–7	ApoB-100	ApoA-I, C-II, C-III, E, A-V
IDL	1.006–1.019	25–30	25–40	20–35	16–24	7–11	ApoB-100	ApoC-II, C-III, E
LDL	1.019–1.063	20–25	4–6	34–35	22–26	6–15	ApoB-100	
HDL	1.063–1.210	8–13	7	10–20	55	5	ApoA-I	ApoA-II, C-III, E, M
Lp(a)	1.006–1.125	25–30	4–8	35–46	17–24	6–9	Apo(a)	ApoB-100

Role of lipids and lipoproteins in the pathophysiology of atherosclerosis

All ApoB-containing lipoproteins <70 nm in diameter, including smaller TG-rich lipoproteins and their remnant particles, can cross the endothelial barrier, especially in the presence of endothelial dysfunction, where they can become trapped after interaction with extracellular structures such as proteoglycans. ApoB-containing lipoproteins retained in the arterial wall provoke a complex process that leads to lipid deposition and the initiation of an atheroma.

Continued exposure to ApoB-containing lipoproteins leads to additional particles being retained over time in the artery wall, and to the growth and progression of atherosclerotic plaques. On average, people with higher concentrations of plasma ApoB-containing lipoproteins will retain more particles and accumulate lipids faster, resulting in more rapid growth and the progression of atherosclerotic plaques.

Because atherosclerotic plaques grow over time as additional ApoB-containing lipoprotein particles are retained, the size of the total atherosclerotic plaque burden is likely to be determined by both the concentration of circulating LDL-C and other ApoB-containing lipoproteins, and by the total duration of exposure to these lipoproteins. Therefore, a person’s total atherosclerotic plaque burden is likely to be proportional to the cumulative exposure to these lipoproteins.

Eventually, the increase of the atherosclerotic plaque burden along with changes in the composition of the plaque reaches a critical point at which disruption of a plaque can result, with the formation of an overlying thrombus that acutely obstructs blood flow resulting in unstable angina, myocardial infarction (MI), or death. Therefore, the risk of experiencing an acute ASCVD event rises

rapidly as more ApoB-containing lipoproteins become retained and the atherosclerotic plaque burden increases. This provides the rationale for encouraging a healthy lifestyle to maintain low levels of ApoB-containing lipoproteins throughout life to slow the progression of atherosclerosis; it also explains the motivation to recommend treatment to lower LDL-C and other ApoB-containing lipoproteins, for both the primary prevention of ASCVD and the secondary prevention of recurrent CV events.

Low-density lipoprotein cholesterol and risk of atherosclerosis

Plasma LDL-C is a measure of the cholesterol mass carried by LDL particles, by far the most numerous of the ApoB-containing lipoproteins, and is an estimate of the concentration of circulating LDL. Numerous epidemiological studies, Mendelian randomization studies, and RCTs have consistently demonstrated a log-linear relationship between the absolute changes in plasma LDL-C and the risk of ASCVD.

The remarkable consistency among these studies, in addition to biological and experimental evidence, provides compelling evidence that LDL-C is causally associated with the risk of ASCVD, and that lowering LDL-C reduces the risk of ASCVD proportionally to the absolute achieved reduction in LDL-C. Furthermore, Mendelian randomization studies have demonstrated that long-term exposure to lower LDL-C levels is associated with a much lower risk of CV events as compared with shorter-term exposure to lower LDL-C (as achieved, for example, in randomized trials). These data provide strong support for the concept that LDL particles have both a causal and cumulative effect on the risk of ASCVD. Therefore, the effect of LDL-C on the risk of ASCVD appears to be determined by both the absolute magnitude and the total duration of exposure to LDL-C. The clinical benefit of lowering LDL-C is determined by the reduction in circulating LDL particles as estimated by ApoB, which is usually mirrored by a reduction of cholesterol carried by those particles.Therefore, the clinical benefit of therapies

that lower LDL-C by reducing LDL particle mass will be proportional to the absolute reduction in LDL-C, because on average the reduction in LDL-C and LDL particles will be concordant. In contrast, the clinical benefit of therapies that lower LDL-C by a mechanism that may dramatically modify their composition may not be proportional to the observed absolute reduction in LDL-C, but instead would be expected to be proportional to the absolute change in LDL particle concentration as measured by a reduction in ApoB.

Triglyceride-rich lipoproteins and risk of atherosclerosis

TG-rich VLDL particles and their remnants carry most of the circulating TGs. Therefore, the plasma TG concentration reflects the concentration of circulating ApoB-containing TG-rich lipoproteins. Elevated plasma TG levels are associated with an increasing risk of ASCVD, but this association becomes null after adjusting for nonHDL-C, an estimate of the total concentration of all ApoB-containing lipoproteins. Similarly, lowering TG with fibrates reduces the risk of CV events by the same amount as LDL-C-lowering therapies when measured per unit change of non-HDL-C, suggesting that the effect of plasma TGs on ASCVD is mediated by changes in the concentration of TG-rich lipoproteins as estimated by non-HDL-C.

High-density lipoprotein cholesterol and risk of atherosclerosis

There is currently no randomized trial or genetic evidence to suggest that raising plasma HDL-C is likely to reduce the risk of ASCVD events. Whether therapies that alter the function of HDL particles will reduce the risk of ASCVD is unknown.

Lipoprotein(a) and risk of atherosclerosis

Lp(a) is an LDL particle with an Apo(a) moiety covalently bound to its ApoB component. It is <70 nm in diameter and can freely flux across the endothelial barrier, where it can become similarly to LDL retained within the arterial wall and thus may increase the risk of ASCVD. Pro-atherogenic effects of Lp(a) have also been attributed to pro-coagulant effects as Lp(a) has a similar structure to plasminogen, and it has pro-inflammatory effects most likely related to the oxidized phospholipid load carried by Lp(a). Higher plasma Lp(a) concentrations are associated with an increased risk of ASCVD, but it appears to be a much weaker risk factor for most people than LDL-C. In contrast, Mendelian randomization studies have consistently demonstrated that lifelong exposure to higher Lp(a) levels is strongly and causally associated with an increased risk of ASCVD. While randomized trials evaluating therapies that lower Lp(a) by 2030% (including niacin and CETP inhibitors) have not provided evidence that lowering Lp(a) reduces the risk of ASCVD beyond that which would be expected from the observed reduction in ApoB-containing lipoproteins, recent data with PCSK9 inhibitors have suggested a possible role for Lp(a) lowering in reducing CV risk. This conflicting evidence appears to have been reconciled by a recent Mendelian randomization study that showed that the causal effect of Lp(a) on the risk of ASCVD is proportional to the absolute change in plasma Lp(a) levels. Importantly, this study also suggested that people with extremely high Lp(a) levels >180 mg/dL (>430 nmol/L) may have an increased lifetime risk of ASCVD similar to that of people with heterozygous FH (HeFH). Because about 90% of a person's Lp(a) level is inherited, extremely elevated Lp(a) may represent a new inherited lipid disorder that is associated with extremely high lifetime risk of ASCVD and is twofold more prevalent than HeFH. However, this study and another based on the Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial78 have shown that large absolute changes in Lp(a) may be needed to produce a clinically meaningful reduction in the risk of ASCVD events.

