Dyslipidemia: Current Perspectives and Implications for Clinical Practice

Klobučar Majanović, Sanja; Cvijanović Peloza, Olga; Detel, Dijana; Kenđel Jovanović, Gordana; Bakula, Miro; Rahelić, Dario; Čaljkušić-Mance, Tea; Šoić Vranić, Tamara; Zoričić Cvek, Sanja

Source / Izvornik: **Management of Dyslipidemia, 2021, 148 - 158**

Book chapter / Poglavlje u knjizi

Publication status / Verzija rada: **Published version / Objavljena verzija rada (izdavačev PDF)**

https://doi.org/10.5772/intechopen.87280

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:184:104768

Chapter

Dyslipidemia: Current Perspectives and Implications for Clinical Practice

Sanja Klobučar Majanović, Olga Cvijanović Peloza, Dijana Detel, Gordana Kenđel Jovanović, Miro Bakula, Dario Rahelic, Tea Čaljkušić Mance, Tamara Šoić Vranić and Sanja Zoričić Cvek

Abstract

Dyslipidemia refers to a broad spectrum of various genetic and acquired disorders that affect blood lipid levels and largely contribute to global cardiovascular disease burden. Consistent evidence from epidemiological and clinical studies, supports the key role of the circulating LDL-cholesterol and other apoB containing lipoproteins in atherogenesis. All ApoB-containing lipoproteins with size less than 70 nm can cross the endothelial barrier, particularly in the presence of endothelial dysfunction. Uptake and accumulation of apoB-containing lipoproteins in the arterial wall is a critical initiating event in the development of atherosclerosis. Statin treatment, targeting LDL cholesterol reduction, remains the cornerstone of dyslipidemia management. There are abundant data supporting the concept of 'the lower LDL-C, the better' in the primary and secondary cardiovascular disease prevention. This chapter provides an overview of the key insights into the lipid abnormalities associated with an increased risk of CV events particulary in the context of dyslipidemia management in everyday clinical practice. Understanding the important role that metabolic derangements play in the pathogenesis of atherosclerosis pave the way for stronger implementation of current guidelines for CVD risk assessment and prevention.

Keywords: atherosclerosis, dyslipidemia, cardiovascular disease, lipid-lowering therapies, lipoproteins

1. Introduction

Cardiovascular disease (CVD) remains a major cause of global mortality and rising health care costs worldwide. CVD burden is predominantly attributable to modifiable behavioral and metabolic risk factors with dyslipidemia being one of them [1, 2]. Dyslipidemia is a term that encompasses a broad spectrum of various genetic and acquired disorders that affect blood lipid levels. This chapter provides an overview of the key insights into the lipid abnormalities associated with an increased risk of CV events particularly in the context of dyslipidemia management in everyday clinical practice. Understanding the important role that

metabolic derangements play in the pathogenesis of atherosclerosis paves the way for stronger implementation of current guidelines for CVD risk assessment and prevention.

2. Lipids and lipoproteins

Lipids are essential components of the human body, having several important biological functions such as storing energy, acting as structural components of cell membranes and participating in signaling pathways. The three main types of lipids are phospholipids, sterols, and triglycerides (also known as triacylglycerols) [3]. In view of the fact that the term "lipid" has been defined as any of a group of organic compounds that are insoluble in water but soluble in organic solvents, lipids comprise a broad range of molecules such as fatty acids, triglycerides (TG), phospholipids, sterols, sphingolipids and many others. However, from a clinical standpoint, given their role in the pathogenesis of CVD, the two major forms of circulating lipids in the body are TG and cholesterol. Although insoluble in plasma, these lipids can be transported throughout the bloodstream as lipoproteins when packaged with phospholipids and proteins known as apoproteins or apolipoproteins.

Lipoproteins are complex particles that have a central hydrophobic core composed of non-polar lipids, primarily cholesterol esters (CE) and TG and a hydrophilic surface consisting of polar lipids (phospholipids and free cholesterol) and apoproteins. The protein component provides structural integrity to the framework of the lipoproteins and being attached to the surface of particles, make them detectable for enzymes and receptors. Hence, apoproteins modulate enzyme activity (eg, apoprotein C-II activates lipoprotein lipase) and serve as ligands, specific recognition sites for cell surface receptors during cellular uptake (eg, apoprotein B-100 binds to the low-density lipoprotein receptor).

Lipoproteins are synthesized in both the liver and the intestines, playing a key role in the absorption and transport of dietary lipids by the small intestine, in the transport of lipids from the liver to peripheral tissues, and from peripheral tissues to the liver and intestine (a process known as reverse cholesterol transport). Within the circulation, lipoproteins go through constant change in composition and physical structure as the peripheral tissues take up the various components before the remnants return to the liver [4].

3. Classification and composition of plasma lipoproteins

Lipoproteins vary in size, density and composition which affects their functions, atherosclerotic risk profiles and other effects on health [3]. Based on major lipid and apolipoprotein content which determines their density, lipoproteins are classified into six categories; chylomicrons, very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL), lipoprotein (a) [Lp(a)], and high-density lipoprotein (HDL) (**Table 1**). Accompanying apolipoproteins and their functions are described in **Table 2**.

The main function of chylomicrons is the transport of dietary triglycerides from the intestine to the liver and other peripheral tissues, while VLDL particles carry endogenously synthesized triglycerides from the liver to other tissues. LDL particles are the major carriers of cholesterol in the circulation, supplying it to the cells, whereas the role of HDL is to transfer cholesterol from peripheral tissues to the liver.

Lipoprotein	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, II, IV, 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-II, E, M
Lp(a)	1.006-1.125	25-30	4-8	35-46	17-24	6-9	Apo(a)	ApoB-100

Apo - apolipoprotein; HDL - high-density lipoprotein; IDL - intermediate-density lipoprotein; LDL - low-density lipoprotein; Lp(a) - lipoprotein(a); PLs - phospholipids; TGs - triglycerides; VLDL - very low-density lipoprotein. Adapted from Ref. [5].

