Hyperlipidemias and Cardiovascular Disease

Faculty
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Faculty Disclosure
Contributing faculty, A. José Lança, MD, PhD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Division Planners Disclosure
The division planners have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience
This course is designed for physicians, physician assistants, nurses, and nurse practitioners who may intervene to limit the effects of hyperlipidemias in their patients, promoting better long-term health and preventing cardiovascular disease.

Accreditations & Approvals
In support of improving patient care, NetCE is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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The purpose of this course is to increase awareness of the crucial role of hyperlipidemias in the development of cardiovascular disease, evaluate the therapeutic benefits of pharmacological and nonpharmacological approaches to lipid control, and contribute to a more positive interaction between the healthcare professional and the patient, through fostering patient awareness, implementation of lifestyle changes, and compliance to therapy.

**Learning Objectives**

Upon completion of this course, you should be able to:

1. Discuss the incidence of cardiovascular disorders, expected epidemiological trends, and relevance to society and healthcare systems.
2. Discuss the relevance of hyperlipidemias in the etiology of atherosclerosis and cardiovascular diseases.
3. Identify risk factors for hyperlipidemias.
4. Describe the exogenous and endogenous pathways of lipid synthesis and metabolism.
5. Describe the various types of lipoproteins.
6. Evaluate lipid profiles and identify the most clinically relevant types of hyperlipidemias.
7. Analyze the importance of lifestyle modification in managing hyperlipidemias.
8. Discuss the targeting of specific steps in lipid synthesis and metabolism related to the mechanism of action of drugs that inhibit cholesterol absorption in the intestine.
9. Describe the therapeutic efficacy and indications of fibrates, statins, and nicotinic acid derivatives.
10. Determine the role of fish oil derivatives and sterols and stanols in the management of hyperlipidemias.
11. Identify patients at risk for coronary heart disease and outline the evidence-based guidelines for the treatment of these patients.

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.
INTRODUCTION AND EPIDEMIOLOGY OF CARDIOVASCULAR DISEASES

Cardiovascular disease (CVD) is the leading cause of death in developing countries and accounts for 30.8% of all deaths in the United States and 47% of deaths in Europe [1; 2]. It has been estimated that by 2030 CVD will account for approximately 23 million deaths worldwide [3].

In developed countries, both the prevalence of CVD and the rate of mortality have declined. In the United States, from 2003 to 2013, the number of heart-related deaths declined by 12%. The prevalence and mortality rates have decreased as the result of risk factor reduction and advances in diagnosis and medical and surgical treatments [1; 4; 5; 6]. Developing countries, however, are continuing to face an increase in CVD, which has been partially attributed to an increased prevalence of hypertension, hyperlipidemia, and diabetes, as well as a 75% increase in tobacco consumption between 1991 and 2001 [7]. Tobacco smoking is among the top three risk factors that account for the most disease burden in China and India [8].

In the United States in 2011–2012, the estimated direct and indirect cost of CVD was $316.6 billion [1]. This figure is projected to increase to $1.21 trillion by 2030 [1]. As a comparison, the estimated 2011 annual direct cost of all cancer and benign neoplasms combined is $88.7 billion, versus $193.1 billion for direct costs of CVD [1].

The elevated costs of cardiovascular pathology for individuals, society, and healthcare systems require a novel approach based not only on improved diagnosis and management of disease but primarily on more effective prevention and early intervention. This not only requires a change in general perceptions but also a different approach toward prevention by physicians and other healthcare professionals [9; 10].

The etiology of CVD is complex and multifactorial and influenced by a variety of modifiable (e.g., hyperlipidemia, obesity, hypertension, diabetes, smoking, physical inactivity, diet) and non-modifiable (e.g., family history, age, gender) risk factors. Modifiable risk factors play a fundamental role in primary and secondary prevention of CVD and account for up to 90% of population-attributable cardiac risk [11; 12].

A high concentration of plasma lipids (i.e., hyperlipidemia), and high concentrations of low-density lipoprotein (LDL) cholesterol in particular, are implicated in the etiology of atherosclerosis and increased incidence of CVD such as coronary artery disease, peripheral vascular disease, and ischemic cerebrovascular disease. Hyperlipidemias are also associated with primary hypertension and metabolic syndrome [13; 14].

Data published in the National Health and Nutrition Examination Survey revealed that an estimated 12.1% of Americans 20 years of age and older have total blood cholesterol concentrations of 240 mg/dL (6.2 mmol/L) or greater, which are associated with high risk of cardiovascular morbidity and mortality [15].

Hyperlipidemia, and specifically hypertriglyceridemia (150–400 mg/dL or 1.7–4.5 mmol/L), is often present in patients with metabolic syndrome, which is characterized by a constellation of signs and symptoms including abdominal obesity, hypertension, insulin resistance, low levels of high-density lipoprotein (HDL), and increased risk of CVD [13]. Hypertriglyceridemia has also been reported to be a sign of underlying pancreatitis, and severe hypertriglyceridemia has been established as the etiology of up to 7% of pancreatitis. However, it should be pointed out that hypertriglyceridemia-induced pancreatitis rarely occurs unless levels exceed 1,700 mg/dL (20 mmol/L) [16].
It is well established that effective lipid management slows the progression of atherosclerosis and lowers morbidity and mortality of CVD [17; 18; 19; 20; 21; 22; 23; 24]. As a result, early diagnosis and appropriate clinical management of hyperlipidemias has become a public health priority in the primary and secondary prevention of CVD. Guidelines for the management of hyperlipidemias focus not only on the administration of lipid-lowering drugs but also the implementation of lifestyle changes [25]. Together, these interventions assist with patient adherence and improve clinical outcomes [22; 23; 24]. This approach requires collaboration among all members of the multidisciplinary team of healthcare providers, including physicians, nurses, pharmacists, dietitians, counselors, and physiotherapists [9; 25].