Classification of dyslipidemia

World Health Organization/Fredrickson classification

Classically, dyslipidaemia can be classified phenotypically by lipid electrophoresis based on which lipoprotein is raised.

Type:

• I - elevated chylomicrons; associated with lipoprotein lipase deficiency, apolipoprotein C-II deficiency

• IIa - elevated LDL; associated with familial hypercholesterolaemia, polygenic hypercholesterolaemia, nephrosis, hypothyroidism, familial combined hyperlipidaemia

• IIb - elevated LDL and very low-density lipoprotein (VLDL); associated with familial combined hyperlipidaemia

• III - elevated intermediate-density lipoprotein; associated with dysbetalipoproteinaemia

• IV - elevated VLDL; associated with familial hypertriglyceridaemia, familial combined hyperlipidaemia, sporadic hypertriglyceridaemia, abdominal obesity, diabetes

• V - elevated chylomicrons and VLDL; associated with diabetes.

Clinical classification

In a more simple and practical way, dyslipidaemia can also be classified as:

• Isolated hypercholesterolaemia: mostly due to LDL-C elevation

• Mixed or combined dyslipidaemia: elevations in total or LDL-C, and in triglycerides

• Isolated hypertriglyceridaemia: elevation in triglycerides only

• Low HDL-cholesterol (HDL-C): either isolated or in association with hypercholesterolaemia or hypertriglyceridaemia. Causes of low HDL-C include abdominal obesity with insulin resistance, hypertriglyceridaemia, smoking, and genetic diseases such as apoA-I , ABCA1 (adenosine triphosphate-binding cassette transporter), or lecithin-cholesterol acyltransferase deficiency.

Diagnosis

Patients with hypercholesterolaemia may be incidentally diagnosed on routine blood testing and have no presenting clinical features.

In most cases the clinician is presented with the consequences of long-standing dyslipidaemia. It is therefore wise to carry out a systematic review for vascular disease, focusing on symptoms of coronary artery disease, cerebrovascular disease, and peripheral arterial disease, such as chest pain, shortness of breath, weakness, dysphasia, or claudication. It is also helpful to take a detailed family history for early onset of coronary heart disease and dyslipidaemia in first-degree relatives, and ask the patient about their level of exercise and diet at this stage.

Physical examination

The patient can be examined for direct signs of hypercholesterolaemia, such as eyelid xanthelasmas, arcus cornealis (with onset before the age of 45 years), and xanthomata (fig.1,2). Tendinous xanthomas at the Achilles, elbow, and knee tendons, and over metacarpophalangeal joints, are characteristics of heterozygous and homozygous forms of familial hypercholesterolaemia.

• Palmar or cutaneous xanthomas may be present in the homozygous form of familial hypercholesterolaemia.

• Eruptive xanthomas over the trunk, back, elbows, buttocks, knees, hands, and feet may be present in severe elevations of triglycerides.

• Palmar and tuberous xanthomas are seen in patients with dysbetalipoproteinaemia. There may also be evidence of vascular disease, such as elevated neck veins or bibasal crepitations on lung auscultation (heart failure), hemiplegia (stroke), or diminished pulses (peripheral arterial disease).

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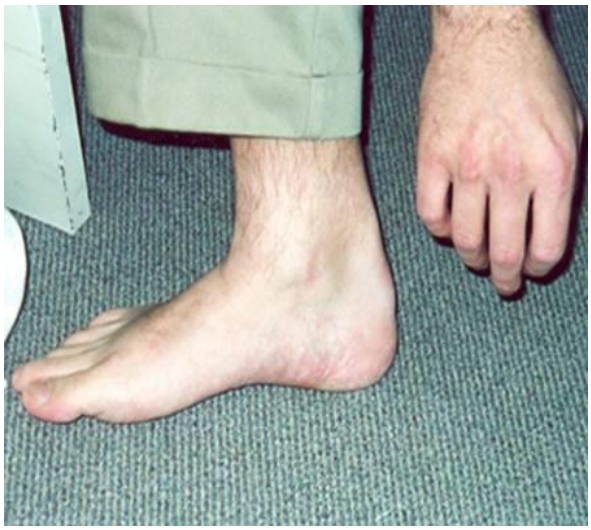


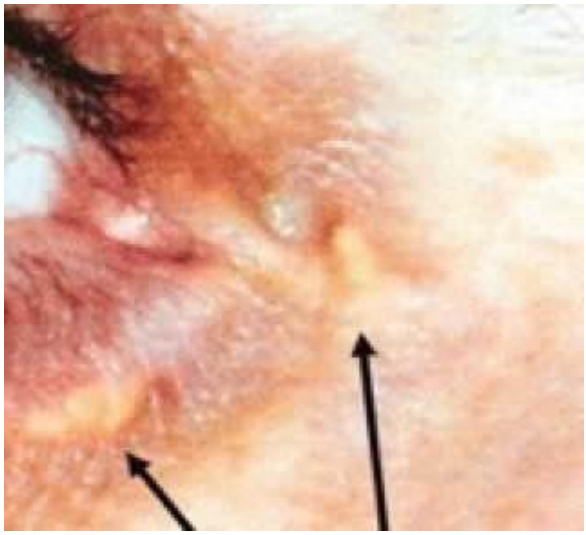


Fig. 1. Fig. 2.

Xanthomata of the Achilles' tendon (Fig. 1.)

Extravascular lipid deposits (xanthelasma) (arrows) in a patient treated with margarine enriched in plant sterols (Fig. 2.)

Investigations

Usually lipids are measured in the fasting state. This includes total cholesterol (TC), triglycerides, highdensity lipoprotein (HDL), and estimated low-density lipoprotein (LDL) (tab.3). Non-HDL-cholesterol (HDLC), defined as the subtraction of HDL-C from TC, is a marker of cholesterol carried by pro-

atherogenic lipoproteins: very low-density lipoprotein and remnants, intermediate-density lipoproteins, LDL, and lipoprotein(a). Non-HDL-C, as well as TC, HDL-C, and apolipoproteins B and A-I, can be measured in non-fasting states. However, evidence showed that even LDL can be accurately estimated in non-fasting states if triglyceride levels are < 4.5 mmol/L especially if the outdated Friedewald estimation is updated to modern higher precision methods (Martin-Hopkins method). Extremely high lipid levels may give a lactescent (milky) appearance to blood plasma. Routine thyroidstimulating hormone rules out most cases of hypothyroidism. Additional tests may be indicated by the history and examination findings to identify complications of hypercholesterolaemia. These may include creatinine levels, fasting blood glucose and glycated haemoglobin, urinalysis, ECG, echocardiogram, cardiac stress testing, cardiac computed tomography to measure coronary calcium scores or luminal obstruction, cardiac catheterisation, and vascular studies such as Doppler examination or ankle-brachial indices.