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

Apolipoprotein	Location	Origin	Function
Apo A-I	HDL	Liver, intestine	Major component of HDL, activates LCAT
Apo A-II	HDL	Liver	Component of HDL
Apo B-48	Chylomicrons	Intestine	Major component of chylomicron, synthesized in the intestine
Apo B-100	VLDL, IDL, LDL, Lp(a)	Liver	LDL receptor ligand
Apo C-II	Chylomicrons, VLDL, HDL	Liver	co-factor for LPL, stimulates triglyceride hydrolysis
Apo C-III	Chylomicrons, VLDL, HDL	Liver	Inhibits LPL
Apo E	Chylomicrons, remnants, VLDL, HDL	Liver, intestine	LDL receptor ligand
Apo(a)	Lp(a)	Liver	Component of Lp(a), links to LDL, inhibits fibrinolysis

Apo - apolipoprotein; HDL - high-density lipoprotein; IDL - intermediate-density lipoprotein; LCAT - lecithin-cholesterol acyltransferase; LDL - low-density lipoprotein; LPL - lipoprotein lipase; Lp(a) - lipoprotein (a); VLDL - very-low-density lipoprotein.

Table 2.
Major apolipoprotein characteristics.

3.1 Chylomicrons

Chylomicrons are the largest particles in the lipoprotein family with the highest lipid to protein ratio. These triglyceride-rich particles contain apolipoproteins A-I, A-II, A-IV, A-V, B-48, C-II, C-III, and E, nevertheless, apo B-48 is the core structural protein and each chylomicron particle contains one Apo B-48 molecule [6]. The size of chylomicrons varies depending on the amount of fat ingested. A meal high in fat results in the formation of large chylomicron particles due to the increased quantity

of TG being transported whereas in the fasting state the chylomicron particles are smaller since they are carrying decreased amount of TG.

3.2 Chylomicron remnants

The removal of TG from chylomicrons by peripheral tissues results in smaller particles called chylomicron remnants. Compared to chylomicrons these particles are enriched in cholesterol and are pro-atherogenic [7].

3.3 Very low-density lipoproteins (VLDL)

Very low-density lipoproteins are also triglyceride-rich particles, however, they are smaller than chylomicrons and contain relatively less TG but more cholesterol and protein. Similar to chylomicrons the size of the VLDL particles vary depending on the amount of TG carried in the particle. Hence, when TG production in the liver is increased, the secreted VLDL particles are large. VLDL particles contain apolipoproteins B-100, C-I, C-II, C-III, and E. Apo B-100 is the core structural protein and each VLDL particle contains one Apo B-100 molecule [8].

3.4 Intermediate-density lipoproteins (IDL; VLDL remnants)

The removal of TG from VLDL by peripheral tissue (muscle and adipose tissue) results in the formation of IDL particles which are enriched in cholesterol. These particles contain apolipoprotein B-100 and E and are pro-atherogenic [8].

3.5 Low-density lipoproteins (LDL)

Low density lipoproteins are derived from VLDL and IDL particles by the lipoprotein lipase-mediated intravascular removal of TGs and are further enriched in cholesterol. Therefore, the LDL inner core is predominately composed of cholesterol esters. LDL particles are the primary transport mechanism for the delivery of cholesterol to peripheral tissues, accounting for the majority of circulating cholesterol in humans. Apo B-100 is the predominant structural protein and each LDL particle contains one Apo B-100 molecule [3]. LDL comprise a range of particles differing in size and density. Small dense LDL (sdLDL) particles are considered to be more atherogenic than larger LDL subfractions [9]. A growing body of evidence suggests that sdLDL particles have a decreased affinity for the LDL receptor resulting in a prolonged retention time in the circulation. Longer circulation times lead to multiple atherogenic modifications of sdLDL particles, further increasing its atherogenicity. Moreover, sdLDL particles bind more avidly to intraarterial proteoglycans and are characterized by the enhanced ability to enter the arterial wall. Finally, sdLDL particles are more susceptible to oxidation, which could result in an enhanced uptake by macrophages [10].

The predominance of sdLDL has been associated with hypertriglyceridemia, low HDL and high-hepatic lipase activity. This lipid phenotype was found to be present across the broad spectrum of metabolic disorders including obesity, metabolic syndrome, type 2 diabetes and is considered as a risk factor of coronary heart disease.

3.6 High-density lipoproteins (HDL)

High density lipoproteins are the smallest particles in the lipoprotein family composed of a relatively high proportion of protein thus having the lowest lipid to protein ratio. Their core is mainly composed of cholesterol esters. HDL particles

contain apolipoproteins A-I, A-II, A-IV, C-I, C-II, C-III, and E. Apo A-I is the core structural protein and each HDL particle may contain multiple Apo A-I molecules. The main physiological role of HDL is in the transport of cholesterol from peripheral tissues to the liver, which is one possible mechanism to explain their ability to inhibit atherosclerosis [11]. In addition, HDL particles have anti-oxidant, anti-inflammatory, anti-thrombotic, and anti-apoptotic properties, which may also contribute to their anti-atherogenic potential. HDL comprise a range of particles varying in size, density and apolipoprotein composition.