Abnormal test results:

TC >5.18 mmol/L (>200 mg/dL);

LDL-cholesterol >2.6 mmol/L (>100 mg/dL);

non-HDL-cholesterol <3.4 mmol/L (<130 mg/dL);

HDL-cholesterol <1.04 mmol/L (<40 mg/dL) for men and <1.29 mmol/L (<50 mg/dL) for women;

triglycerides >1.7 mmol/L (>150 mg/dL)

- TSH may be low in secondary hypothyroidism or elevated in primary hypothyroidism
- Lipoprotein(a) is an LDL particle with apolipoprotein(a) covalently bound to apolipoprotein B of LDL (values >50 mg/dL or >125 nmol/L are considered high)
- Genetic testing can help to confirm a diagnosis of familial hypercholesterolaemia, though a pathogenic variant in the most common genes is only identified in 30% to 80% of individuals with clinical familial hypercholesterolaemia (FH) (identification of pathogenic variant).

Diagnosis of familial hypercholesterolaemia (FH)

Patients with LDL-cholesterol (LDL-C) ≥4.9 mmol/L (≥190 mg/dL), physical findings of FH (tendinous xanthomata, arcus cornealis onset before the age of 45 years), or a personal or familial history of premature atherosclerotic cardiovascular disease with LDL-C ≥4.01 mmol/L (≥155 mg/dL) should be considered for referral to a lipid clinic, formal evaluation for FH, and/or genetic testing. Importantly, for patients already on lipid-lowering therapy, pre-treatment LDL-C levels should be accessed to evaluate for FH. If not available, providers should estimate pre-treatment LDL-C levels based on the achieved levels and the potency of lipid-lowering therapy. For instance, an LDL-C of 3.1 mmol/L (120 mg/dL) on a high-intensity statin may be the result of a 50% reduction from a baseline LDL-C of around 6.2 mmol/L (240 mg/dL). Homozygous FH is a rare but life-threatening disease, affecting 1 in 250,000-360,000 people. Early identification and specialist referral are essential and European consensus recommends screening for homozygous FH whenever it is suspected clinically and/or with premature ASCVD. Untreated LDL-C levels >10 mmol/L (>400 mg/dL) are suggestive of homozygous FH.

Dutch Lipid Clinic Network criteria (DLCNC) may be used to evaluate for FH (tab.2). Definite, probable, possible, and unlikely FH are diagnosed as with >8 points, 6-8 points, 3-5 points, and < 3 points, respectively. The 2019 Canadian Cardiovascular Society Position Statement on FH highlights that there is no definitive gold standard for the diagnosis of FH. Current scoring systems, such as the DLCNC, rely on a scoring system to increase confidence in the diagnosis. The key message is that clinicians should consider the diagnosis when caring for individuals with very elevated levels of LDL-C and seek supportive findings. The Canadian Statement suggests the following screening criteria: LDL-C ≥5.0 mmol/ L (193 mg/dL) in those ≥40 years old; ≥4.5 mmol/L (174 mg/dL) in those aged 18 to 39 years old; and ≥4 mmol/L (154 mg/dL) in individuals < 18 years old.[40] The

2019 European Society of Cardiology/ European Atherosclerosis Society guidelines recommend considering FH in patients with coronary heart disease under the age of 55 in men or 60 years in women, in those with family members with premature cardiovascular disease, in patients with relatives who have xanthomas, in adults with LDL >5 mmol/L (>190 mg/dL) or children with LDL >4 mmol/L (>154 mg/dL), and those with a first-degree relative with FH.

Table 2. Dutch Lipid Clinic Network criteria for familial hypercholesterolaemia.

Dutch Lipid Clinic Network criteria for familial hypercholesterolaemia	Points
First-degree relative with premature coronary/vascular disease (age <55 years in men, <60 years in women) OR with known LDL-cholesterol (LDL-C) >95th percentile	1
First-degree relative with tendinous xanthomata and/or arcus cornealis OR children <18 years with LDL-C >95th percentile	2
Patient with premature coronary artery disease	2
Patient with premature cerebral or peripheral vascular disease	1
Tendinous xanthomata	6
Arcus cornealis prior to age 45 years	4
LDL-C ≥8.6 mmol/L (≥330 mg/dL)	8
LDL-C 6.5-8.5 mmol/L (250-329 mg/dL)	5
LDL-C 4.9-6.5 mmol/L (190-249 mg/dL)	3
LDL-C 4.0-4.9 mmol/L (155-189 mg/dL)	1
Functional mutation in the LDL-receptor, apolipoprotein B, or PCSK9 gene	8

Table 3. Classification of low-density lipoprotein cholesterol (LDL-C), total cholesterol, triglycerides, and high-density lipoprotein cholesterol (HDL-C)

LDL-C:	**Total cholesterol:**	**Triglycerides:**	**HDL-C:**
• Optimal: <2.6 mmol/L (<100 mg/dL) • Near or above optimal: 2.6 to 3.3 mmol/L (100-129	• Desirable: <5.2 mmol/L (<200 mg/dL) • Borderline high: 5.2 to 6.2 mmol/L (200-239 mg/dL)	• Normal: <1.7 mmol/L (<150 mg/dL) • Borderline high: ≥1.7 mmol/L (≥150 mg/dL)	• Low: <1 mmol/L (<40 mg/dL). • High: ≥1.6 mmol/L (≥60 mg/dL).

mg/dL) • Borderline high: 3.4 to 4.1 mmol/L (130-159 mg/dL) • High: 4.1 to 4.9 mmol/L (160-189 mg/dL) • Very high: ≥4.9 mmol/L (≥190 mg/dL).	•High: ≥6.2 mmol/L (≥240 mg/dL).	• High: 2.3 to 5.6 mmol/L (200-499 mg/dL) • Very high: ≥5.7 mmol/L (≥500 mg/dL).	

Risk factors and screening

STRONG RISK FACTORS	WEAK RISK FACTORS	SCREENING
Insulin resistance and type 2 diabetes mellitus (hypercholesterolaemia due to increased very low-density lipoprotein cholesterol (VLDL-C) and expressed by high total cholesterol and non-high-density lipoprotein cholesterol (HDL-C) but not lowdensity lipoprotein cholesterol (LDL-C) can be seen in the context of mixed dyslipidaemia, and is associated with insulin resistance. The total number of LDL,	**Cigarette smoking** (patients smoking 2 packs of cigarettes per day had a mild reduction of high-density lipoprotein cholesterol. This reduction may be more pronounced in the setting of concomitant alcohol intake. It has been suggested that smoking may induce insulin resistance, with associated increases in the size and number of low-density lipoprotein and very low-density lipoprotein particles)	The American Association of Clinical Endocrinologists and American College of Endocrinology guidelines recommend that all adults 20 years of age or older should be evaluated for dyslipidaemia every 5 years, with more frequent testing recommended as patients become older. In the UK and Europe, lipid screening usually starts at age 40. Screening may begin earlier for those with diabetes in childhood or a family

intermediate-density lipoprotein, and VLDL particles is also increased in patients with insulinresistance)		history of dyslipidaemia, and the 2018 American College of Cardiology/American Heart Association guidelines additionally recommend screening as early as age 2 years for those with a family history suggestive of early atherosclerotic cardiovascular disease (ASCVD). The US Preventive Services Task Force found that the current evidence is insufficient to assess the balance of benefits and harms of screening for lipid disorders in asymptomatic children and adolescents aged 20 years or younger.
excess body weight (body mass index >25 kg/m²) (waist circumference that is >94 cm in white and black men, >80 cm in white and black women, >90	**nephrotic syndrome** **(**hyperlipidaemia observed in patients with nephrotic syndrome is partially due to a reduction in lipid catabolism. The low	

cm in Asian men, and >80 cm in Asian women)	oncotic pressure seen in these patients is thought to lead to increased hepatic synthesis of lipoproteins)	
hypothyroidism (the severity of lipid abnormalities increases with the severity of the hypothyroidism)	**use of certain medications** (high-dose thiazide diuretics, oral oestrogens, glucocorticoids, anabolic steroids, atypical antipsychotics, such as olanzapine and clozapine, isotretinoin, protease inhibitors)	
cholestatic liver disease		

Differential diagnosis

Diseases	Differentiating sings and tests
Obstructive liver disease	Jaundice, abdominal tenderness can be observed. ⇧ ALT, AST, GGT, ALP, bilirubin MRI, CT may show dilated biliary ducts.
Nephrotic syndrome	Reduction in plasma oncotic pressure. ⇧ Cholesterol, triglycerides, lipoproteins.
Chronic renal insufficiency	Diminished clearance. Patients undergoing peritoneal dialysis are more likely to have an atherogenic lipid profile than those undergoing haemodialysis.
Hypothyroidism	Lethargy, cold intolerance, constipation, dry hair or skin, goitre, or delayed return of deep tendon reflexes. A significant reduction in the serum cholesterol concentration during thyroid hormone replacement was only seen in those patients with a serum

	TSH concentration >10 milliunits/L. ⇧ Serum TSH, serum free thyroxine may be low.

Treatment

The targeted approach to lipid management is primarily aimed at reducing atherosclerotic risk by substantially lowering **LDL-C** to levels that have been achieved in recent large-scale trials of PCSK-9 inhibitors. Therefore, for patients at very high CV risk, whether in secondary prevention or (rarely) in primary prevention (tab.6), LDL-C reduction of >50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended (tab.7). For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin-based therapy, an LDL-C goal <1.0 mmol/L (<40 mg/dL) may be considered. For people at high CV risk, an LDL-C reduction of > 50% from baseline and an LDL-C goal <1.8 mmol/L (<70 mg/dL) are recommended. In patients at moderate CV risk, an LDL-C goal <2.6 mmol/L (<100 mg/dL) should be considered, while for low-risk individuals a goal of <3.0 mmol/L (<116 mg/dL) may be considered.

Secondary goals have also been defined by inference for **non-HDL-C** and for **ApoB**; they receive a moderate grading, as they have not been extensively studied in RCTs. The specific goal for non-HDL-C should be 0.8 mmol/L (30 mg/dL) higher than the corresponding LDL-C goal; the adjustment of lipid-lowering therapy in accordance with these secondary goals may be considered in patients at very high CV risk after achievement of an LDL-C goal, although the clinical advantages of this approach with respect to outcomes remain to be addressed. When secondary targets are used the recommendations are: non-HDL-C

<2.2 mmol/L (<85 mg/dL), <2.6 mmol/L (<100 mg/dL), and <3.4 mmol/L (<130 mg/dL) in people at very high, high, and moderate CV risk, respectively; and ApoB <65 mg/dL, <80 mg/dL, and <100 mg/dL in very-high, high, and moderate total CV risk, respectively. To date, no specific goals for HDL-C or TG levels have been determined in clinical trials, although increases in HDL-C predict atherosclerosis regression, and low HDL-C is associated with excess events and mortality in coronary artery disease (CAD) patients, even at low LDL levels. Clinicians should use clinical judgment when considering further treatment intensification in patients at high or very high total CV risk.

Current available evidence from meta-analyses suggests that the clinical benefit of statin treatment is largely a class effect, driven by the absolute LDL-C reduction; therefore, the type of statin used should reflect the treatment goals for a given patient.

The following scheme may be proposed.

• *Evaluate the total CV risk of the individual* (tab.4).

• *Determine the treatment goals (depending on current risk)* (tab.5, 8).

• *Involve the patient in decisions on CV risk management*.

• *Choose a statin regimen and, where necessary, additional treatments (e.g. ezetimibe or PCSK9 inhibitors) that can meet the treatment goals (percent and absolute value).*

• *Response to statin treatment is variable, therefore uptitration of the statin dose may be required before additional LDL-lowering treatments are started.*

Total cardiovascular risk estimation

All current guidelines on the prevention of ASCVD in clinical practice recommend the assessment of total CVD risk. Prevention of ASCVD in a given person should relate to his or her total CV risk: the higher the risk, the more intense the action should be.

The SCORE (Systematic Coronary Risk Estimation) system can be recalibrated for use in different populations by adjusting for secular changes in CVD mortality and risk factor prevalence (fig.3, 4). Calibrated country-specific versions are available for many European countries and can be found at http:// www.heartscore.org. These are now being updated to provide recalibrated, contemporaneous country-specific charts for all European countries. Other risk estimation systems—using both fatal and nonfatal events—can also be recalibrated, but the process is easier and scientifically more robust for mortality than for total events. The European Guidelines on CVD prevention in clinical practice recommend the use of the SCORE system because it is based on large, representative European cohort data sets and because it is relatively straightforward to recalibrate for individual countries. Persons with documented ASCVD, type 1 or type 2 DM very high levels of individual risk factors, or chronic kidney disease (CKD) are generally at very-high or high total CV risk. No risk estimation models are needed for such persons; they all need active management of all risk factors.

For other, apparently healthy people, the use of a risk estimation system such as SCORE, which estimates the 10 year cumulative risk of a first fatal atherosclerotic event, is recommended to estimate total CV risk, since many people have several risk factors that, in combination, may result in high levels of total CV risk. Risk estimates have been produced as charts for high- and low-risk regions in Europe.