3.7 Lipoprotein(a) [Lp(a)]

Lipoprotein(a) consists of an LDL particle and the specific apolipoprotein(a), which is attached via a single disulfide bond to the Apo B-100. Lp(a) contain Apo(a) and Apo B-100 in a 1:1 molar ratio. The structure of apolipoprotein(a) is similar to plasminogen and tissue plasminogen activator (tPA) containing multiple kringle repeats. Due to a variable number of kringle repeats, each of which consists of 114 amino acids, the molecular weight of apo(a) isoforms can range from 250,000 to 800,000 [12]. The production rate of Lp(a) is predominantly genetically determined resulting in highly variable Lp(a) plasma concentration ranging from undetectable to more than 200 mg/dl. There is a general inverse correlation between the Lp(a) concentration in plasma and the size of the apo(a) isoform. Individuals with low molecular weight Apo (a) tend to have higher levels while individuals with high molecular weight Apo(a) isoforms tend to have lower levels of Lp(a). It is hypothesized that the larger the isoform, the more Apo(a) precursor protein accumulates intracellularly in the endoplasmic reticulum and consequently the liver is less efficient in secreting high molecular weight Apo(a) [13]. The mechanism of Lp (a) clearance is still not fully elucidated but does not seem to include LDL receptors. As kidney disease is associated with an increase in Lp (a) levels, the kidney appears to have an important role in Lp (a) clearance. Elevated plasma Lp(a) levels are associated with an increased risk of atherosclerosis. There are several proposed mechanisms to explain a proatherogenic role of Lp(a). As the structure of Apo(a) is similar to plasminogen and tPA it competes with plasminogen for its binding site, leading to reduced fibrinolysis. Moreover, Lp(a) stimulates the secretion of PAI-1, which results in enhanced thrombogenesis. Also, Lp(a) particles are preferential carriers of atherogenic pro-inflammatory oxidized phospholipids in human plasma that attracts inflammatory cells to vessel walls and stimulate smooth muscle cell proliferation [14]. However, statin therapy as well as other therapies that accelerate LDL clearance and decrease LDL levels do not decrease Lp(a) levels [15].

4. The role of lipids and lipoproteins in atherogenesis

Consistent evidence from epidemiologic and clinical studies, supports the key role of the apoB containing lipoproteins in atherogenesis. All ApoB-containing lipoproteins with size less than 70 nm can cross the endothelial barrier, particularly in the presence of endothelial dysfunction [16]. Uptake and accumulation of apoB-containing lipoproteins in the arterial wall is a critical initiating event in the development of atherosclerosis. Upon entry, apoB-containing lipoproteins are modified and oxidized into proinflammatory particles, which provoke the activation of the innate immune system within the arterial intima. The endothelial cells secrete adhesion molecules, and the smooth muscle cells (SMCs) secrete chemokines, which together attract monocytes and other immune cells into the arterial wall. When monocytes enter the subendothelial space, they transform into macrophages.

Macrophage inflammation leads to enhanced oxidative stress and cytokine secretion, further promoting apoB-containing lipoproteins oxidation, endothelial cell activation, proliferation of SMCs and monocyte recruitment [17]. Uptake of the apoB containing particles by macrophages promotes foam cell formation which accumulate in early atherosclerotic lesions known as fatty streaks [18]. Fatty streaks are not clinically significant, but they are the precursors of more advanced lesions characterized by the accumulation of lipid-rich necrotic debris and SMCs. With the secretion of fibrous elements by the SMCs, forming a fibrous cap over the lipid-rich necrotic cores, atherosclerotic fibrous plaques develop. Continued exposure to apoB-containing lipoproteins results in additional particles being retained over time in the arterial wall, and to the growth and progression of atherosclerotic plaques [19]. A person's total atherosclerotic plaque burden is determined by the concentration of circulating LDL and other apoB-containing lipoproteins, and by the cumulative exposure to these particles. In general, 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 ultimately leading to the reduced vascular lumen and clinically significant ischemia. Plaques can become increasingly complex, with calcification, ulceration at the luminal surface, and hemorrhage within the arterial wall from small fragile vessels growing into the lesion from the media. Eventually, changes in the composition of the plaque reach a critical point at which disruption of a plaque can result, with the formation of an overlying thrombus that acutely obstructs blood flow. Atherosclerotic plaque formation is greatest at the branching points of major vessels and in areas of turbulent flow [17]. Depending on the location, atherosclerosis may lead to a variety of conditions, such as coronary heart disease, cerebrovascular and peripheral artery disease.

Epidemiological studies have consistently shown that HDL-C levels are inversely related to atherosclerotic cardiovascular events [20, 21]. HDL-C has been traditionally considered as „good "cholesterol having a protective role against atherosclerosis. The proposed mechanism underlying its protective effect is the role in the removal of excess cholesterol from peripheral tissues. Besides, it has been considered that HDL prevents lipoprotein oxidation and removes oxidized lipids from LDL due to its anti-inflammatory and anti-oxidant properties. However, the protective role has been seriously challenged by the evidence from recent clinical trials aimed at raising HDL-C that failed to reduce cardiovascular events. Modern genome-wide and Mendelian randomization studies have failed to show a causal link between total HDL-C concentration and CAD, which might be related to the fact that HDL comprise a range of particles differing in size and density [22, 23]. It has been shown that the concentration of large HDL particles is inversely associated with CVD while that of small HDL particles is positively associated with CVD.

5. Clinical classification of dyslipidemias

Dyslipidemia may present as a single disorder affecting only one specific type of lipid, such as pure or isolated hypertriglyceridemia or hypercholesterolemia or may represent as a combination of lipid abnormalities, such as mixed or combined dyslipidemias. Lipid disorders were traditionally categorized by patterns of elevation in lipids and lipoproteins into six phenotypes according to the Fredrickson classification (**Table 3**). A more practical approach is to classify dyslipidemias as primary or secondary. Primary dyslipidemias are genetic disorders caused by single or multiple gene mutations that result in either overproduction or defective clearance of LDL and TG or excessive clearance of HDL. The understanding of the

Phenotype	Elevated Lipoprotein(s)	Elevated Lipids
I	Chylomicrons	TG
IIa	LDL	Cholesterol
IIb	LDL and VLDL	TG and cholesterol
III	VLDL and chylomicron remnants	TG and cholesterol
IV	VLDL	TG
V	Chylomicrons and VLDL	TG and cholesterol

LDL - low-density lipoprotein; TG - triglycerides; VLDL - very-low-density lipoprotein.

Table 3.
Fredrickson classification of dyslipidemias.

genetic and biochemical basis of these disorders has revealed a large and diverse group of diseases, many of which have similar clinical expressions (**Table 4**) [24]. The names of many primary dyslipidemias reflect an old nomenclature in which lipoproteins were differentiated by how they separated into alpha (HDL) and beta (LDL) bands on electrophoretic gels. Individuals with primary dyslipidemias are at higher risk of developing complications, such as atherosclerotic cardiovascular disease, at a younger age. Patients may also present with acute pancreatitis and deposition of cholesterol in the skin and tendons (xanthomas), eyelids (xanthelasma), and corneas (arcus corneae).

Familial hypercholesterolemia (FH) is one of the most common monogenic lipid disorders associated with premature CVD due to significantly elevated plasma levels of LDL-C. FH is caused by loss-of-function mutations in the LDL receptor or apoB genes, or a gain-of-function mutation in the PCSK9 gene [25]. There are two main types of FH; homozygous (HoFH) and heterozygous (HeFH). The prevalence of HeFH in the population is estimated to be 1/200-250, making it the most common genetically transmitted disease [26, 27]. If left untreated, men and women with HeFH typically develop early coronary artery disease (CAD) before the ages of 55 and 60 years respectively. However, early diagnosis and appropriate treatment can dramatically reduce the risk for CAD. HoFH is a rare and life-threatening disease with a prevalence estimated to be 1/160,000-320,000. Patients present with extensive xanthomas, premature and progressive CVD, and total cholesterol level exceeds 13 mmol/L. Most patients die before 30 years of age [28].

Secondary dyslipidemias are caused by lifestyle factors or medical conditions that interfere with blood lipid levels [29, 30]. The most important cause is a sedentary lifestyle with excessive dietary intake of total calories, saturated fats, cholesterol and trans fats. Some diseases that are associated with a higher risk of dyslipidemia are diabetes mellitus, cholestatic liver disease, chronic kidney disease, nephrotic syndrome, hypothyroidism and obesity [31, 32].

Diabetes is an especially important secondary cause of dyslipidemia characterized by an atherogenic combination of high TGs, high sdLDL particles and low HDL [33]. Patients with type 2 diabetes are particularly at risk [34]. It has been shown that the lipoprotein abnormalities are related to the severity of the insulin resistance and the degree of visceral adiposity. Poor glycemic control and inflammation of visceral adipose tissue increase the concentration of circulating free fatty acids (FFAs), leading to increased VLDL production in the liver. TG-rich VLDL then transfers TG and cholesterol to LDL and HDL, promoting formation of TG-rich, sdLDL and clearance of TG-rich HDL. Diabetic dyslipidemia is additionally promoted by unhealthy diet and physical inactivity. Other factors that increase the risk of dyslipidemias are smoking, alcohol overuse and certain medications such as thiazide

Disorder	Genetic Defect	Inheritance	Clinical Features
Apo C-II deficiency	Apo C-II (causing functional LPL deficiency)	Recessive	• metabolic syndrome (often present) • pancreatitis (in some adults) • TG: > 8.5 mmol/L
Cerebrotendinous xanthomatosis	Hepatic mitochondrial 27-hydroxylase defect accumulation of cholestanol due to the blockage of bile acid synthesis and conversion of cholesterol to cholestanol	Recessive	• cataracts • premature CAD • neuropathy • ataxia
Cholesteryl ester storage disease and Wolman disease	Lysosomal acid lipase deficiency	Recessive	• premature CAD • accumulation of cholesteryl esters and TG in lysosomes in the liver, spleen, and lymph nodes • cirrhosis
Familial apo AI deficiency/mutations	Apo AI	Unknown	• corneal opacities, xanthomas, premature CAD (in some people) • HDL: 0.39–0.78 mmol/L
Familial combined hyperlipidemia	Unknown, possibly multiple defects and mechanisms	Dominant	• premature CAD, responsible for about 15% of MIs in people < 60 years • Apo B: Disproportionately elevated • TC: 6.5–13.0 mmol/L • TG: 2.8–8.5 mmol/L
Familial defective apo B-100	Apo B (LDL receptor–binding region defect) Diminished LDL clearance	Dominant	• xanthomas, arcus corneae, premature CAD • TC: 6.5–13 mmol/L
Familial dysbetalipoproteinemia	Apo E (usually e2/e2 homozygotes) Diminished chylomicron and VLDL clearance	Recessive or dominant	• xanthomas (especially tuberous and palmar), yellow palmar creases, premature CAD • TC: 6.5–13.0 mmol/L • TG: 2.8–5.6 mmol/L

Disorder	Genetic Defect	Inheritance	Clinical Features
Familial HDL deficiency	ABCA1 gene	Dominant	• premature CAD
Familial hypercholesterolemia	Loss-of-function mutations in the LDL receptor or apoB genes, or a gain-of-function mutation in the PCSK9 Diminished LDL clearance	Codominant	Heterozygotes: • tendon xanthomas, arcus corneae, premature CAD (ages 30–50), responsible for about 5% of MIs in people < 60 years • TC: 6.5–13 mmol/L Homozygotes: • planar and tendon xanthomas and tuberous xanthomas, premature CAD (before age 18) • TC > 13 mmol/L
Familial hypertriglyceridemia	Unknown, possibly multiple defects and mechanisms	Dominant	• Usually no symptoms or findings; occasionally hyperuricemia, sometimes early atherosclerosis • TG: 2.3–5.6 mmol/L, possibly higher depending on diet and alcohol use
Familial LCAT deficiency	LCAT gene	Recessive	• Corneal opacities, anemia, chronic kidney disease • HDL: < 0.26 mmol/L
Fisheye disease (partial LCAT deficiency)	LCAT gene	Recessive	• Corneal opacities • HDL: < 0.26 mmol/L
Hepatic lipase deficiency	Hepatic lipase	Recessive	• premature CAD • TC: 6.5–39 mmol/L • TG: 4.5–93 mmol/L • HDL: variable

Disorder	Genetic Defect	Inheritance	Clinical Features
LPL deficiency	Endothelial LPL defect Diminished chylomicron clearance	Recessive	• failure to thrive (in infants), eruptive xanthomas, hepatosplenomegaly, pancreatitis • TG: > 8.5 mmol/L
PCSK9 gain of function mutations	Increased degradation of LDL receptors	Dominat	• similar to familial hypercholesterolemia
Polygenic hypercholesterolemia	Unknown, possibly multiple defects and mechanisms	Variable	• premature CAD • TC: 6.5–9.0 mmol/L
Primary hypoalphalipoproteine-mia (familial or nonfamilial)	Unknown, possibly apo A-I, C-III, or A-IV	Dominat	• premature CAD • HDL: 0.39–0.91 mmol/L
Sitosterolemia	ABCG5 and ABCG8 genes	Recessive	• tendon xanthomas, premature CAD
Tangier disease	ABCA1 gene	Recessive	• premature CAD (in some people), peripheral neuropathy, hemolytic anemia, corneal opacities, hepatosplenomegaly, orange tonsils • HDL: < 0.13 mmol/L