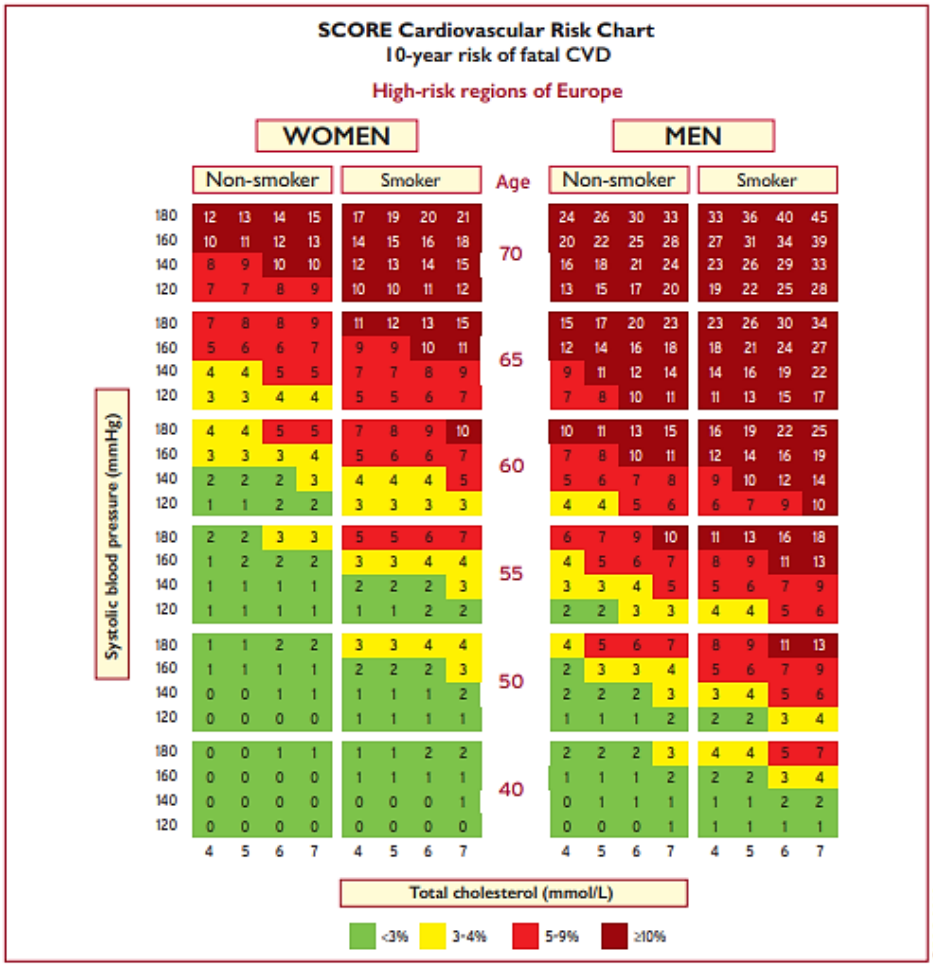
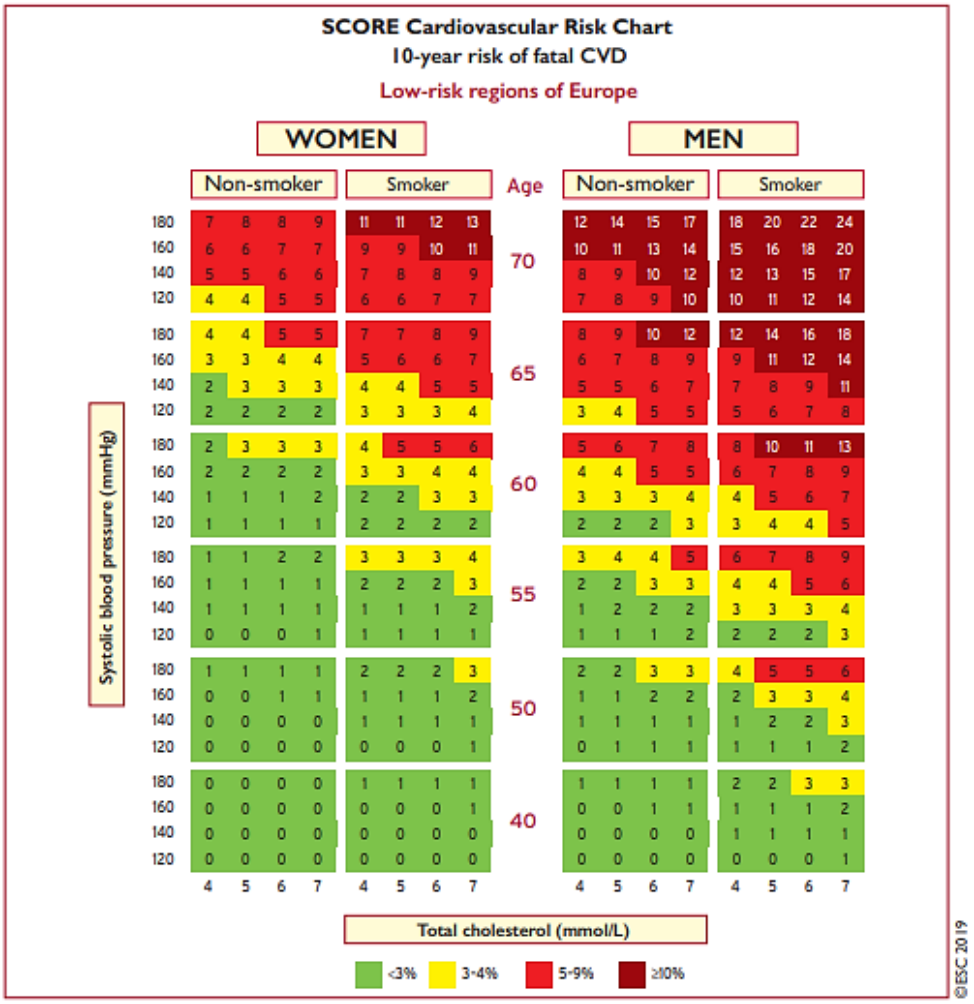


Fig.3. SCORE Cardiovascular Risk CHART (High-risk regions of Europe)



. Fig.4. SCORE Cardiovascular Risk CHART (Low-risk regions of Europe)

How to use the risk estimation charts

To estimate a person's 10-year risk of CVD death, find the table for his/ her gender, smoking status, and age. Within the table, find the cell nearest to the person's BP and TC. Risk estimates will need to be adjusted upwards as the person approaches the next age category. Risk is initially assessed on the level of TC and systolic BP before treatment, if known. The longer the treatment and the more effective it is, the greater the reduction in risk, but in general it will not be more than about one-third of the baseline risk. For example, for a person on antihypertensive drug treatment in whom the pre-treatment BP is not known, if the total CV SCORE risk is 6%, then the pre-treatment total CV risk may have been 9%. Low-risk persons should be offered advice to maintain their low-risk status. While no threshold is universally applicable, the intensity of advice should increase with increasing risk. The charts may be used to give some indication of the effects of reducing risk factors, given that there is apparently a time lag before the risk reduces. In general, people who stop smoking halve their cumulative risk over a relatively short period of time.

In adult patients without previous ASCVD, risk scores may be used for risk estimation. Several are available, such as Framingham, QRISK, [QRISK risk calculator] (http://www.qrisk.org) PROCAM, the Pooled Cohort Equations, [Pooled Cohort Equations CV Risk Calculator] (https://professional.heart.org/professional/GuidelinesStatements/ASCVDRiskCalculator/UCM_457698_ASCVD-Risk-Calculator.jsp) and SCORE2 and SCORE2-OP. When applied to populations similar to their derivation cohort, these tools perform well. Therefore, healthcare providers should be familiar with the best risk prediction tool in their patient population.

When using the Pooled Cohort Equations, patients may be classified according to their predicted 10-year risk of ASCVD events (fatal and non-fatal myocardial infarction or stroke): low risk (<5%), borderline risk (5.0% to <7.5%), intermediate risk (≥7.5% to <20%), and high risk (>20%). In borderline- and intermediate-risk patients, clinical and laboratory risk-enhancing factors may be considered to decide the use of lipid-lowering therapies. These factors include: a family history of premature ASCVD (men aged <55 years, women <65 years), primary hypercholesterolaemia (LDL -cholesterol ≥4.1 mmol/L [≥160 mg/dL] or non-HDL -cholesterol ≥4.9 mmol/L [≥190 mg/dL], metabolic syndrome, estimated GFR 15-59 mL/min/1.73 m², chronic inflammatory conditions (psoriasis, rheumatoid arthritis, HIV/AIDS), premature menopause, preeclampsia, South Asian ancestry , elevated high-sensitivity CRP ≥19.1 nmol/L (≥2 mg/L), elevated lipoprotein(a) (>50 mg/dL or >125 nmol/L), elevated apolipoprotein B (≥1.3 g/L [≥130 mg/dL]), or an ankle-brachial index <0.9.

Cardiovascular risk categories

Very-high risk

People with any of the following:

Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial

revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound. DM with target organ damage,a or at least three major risk factors, or early onset of T1DM of long duration (>20 years). Severe CKD (eGFR <30 mL/min/1.73 m2). A calculated SCORE >10% for 10-year risk of fatal CVD. FH with ASCVD or with another major risk factor.

High-risk

People with:

Markedly elevated single risk factors, in particular TC >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or BP ≥180/110 mmHg. Patients with FH without other major risk factors. Patients with DM without target organ damage,a with DM duration ≥10 years or another additional risk factor. Moderate CKD (eGFR 3059 mL/min/1.73 m2). A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.

Moderate-risk

Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors. Calculated SCORE ≥1 % and <5% for 10-year risk of fatal CVD.

Low-risk

Calculated SCORE <1% for 10-year risk of fatal CVD.

Table 4. Intervention strategies as a function of total cardiovascular risk and untreated low-density lipoprotein cholesterol levels.

	Total CV risk (SCORE) %	Untreated LDL-C levels					
		<1.4 mmol/L (55 mg/dL)	1.4 to <1.8 mmol/L (55 to <70 mg/dL)	1.8 to <2.6 mmol/L (70 to <100 mg/dL)	2.6 to <3.0 mmol/L (100 to <116 mg/dL)	3.0 to <4.9 mmol/L (116 to <190 mg/dL)	≥4.9 mmol/L (≥190 mg/dL)
Primary prevention	<1, low-risk	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	I/C	I/C	I/C	I/C	IIa/A	IIa/A
	≥1 to <5, or moderate risk (see *Table 4*)	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	I/C	I/C	IIa/A	IIa/A	IIa/A	IIa/A
	≥5 to <10, or high-risk (see *Table 4*)	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	IIa/A	IIa/A	IIa/A	I/A	I/A	I/A
	≥10, or at very-high risk due to a risk condition (see *Table 4*)	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	IIa/B	IIa/A	I/A	I/A	I/A	I/A
Secondary prevention	Very-high-risk	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	IIa/A	I/A	I/A	I/A	I/A	I/A

Table 5. Recommendations for treatment goals for low-density lipoprotein cholesterol.

Recommendations	Class[a]	Level[b]
In secondary prevention for patients at very-high risk,[c] an LDL-C reduction of ≥50% from baseline[d] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.[33–35,119,120]	I	A
In primary prevention for individuals at very-high risk but without FH,[c] an LDL-C reduction of ≥50% from baseline[d] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.[34–36]	I	C
In primary prevention for individuals with FH at very-high risk, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) should be considered.	IIa	C
For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin-based therapy, an LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered.[119,120]	IIb	B
In patients at high risk,[c] an LDL-C reduction of ≥50% from baseline[d] and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) are recommended.[34,35]	I	A
In individuals at moderate risk,[c] an LDL-C goal of <2.6 mmol/L (<100 mg/dL) should be considered.[34]	IIa	A
In individuals at low risk,[c] an LDL-C goal <3.0 mmol/L (<116 mg/dL) may be considered.[36]	IIb	A

Table 6. Treatment targets and goals for cardiovascular disease prevention.

Smoking	No exposure to tobacco in any form.
Diet	Healthy diet low in saturated fat with a focus on wholegrain products, vegetables, fruit, and fish.
Physical activity	3.5–7 h moderately vigorous physical activity per week or 30–60 min most days.
Body weight	BMI 20–25 kg/m^2, and waist circumference <94 cm (men) and <80 cm (women).
Blood pressure	<140/90 mmHg.[a]
LDL-C	**Very-high risk in primary or secondary prevention:** A therapeutic regimen that achieves ≥50% LDL-C reduction from baseline[b] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL). No current statin use: this is likely to require high-intensity LDL-lowering therapy. Current LDL-lowering treatment: an increased treatment intensity is required. **High risk:** A therapeutic regimen that achieves ≥50% LDL-C reduction from baseline[b] and an LDL-C goal of <1.8 mmol/L (<70 mg/dL). **Moderate risk:** A goal of <2.6 mmol/L (<100 mg/dL). **Low risk:** A goal of <3.0 mmol/L (<116 mg/dL).
Non-HDL-C	Non-HDL-C secondary goals are <2.2, 2.6, and 3.4 mmol/L (<85, 100, and 130 mg/dL) for very-high-, high-, and moderate-risk people, respectively.
ApoB	ApoB secondary goals are <65, 80, and 100 mg/dL for very-high-, high-, and moderate-risk people, respectively.
Triglycerides	No goal, but <1.7 mmol/L (<150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors.
Diabetes	HbA1c: <7% (<53 mmol/mol).

Table 7. Intensity of lipid lowering treatment.