ABCA1 - ATP-binding cassette transporter A1; ABCG5 and 8 - ATP-binding cassette subfamily G members 5 and 8; apo - apoprotein; CAD - coronary artery disease; HDL - high-density lipoprotein; LCAT - lecithin-cholesterol acyltransferase; LDL - low-density lipoprotein; LPL - lipoprotein lipase; MI - myocardial infarction; PCSK9 - proprotein convertase subtilisin-like/kexin type 9; TC - total cholesterol; TG - triglyceride; VLDL - very-low-density lipoprotein.
Adapted from Ref. [23].

Table 4.
Primary dyslipidemias.

Medical conditions	Lipid abnormalities
Diabetes mellitus, metabolic syndrome	↑ sdLDL-C, ↓ HDL-C, ↑ TG
Cholestatic liver disease	↑ TC ↑ LDL-C
Nephrotic syndrome	↑ TC, ↑ LDL-C
Chronic kidney disease	↑ LDL-C, ↓ HDL-C, ↑ TG
Hypothyroidism	↑ LDL-C, ↑ TG
Obesity	↑ TC, ↑ LDL-C, ↓ HDL-C, ↑ TG
Cigarette smoking	↓ HDL-C
Excessive alcohol consumption	↑ TG
Medications	
Diuretics, cyclosporine, glucocorticoids, amiodarone	↑ LDL-C
Oral estrogens, glucocorticoids, protease inhibitors, sirolimus, beta blockers, thiazides, anabolic steroids	↑ TG

HDL-C - high density lipoprotein cholesterol; LDL-C - low density lipoprotein cholesterol; sdLDL-C -small dense low density lipoprotein cholesterol; TC-total cholesterol; TG - triglycerides.

Table 5.
Secondary causes of dyslipidemia.

diuretics, beta blockers, oral contraceptives, atypical antipsychotics, antiretroviral agents, corticosteroids, tacrolimus, and cyclosporine. Secondary causes of dyslipidemia and their major lipid abnormalities are shown in **Table 5**.

6. Treatment strategies

6.1 Impact of diet and lifestyle modifications on lipid levels

Consistent evidence from epidemiological studies indicates that saturated fatty acids (SFAs) and trans unsaturated fatty acids are the dietary factors with the greatest elevating impact on LDL-C levels [5]. Therefore, current dietary guidelines uniformly recommend reducing intakes of saturated and trans fatty acids with replacement by increasing intake of mono- and polyunsaturated fatty acids [35]. Moreover, recommended food choices to lower LDL-C and improve the overall lipoprotein profile include higher consumption of non-starchy vegetables, fruit, legumes, nuts, fish, vegetable oils, yoghurt, and wholegrains, along with a lower intake of red and processed meats, foods higher in refined carbohydrates, and salt [36, 37]. Dietary patterns that may have a role in the prevention and management of dyslipidemia are the Mediterranean diet and the DASH diet [38, 39]. Excessive body weight loss exhibits the LDL-C decreasing effect, but the magnitude of the effect is small. In people with obesity, a decrease in LDL-C concentration of 0.2 mmol/L is observed for every 10 kg of weight reduction [40, 41]. Regular physical exercise results in even smaller reduction of LDL-C levels [42, 43]. Overall, through dietary changes and weight loss, LDL-C can be lowered by approximately 10–15% [44].

6.2 Drugs for treatment of dyslipidemias

Statin treatment, targeting LDL cholesterol reduction, remains the cornerstone of dyslipidemia management. There is a clear linear relationship between the degree of LDL-cholesterol lowering achieved with statins and CV benefits, pointing out

that a reduction of 1 mmol/L of LDL-C is associated with a 20–25% reduction in the relative risk of major CV events including cardiovascular mortality, non-fatal myocardial infarction and non-fatal stroke [45]. Statins reduce the biosynthesis of cholesterol in the liver by competitively inhibiting the enzyme hydroxymethylglutaryl CoA (HMG-CoA) reductase, the rate-limiting step in the production of cholesterol. The reduction in intracellular cholesterol promotes up-regulation of LDL receptor (LDLR) at the surface of the hepatocytes, which in turn results in increased hepatic uptake of LDL from the blood, thereby lowering plasma concentrations of LDL- and other ApoB-containing lipoprotein particles. The degree of LDL-C reduction is dose-dependent and varies between the different statins. A high intensity statin, on average, reduces LDL-C by >50%, while, moderate-intensity therapy is defined as the dose expected to reduce LDL-C by 30-50% [35]. Statins should be initiated with the highest tolerated dose to reach the LDL-C goal determined by the individual's risk category. There are abundant data supporting the concept of 'the lower LDL-C, the better' in the primary and secondary cardiovascular disease prevention. Statins are generally safe and well tolerated apart from myalgia which is the most commonly reported statin adverse effect, although its frequency is higher in everyday clinical practice than in RCTs [46]. However, due to low adherence to statin therapy or statin intolerance, many patients do not reach LDL-C target levels. Because the LDL-C targets suggested in guidelines, currently <1.4 mmol/L in patients with very-high CV risk, < 1.8 in patients with high CV risk and < 2.6 mmol/L in those with moderate CV risk respectively, are often not achieved, additional and more aggressive LDL-C lowering therapies are needed [35].