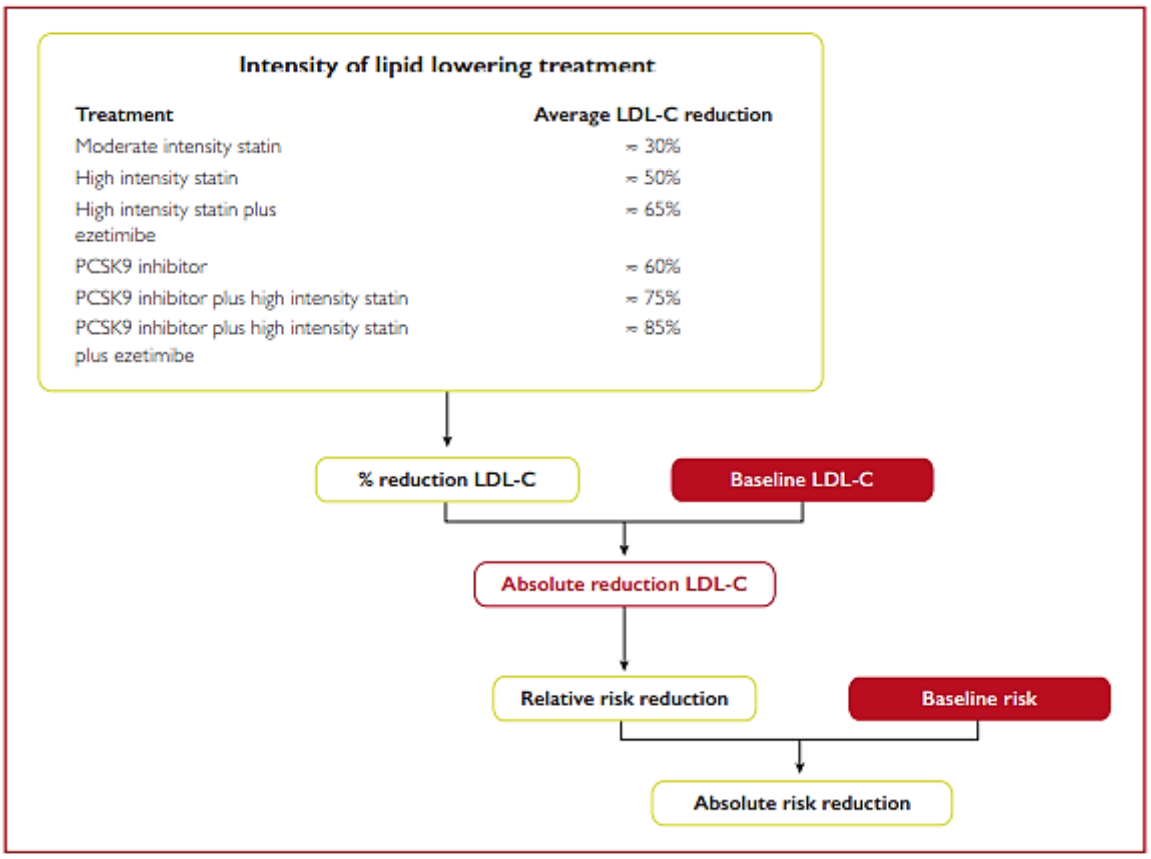
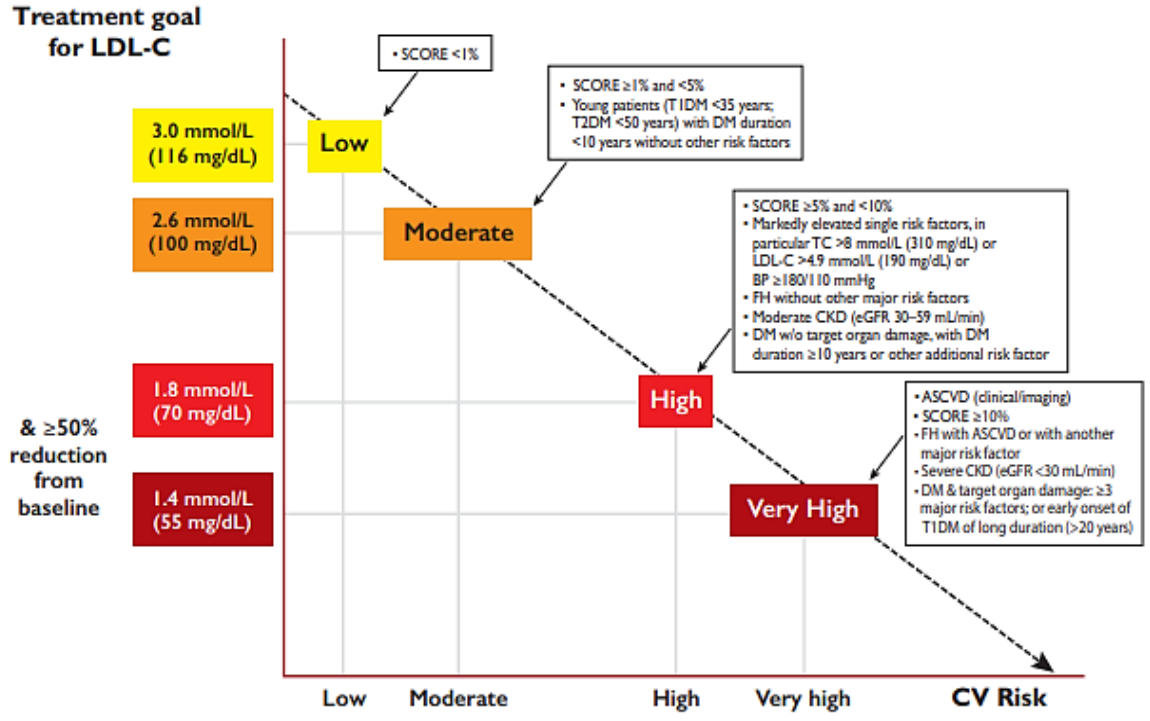


Table 8. Treatment goal for LDL-C.



Treatment algorithm

Total cardiovascular risk +/- comorbidity	Treatment algorithm	Dosage
Very high risk + clinical ASCVD	High-intensity statin + lifestyle modification (+ ezetimibe/PCSK9 inhibitor if don't reduce LDL-C (on 50% from the output level) LDL-C ≥1.4 mmol/L, non-HDL-C ≥2.2 mmol/L on maximally tolerated statin therapy.	**<u>High-intensity statin:</u>** - atorvastatin: 40-80 mg orally once daily - rosuvastatin: 20-40 mg orally once daily **<u>Moderate-intensity statin:</u>** - atorvastatin: 10-20 mg orally once daily - rosuvastatin: 5-10 mg orally once daily - simvastatin: 20-40 mg orally once daily; increased risk of myopathy with 80 mg/day dose - pravastatin: 40-80 mg orally once daily - lovastatin: 40-80 mg orally (immediaterelease) once daily - fluvastatin: 40 mg orally (immediaterelease) twice daily; 80 mg orally (extendedrelease) once daily **<u>ezetimibe</u>**: 10 mg orally once
Not very high risk + age ≤75 years + clinical ASCVD	High-/moderate-intensity statin + lifestyle modification + ezetimibe if don't reduce LDL-C (on 50% from the output level) LDL-C ≥1.8 mmol/L, non-HDL-C ≥2.6 mmol/L on maximally tolerated statin therapy. + PCSK9 inhibitor (if you don't achieve the	

	aim (reduction LDL-C or non-HDL-C on 50 % from baseline on maximally tolerated statin + ezetimibe therapy)	daily » Ezetimibe may be added to maximally tolerated statin therapy when the target level of LDL – cholesterol don't achieved
Not very high risk + age >75 years + clinical ASCVD	High- or moderate intensity statin + lifestyle modification	**<u>Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor:</u>** - alirocumab: 75-150 mg subcutaneously every 2 weeks; or 300 mg subcutaneously every 4 weeks - evolocumab: 140 mg subcutaneously every 2 weeks; or 420 mg subcutaneously once monthly **<u>Bile acid sequestrant:</u>** - colestyramine: 4 g orally once daily initially, adjust dose according to response, maximum 36 g/day given in 1-4 divided doses
LDL-C ≥4.9 mmol/L + age 20-75 years (without DM, clinical ASCVD)	High-intensity statin + lifestyle modification + ezetimibe and/or PCSK 9 inhibitor if don't reduce LDL-C (on 50% from the output level) LDL-C ≥2.6 mmol/L, non-HDL-C ≥3.4 mmol/L on maximally tolerated statin therapy + bile acid sequestrant if on maximally tolerated statin and ezetimibe therapy and <50% reduction in LDL-C, with fasting triglycerides ≤3.4 mmol/L.	