Ezetimibe inhibits dietary and biliary cholesterol absorption by interacting with the Niemann-Pick C1-Like 1 protein (NPC1L1), thereby lowering the amount of cholesterol delivered to the liver. In response to reduced cholesterol delivery, the liver reacts by upregulating LDL receptor expression, which in turn leads to increased clearance of LDL from the blood. A large clinical trial evaluating the addition of ezetimibe to statins in patients with prior acute coronary syndrome found a 24% reduction in LDL-C levels and a 6.4% reduction in the relative risk of CV death, major coronary events, or nonfatal stroke at 7 years [47]. Statin-ezetimibe combination treatment is the first choice for managing elevated LDL-C in very-high-risk patients with high LDL-C unlikely to reach goal with a statin, and in primary prevention familial hypercholesterolaemia patients [48].

A new class of drugs, PCSK9 inhibitors, that targets a proprotein convertase subtilisin/kexin type 9 (PCSK9) is recommended by current guidelines for the secondary prevention of very high-risk individuals not at LDL-C goal despite maximally tolerated statin doses and ezetimibe [35]. This protein regulates plasma concentrations of LDL-C by interacting with LDL receptors on hepatocytes. After binding to an LDL receptor, PCSK9 directs it to lysosomal degradation. Consequently, it inhibits recycling of the receptor to the surface of the hepatocyte and delays catabolism of LDL particles [49]. Currently approved PCSK9 inhibitors are the human monoclonal antibodies, alirocumab and evolocumab. The mechanism of action relates to the reduction of the plasma level of PCSK9, which in turn results in decreased intracellular degradation and increased expression of LDL receptors at the cell surface and therefore in a reduction of circulating LDL-C levels [50]. Co-administration with statin treatment has a sound rationale because statins upregulate PCSK9. In clinical trials, PCSK9 inhibitors either alone or in combination with statins, and/or other lipid-lowering therapies have been shown to significantly reduce LDL-C levels on average by 60%, depending on dose. In contrast to statins, inhibiting PCSK9 with monoclonal antibodies also reduces Lp(a) plasma levels.

An alternative approach targeting PCSK9 consists of RNA interference. Recently, the small interfering RNA (siRNA) molecule inclisiran, which inhibits the intracellular hepatic translation of PCSK9, has been approved in Europe based on a robust clinical development program demonstrating effective and sustained LDL-C reduction of up to 52% in patients with elevated LDL-C despite maximally tolerated statin therapy [51, 52]. With two doses a year, this new lipid lowering strategy is expected to support long-term adherence.

The cholesterol efflux capacity, mainly mediated by HDL-C, from arterial tissues to liver has demonstrated its association with major adverse cardiovascular events [53]. The pharmacological approach that has led to the greatest elevations in HDL-C levels has been direct inhibition of cholesterol ester transfer protein (CETP) by small-molecule inhibitors, which may induce an increase in HDL-C by >100% on a dose-dependent basis. Although CETP inhibitors significantly increased HDL-C levels in trials, they have not displayed benefits on cardiovascular outcomes [22].

Hypertriglyceridemia is a well-described contributor to the residual cardiovascular risk [54]. Statin treatment is recommended as the first drug of choice to reduce CVD risk in high-risk individuals with TG levels >2.3 mmol/L. In high and very high-risk patients with TG levels between 1.5-5.6 mmol/L despite statin treatment, n-3 PUFAs (icosapent ethyl 2x2 g/day) should be considered in combination with a statin. It has been demonstrated that icosapent ethyl, a highly purified and stable eicosapentaenoic acid (EPA), on top of statins was associated with a 25% relative CV risk reduction and a 4.8% absolute risk reduction in major adverse CV events in high-risk individuals [55]. The underlying mechanism how omega-3 fatty acids affect serum lipids and lipoproteins, in particular VLDL concentrations is poorly understood, although it may be related, at least in part, to their ability to interact with peroxisome proliferator-activated receptors (PPARs) and to decreased secretion of ApoB. In primary prevention patients who are at LDL-C goal with TG levels >2.3 mmol/L, fenofibrate may be considered in combination with statins. Fibrates are agonists of PPARs, acting via transcription factors regulating various steps in lipid and lipoprotein metabolism. Consequently, fibrates have good efficacy in lowering fasting and post-prandial TGs and TG-rich lipoprotein remnant particles [56, 57].

Agents that enhance catabolism of TG-rich lipoproteins, such as the antisense oligonucleotide to ApoC-III mRNA, which lead to a concomitant reduction in TGs (>70%) and a marked elevation in HDL-C (>40%) in hypertriglyceridemia, are under development [58].

7. Conclusion

Dyslipidemias largely contribute to global cardiovascular disease burden. Consistent evidence from epidemiological and clinical studies, supports the key role of the circulating LDL-C and other apoB containing lipoproteins in the development of atherosclerosis. Therefore, reducing LDL-C and other ApoB-containing lipoproteins is a core component of lipid management for both the primary prevention of CVD and the secondary prevention of recurrent CV events. A major outstanding challenge is how best to implement use of evidence-based therapies in clinical practice, particularly statins and PCSK9 inhibitors. Understanding the important role that metabolic derangements play in the pathogenesis of atherosclerosis pave the way for stronger implementation of current guidelines for CVD risk assessment and prevention.

Author details

Sanja Klobučar Majanović[1,2], Olga Cvijanović Peloza[3*], Dijana Detel[4], Gordana Kenđel Jovanović[5], Miro Bakula[6,7], Dario Rahelic[7,8,9], Tea Čaljkušić Mance[10,11], Tamara Šoić Vranić[3] and Sanja Zoričić Cvek[3]

1 Department of Endocrinology, Diabetes and Metabolic Diseases, Clinical Hospital Centre Rijeka, Rijeka, Croatia

2 Department of Internal Medicine, Faculty of Medicine, University of Rijeka, Rijeka, Croatia

3 Department of Anatomy, Faculty of Medicine, University of Rijeka, Rijeka, Croatia

4 Department of Chemistry and Biochemistry, Faculty of Medicine, University of Rijeka, Rijeka, Croatia

5 Department of Health Ecology, Teaching Institute of Public Health of Primorsko-goranska County, Rijeka, Croatia

6 Department of Endocrinology, Diabetes and Metabolic Disorders, Clinical Hospital "Sveti Duh", Zagreb, Croatia

7 School of Medicine, University of Zagreb, Zagreb, Croatia

8 Vuk Vrhovac University Clinic for Diabetes, Endocrinology and Metabolic Diseases, Merkur University Hospital, Zagreb, Croatia

9 School of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia

10 Department of Ophtalmology, Faculty of Medicine, University of Rijeka, Rijeka, Croatia

11 Clinical Hospital Centre Rijeka, Rijeka, Croatia

*Address all correspondence to: olga.cvijanovic@uniri.hr

References

[1] Roth GA, Mensah GA, Fuster V. The Global Burden of Cardiovascular Diseases and Risks. Journal of the American College of Cardiology, 2020;76(25):2980-2981.