LDL-C ≥4.1 mmol/L (age 20-39 years) (without clinical ASCVD, DM)	High- or moderate intensity statin + lifestyle modification	
LDL-C 1.8-4.9 mmol/l (age 40-75 years) (without DM, clinical ASCVD) **10-year ASCVD Risk <5%** **10-year ASCVD Risk 5%-<7.5%** **10-year ASCVD Risk ≥7.5% to <20%** **10-year ASCVD Risk ≥20%**	risk discussion + lifestyle modifications +/- moderate intensity statin moderate intensity statin + lifestyle modification High-intensity statin + lifestyle modification +/- ezetimibe	
LDL-C 1.8 to 4.9 mmol/L (age >75 years) (without clinical ASCVD, DM)	Consider moderate intensity statin + lifestyle modification	
DM + risk enhancers (age 20-39 years,	Consider moderate intensity statin + lifestyle modification	

without clinical ASCVD		
10-year risk <7.5% and DM (age 40-75 years) without clinical ASCVD	moderate intensity statin + lifestyle modification switch to high-intensity statin if reduction LDL-C <30%-49, LDL-C ≥2.6 mmol/L or non-HDL-C ≥3.4 mmol/L	
Predicted 10-years ASCVD risk ≥7.5% and risk enhancers (age 40-75 years) with DM, without clinical ASCVD **10-year ASCVD risk ≥20%, LDL-C reduction <50% and/or LDL-C ≥1.8 mmol/L or non-HDL-C ≥2.6 mmol/L on maximally tolerated statin therapy**	High-intensity statin + lifestyle modification + ezetimibe	
DM (age >75 years), without clinical ASCVD	moderate intensity statin + lifestyle modification	

Multiple choice questions

1. How many types of dyslipidemia are distinguished according to the Fredrickson classification?

A. 3

B. 6

C. 5

D. 7

2. What is a complication of lipid-lowering therapy?

A. STEMI

B. Pneumonia

C. Rhabdomyolysis

D. Chronic kidney disease

3. The risk of experiencing an acute ASCVD event rises rapidly as more ApoB-containing lipoproteins become retained and the atherosclerotic plaque burden increases.

A. True

B. False

4. What is the most common risk factor of dyslipidemia?

A. T2DM

B. Cigarette smoking

C. Thiazide diuretics

D. Alcohol abuse

5. Familial combined hyperlipidemia is caused by?

A. Obesity

B. Sedentary lifestyle

C. Overproduction of apo-B-containing lipoproteins

D. Insulin resistance

6. The targeted approach to lipid management is aimed at reducing atherosclerotic risk by lowering blood parameters. Which indicators are targeted for reduction and control?

A. Glucose

B. ALAT, ASAT

C. GGT

D. LDL-C, non-HDL-C

E. HDL-C

MCQ answers: 1-B, 2-C, 3-A, 4-A, 5-C, 6-D

Clinical cases

1. A 61-year old woman presents for a physical examination. She reports her diet is optimal, but otherwise reports a sedentary lifestyle. She has no past medical history and only takes a supplement of vitamin D 1000 IU. Her BP of 144/78 mm Hg and a pulse of 82/min. On physical examination, she has no cardiac murmurs, and her lung sounds are clear to auscultation bilaterally. You order a lipid panel that returns as follows: LDL – 220 mg/dL, HDL– 41 mg/dL, TG – 284 mg/dL. Which of the following medication should be initiated?

A. Simvastatin 20 mg daily
B. Atorvastatin 40 mg daily
C. Fenofibrate 145 mg daily
D. Colesevelam 4 g daily
E. Ezetimibe 5 mg daily

2. Patient K., 58 years, presents to his GP for an annual checkup. He has had type 2 diabetes mellitus for 17 years, for which he has been taking metformin and saxagliptin. He has smoked 15 to 20 cigarettes daily for 20 years. Family history is irrelevant. Vital signs include a temperature of 36.6°C (97.8°F), blood pressure of 158/87 mm Hg, and pulse of 89/minute. Examination reveals moderate abdominal obesity with a body mass index of 34 kg/m². The remainder of the examination is unremarkable. His fasting lipid profile is shown: Total cholesterol (TC) – 291 mg/dL Low-density lipoprotein (LDL)-cholesterol – 222 mg/dL High-density lipoprotein (HDL)-cholesterol – 43 mg/dL Triglycerides (TGs) – 245 mg/dL. Which of the following is the mechanism of action of the best initial therapy for this patient?

A. High-intensity statin + lifestyle modification
B. Ezetimibe 10 mg daily
C. Lifestyle modification + smoking cessation
D. Insulin + colestyramine: 4 g orally once daily initially
E. Moderate-intensity statin + lifestyle modification

3. Patient L., 74-year-old woman with unstable angina, HTN and obesity (BMI - 31 kg/m² visits her doctor for therapy monitoring. Her BP in doctor office 150/60 mm Hg, pulse is 68/min. On physical examination you notice that she has xanthelasmas on both eyelids. Her lipid panel after 6 months of therapy with high-intensity statin are as follows: TC – 220 mg/dL, LDL-C – 135 mg/dL, HDL-C – 48 mg/dL, triglycerides – 170 mg/dL. Which of the following is the best next step in management of patient L. hyperlipidemia?

A. Recommend regular exercise and continue high-intensity statin

B. Switch high-intensity statin therapy to selective cholesterol-absorption inhibitor

C. Recommend to add ezetimibe: 10 mg orally once daily and continue to use rosuvastatin: 20 mg

D. Recommend to add colestyramine: 4 g orally once daily to high-intensity-statin therapy

E. Continue therapy and don’t change anything

Clinical cases answers: 1-B, 2-A, 3-C.

References:

1. Attalla M, Curnew G, Pare G, Cybulska B, Kłosiewicz-Latoszek L, Szostak W. Lipid Disorders. McMaster Textbook of Internal Medicine. Kraków: Medycyna Praktyczna; 2019 [Updated 2022 2 Feb]. Available from: https://empendium.com/mcmtextbook/chapter/B31.II.2.4.

2. C Jerjes-Sanchez. Cardiology in ER. Switherland: Springer; 2019. 329 p.

3. Mach F., Baigent C., Catapano A.L., Koskinas K.C., Casula M., Badimon L., Chapman M.J., De Backer G.G., Delgado V., et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). *European Heart Journal*. [Internet]. 2020 1 Jan; 41(1):111–188. Available from: https://doi.org/10.1093/eurheartj/ehz455.

4. Marcus F. Hill; Bruno Bordoni. Hyperlipidemia. [Updated 2023 8 Aug]. In StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK559182/.

5. Nikos Pappan, Ayoola O. Awosika, Anis Rehman. Dyslipidemia. [Updated 2024 4 Mar]. In StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560891/.

6. Ferraro R.A., Leucker T. Hypercholesterolaemia. BMJ Best Prectice [Internet]. 2024 Mar 14. 97 p. Available from: https://bestpractice.bmj.com/topics/engb/170?q=Hypercholesterolaemia&c=suggested.