[2] Yusuf S et al. Modifiable risk factors, cardiovascular disease, and mortality in 155 722 individuals from 21 high-income, middle-income, and low-income countries (PURE): A prospective cohort study. Lancet 2019;395(10226):795-808.

[3] Fahy E, Cotter D et al. Lipid classification, structures and tools. Biochim Biophys Acta. 2011; 1811(11): 637-647.

[4] Hevonoja T, Pentikäinen MO, Hyvönen MT, Kovanen PT, Ala-Korpela M. Structure of low density lipoprotein (LDL) particles: basis for understanding molecular changes in modified LDL. Biochim Biophys Acta. 2000;1488(3):189-210.

[5] Li Y, Hruby A, Bernstein AM, Ley SH, et al. Saturated Fats Compared With Unsaturated Fats and Sources of Carbohydrates in Relation to Risk of Coronary Heart Disease: A Prospective Cohort Study. J Am Coll Cardiol. 2015;66(14):1538-1548.

[6] Tomkin GH, Owens D. The chylomicron: Relationship to atherosclerosis. International Journal of Vascular Medicine. 2012;2012:784536.

[7] Wilhelm MG, Cooper AD. Induction of atherosclerosis by human chylomicron remnants. Journal of Atherosclerosis and Thrombosis.2 003;10(3):132-139.

[8] Nordestgaard BG, Tybjaerg-Hansen A. IDL, VLDL, chylomicrons and atherosclerosis. European Journal of Epidemiology. 1992;8(Suppl 1):92-98.

[9] Liou L, Kaptoge S. Association of small, dense LDL-cholesterol concentration and lipoprotein particle characteristics with coronary heart disease: A systematic review and meta-analysis. PLoS One. 2020;15(11):e0241993.

[10] Ivanova EA, Myasoedova VA, Melnichenko AA, Grechko AV, Orekhov AN. Small Dense Low-Density Lipoprotein as Biomarker for Atherosclerotic Diseases. Oxid Med Cell Longev. 2017;2017:1273042.

[11] Rye KA, Barter PJ. Cardioprotective functions of HDLs. Journal of Lipid Research. 2014;55(2):168-179.

[12] Nordestgaard BG, Chapman MJ, Ray K, et al. Lipoprotein(a) as a cardiovascular risk factor: Current status. European Heart Journal. 2010;31:2844-2853.

[13] Koschinsky ML. Lipoprotein(a) and atherosclerosis. New perspectives on the mechanism of action of an enigmaticlipoprotein. Current Atherosclerosis Reports. 2005;7:389-395.

[14] Ference BA, Graham I, Tokgozoglu L, Catapano AL. Impact of lipids on cardiovascular health: JACC Health Promotion Series. J Am Coll Cardiol 2018;72:1141-1156.

[15] Bos S, Yayha R, van Lennep JE. Latest developments in the treatment of lipoprotein (a). Curr Opin Lipidol. 2014;25:452-460.

[16] Boren J, Williams KJ. The central role of arterial retention of cholesterol-rich apolipoprotein-B-containing lipoproteins in the pathogenesis of atherosclerosis: a triumph of simplicity. Curr Opin Lipidol 2016;27:473-483.

[17] Lara-Guzman OJ, Gil-Izquierdo A, Medina S, et al. Oxidized LDL triggers

changes in oxidative stress and inflammatory biomarkers in human macrophages. Redox Biology. 2018;15:1-11.

[18] Tabas I, Williams KJ, Boren J. Subendothelial lipoprotein retention as the initiating process in atherosclerosis: update and therapeutic implications. Circulation 2007;116:18321844.

[19] Goldstein JL, Brown MS. A century of cholesterol and coronaries: from plaques to genes to statins. Cell. 2015;161:161-172.

[20] Emerging Risk Factors Collaboration, Di Angelantonio E, Gao P, Pennells L, Kaptoge S, et al. Lipid-related markers and cardiovascular disease prediction. JAMA 2012;307:2499-2506.

[21] Prospective Studies Collaboration, Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, et al. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet 2007;370:1829-1839.

[22] Lincoff AM, Nicholls SJ, Riesmeyer JS, Barter PJ, et al; ACCELERATE Investigators. Evacetrapib and cardiovascular outcomes in high-risk vascular disease. N Engl J Med 2017;376:1933-1942.

[23] HPS/TIMI/REVEAL Collaborative Group, Bowman L, Hopewell JC, Chen F, et al. Effects of anacetrapib in patients with atherosclerotic vascular disease. N Engl J Med 2017;377:1217-1227.

[24] Davidson MH. Dyslipidemia - Lipid disorders - Endocrine and Metabolic Disorders - MSD Manual Professional Edition. [online] MSD Manual Professional Edition. Available at: <http://www.msdmanuals.com/en-au/professional/endocrine-and-metabolic-disorders/lipid disorders/dyslipidemia> [Accessed 30 April 2021].

[25] Marks D, Thorogood M, Neil HA, Humphries SE. A review on the diagnosis, natural history, and treatment of familial hypercholesterolaemia. Atherosclerosis. 2003 May. 168(1):1-14.

[26] Sibley C, Stone NJ. Familial hypercholesterolemia: a challenge of diagnosis and therapy. Cleve Clin J Med. 2006 Jan. 73(1):57-64.

[27] Akioyamen LE, Genest J, Shan SD, Reel RL, Albaum JM, Chu A, Tu JV. Estimating the prevalence of heterozygous familial hypercholesterolaemia: a systematic review and meta-analysis. BMJ Open 2017;7:e016461.

[28] Risk of fatal coronary heart disease in familial hypercholesterolaemia. Scientific Steering Committee on behalf of the Simon Broome Register Group. BMJ 1991;303:893-896.

[29] Yanai H, Yoshida H. Secondary dyslipidemia: its treatments and association with atherosclerosis. Glob Health Med. 2021 Feb 28;3(1):15-23.

[30] Vodnala D, Rubenfire M, Brook RD. Secondary causes of dyslipidemia. Am J Cardiol. 2012; 110:823-825.

[31] Pearce EN. Hypothyroidism and dyslipidemia: modern concepts and approaches. Curr Cardiol Rep. 2004; 6:451-456.

[32] Agrawal S, Zaritsky JJ, Fornoni A, Smoyer WE. Dyslipidaemia in nephrotic syndrome: mechanisms and treatment. Nat Rev Nephrol. 2018; 14:57-70.

[33] Vergès B. Pathophysiology of diabetic dyslipidaemia: where are we? Diabetologia. 2015; 58:886-899.

[34] Juutilainen A, Lehto S, Rönnemaa T, et al. Type 2 diabetes as a "coronary

heart disease equivalent": an 18-year prospective population-based study in Finnish subjects. Diabetes Care 2005;28:2901-7.

[35] Mach F, Baigent C, Catapano AL, Koskinas KC, et al. ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020 Jan 1;41(1):111-188.

[36] Musunuru K. Atherogenic dyslipidemia: cardiovascular risk and dietary intervention. Lipids. 2010;45(10):907-914.

[37] Gerber PA, Berneis K. Regulation of low-density lipoprotein subfractions by carbohydrates. Current opinion in clinical nutrition and metabolic care. 2012;15(4):381-385.

[38] Widmer RJ, Flammer AJ, Lerman LO, Lerman A. The Mediterranean diet, its components, and cardiovascular disease. Am J Med. 2015 Mar;128(3):229-38.

[39] Nordmann AJ, Suter-Zimmermann K, Bucher HC, Shai I, Tuttle KR, Estruch R, Briel M. Meta-analysis comparing Mediterranean to low-fat diets for modification of cardiovascular risk factors. Am J Med. 2011 Sep;124(9):841-51.e2.

[40] Nordmann AJ, Nordmann A, Briel M, Keller U, Yancy WS Jr, Brehm BJ, Bucher HC. Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials. Arch Intern Med 2006;166:285-293.

[41] Dattilo AM, Kris-Etherton PM. Effects of weight reduction on blood lipids and lipoproteins: a meta-analysis. Am J Clin Nutr 1992;56:320-328.

[42] Shaw K, Gennat H, O'Rourke P, Del Mar C. Exercise for overweight or obesity. Cochrane Database Syst Rev 2006;4:CD003817.

[43] Huffman KM, Hawk VH, Henes ST, Ocampo CI, et al. Exercise effects on lipids in persons with varying dietary patterns-does diet matter if they exercise? Responses in studies of a targeted risk reduction intervention through defined exercise I. Am Heart J 2012;164:117-124.

[44] Scirica BM, Cannon CP. Treatment of elevated cholesterol. Circulation 2005;111 :e360-3.

[45] Wadhera RK, Steen DL, Khan I, et al. A review of low-density lipoprotein cholesterol, treatment strategies, and its impact on cardiovascular disease morbidity and mortality. J Clin Lipidol 2016;10:472-89.

[46] Cho L, Rocco M, Colquhoun D, Sullivan D, et al. Clinical profile of statin intolerance in the phase 3 GAUSS-2 Study. Cardiovasc Drugs Ther 2016;30:297-304.

[47] Cannon CP, Blazing MA, Giugliano RP, et al. IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015;372:2387-97.

[48] Averna M, Banach M, Bruckert E, Drexel H, et al. Practical guidance for combination lipid-modifying therapy in high- and very-high-risk patients: A statement from a European Atherosclerosis Society Task Force. Atherosclerosis. 2021 Apr 13:S0021-9150(21)00162-3.

[49] Norata GD, Tibolla G, Catapano AL. Targeting PCSK9 for hypercholesterolemia.Annu Rev Pharmacol Toxicol 2014;54:273-293.

[50] Nozue T. Lipid lowering therapy and circulating PCSK9 concentration. J Atheroscler Thromb 2017;24:895-907.

[51] Raal F, Kallend D, Ray K, et al. Inclisiran for Heterozygous Familial Hypercholesterolemia. N Engl J Med. 2020;382(16):1520-1530.

[52] Ray K, Wright R, Kallend D, et al. Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol. N Engl J Med. 2020;382(16):1507-1519.

[53] Boekholdt SM, Hovingh GK, Mora S, Arsenault BJ, et al. Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials. J Am Coll Cardiol 2014;64:485-494.

[54] Triglyceride Coronary Disease Genetics Consortium, Emerging Risk Factors Collaboration, Sarwar N, Sandhu MS, Ricketts SL, Butterworth AS, et al. Triglyceride-mediated pathways and coronary disease: collaborative analysis of 101 studies. Lancet 2010;375:1634-1639.

[55] Bhatt DL, Steg PG, Miller M, Brinton EA, et al; REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Engl J Med 2019;380:11-22.

[56] Chapman MJ, Redfern JS, McGovern ME, Giral P. Niacin and fibrates in atherogenic dyslipidemia: pharmacotherapy to reduce cardiovascular risk. Pharmacol Ther 2010;126:314345.

[57] Accord Study Group, Ginsberg HN, Elam MB, Lovato LC, Crouse JR III, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med 2010;362:1563-1574.

[58] Digenio A, Dunbar RL, Alexander VJ, Hompesch M, et al. Antisense-mediated lowering of plasma apolipoprotein C-III by volanesorsen improves dyslipidemia and insulin sensitivity in type 2 diabetes. Diabetes Care 2016;39:1408-1415.