**ETIOLOGY OF ATHEROSCLEROSIS**

Atherosclerosis is a chronic inflammatory process that targets medium- and large-sized arteries. This process is initiated during childhood and progresses slowly with age. However, the condition is rapidly accelerated by a variety of genetic and environmental factors, and hyperlipidemia is a major risk factor in the pathogenesis and progression of atherosclerosis [12; 14; 26; 27].

An elevated concentration of LDL is a major cause of atherosclerosis and increased CVD [14; 17; 18; 19; 20; 21; 22; 23]. The causative role of hyperlipidemia has been supported by the finding that decreasing plasma levels of LDL and triglycerides has a beneficial effect on primary and secondary prevention of CVD and the underlying pathology of atherosclerosis [24].

The pathological processes underlying atherosclerosis can be categorized into three progressive stages: fatty streak formation, plaque formation, and plaque disruption [12; 27; 28; 29; 30; 31].

**FATTY STREAK FORMATION**

Fatty streaks are flat yellow discolorations on the arterial inner (i.e., luminal) surface that neither protrude into the lumen nor disrupt blood flow. The precise mechanisms responsible for the formation of fatty streaks are unclear but endothelial dysfunction is accepted as the primary event in atherogenesis. Physical stressors (e.g., turbulent blood flow at branching points) as well as chemical stressors (e.g., hyperlipidemia, cigarette smoking) alter endothelial cell functions in a complex and interdependent process. This results in:

- Impairment of the role of endothelial cells as a barrier, allowing for the abnormal accumulation of lipids in the sub-endothelial layer and their subsequent transformation (oxidation)
- Release of pro-inflammatory cytokines (e.g., interleukin 1 [IL-1] and tissue necrosis factor-α [TNF-α])
- Release of cell surface adhesion molecules that attract leukocytes (e.g., leukocyte adhesion molecules [LAM], monocyte chemotactic protein 1 [MCP-1], intercellular adhesion molecule 1 [ICAM-1])
- Decreased availability of vasodilator compounds such as nitric oxide and prostacyclin
- Stimulation of prothrombotic effect and platelet aggregation

Together, physical and chemical stressors promote endothelial dysfunction and trigger the initial sub-endothelial accumulation and transformation of oxidized LDL. Initially, oxidized LDL acts as a proinflammatory mediator to attract circulating leukocytes (e.g., monocytes and T-lymphocytes) to the sub-endothelium. Second, dysfunctional endothelial cells and modified smooth muscle cells secrete macrophage-stimulating factors that lead to the expression of scavenger receptors or acetyl-LDL receptors on the surface of macrophages and smooth muscle cells [28]. These scavenger receptors selectively bind to oxidized LDL and promote
phagocytosis by macrophages and transformed smooth muscle cells, which become lipid-laden and are known as foam cells. Increased numbers of foam cells and extracellular lipids account for the appearance of fatty streaks [12; 27; 28; 29; 31].

PLAQUE FORMATION

As atherogenesis progresses, arterial fatty streaks increase in size as the result of a continuing infiltration by smooth muscle cells, which migrate from the underlying muscular layer and accumulate oxidized LDL, and T-lymphocytes, which synthesize inflammatory cytokines. This increases the number of foam cells and exacerbates inflammation. Extracellular accumulation of LDL, collagen, elastic fibers, and calcium deposits further contribute to the formation of larger and thicker atherosclerotic lesions known as plaques or atheromas. Histology shows that atherosclerotic plaques present as a large lipid core surrounded by a fibrous cap. After decades of development, the plaque grows in size and presents many features of a chronic inflammatory process [28]. The arterial wall undergoes a restructuring process that initially grows outward and preserves the lumen diameter. At this stage, the condition is asymptomatic and goes undetected in angiographic studies. As time progresses, larger plaques start to protrude into the lumen and partially disrupt blood flow. Disruption of laminar blood flow also inhibits the expression of superoxide dismutase, a powerful antioxidant, further contributing to oxidation of LDL. This more advanced stage is associated with symptoms of ischemia and may be detected by angiography [12; 27; 28; 29; 31; 32].

PLAQUE DISRUPTION

As noted, the lipid core of atherosclerotic plaque is initially surrounded by a thicker fibrous cap that provides some degree of stability. As plaques grow in size, their lipid cores become increasingly larger with high concentrations of foam cells, extracellular calcification, and accumulation of oxidized LDL. Interestingly, it has been shown that oxidized LDL promotes apoptosis (i.e., programmed cell death) and causes foam cell death, which leads to plaque necrosis, instability, and increased potential for thrombogenesis [33; 34]. At this stage, plaques further protrude into the lumen and disrupt blood flow. Turbulent blood flow increases shear stress in the periphery of the plaque, known as the shoulder region, and further increases the risk of instability, plaque disruption, clot formation, and thrombogenesis. These events are often accompanied by symptoms associated with acute ischemia (e.g., angina, myocardial infarction, intermittent claudication, stroke). Lesions at this stage are able to be detected in angiographic studies and ultrasonography [12; 27; 28; 29; 31; 32].

RISK FACTORS FOR HYPERLIPIDEMIA

As noted, hyperlipidemia has been established as a main risk factor in the development of atherosclerosis and CVD. Together with obesity, hypertension, diabetes, smoking, and physical inactivity, hyperlipidemia is a known modifiable risk factor of CVD. Additionally, several biomarkers, including C-reactive protein (CRP), hyper-homocysteinemia, and lipoprotein(a), are also considered modifiable risk factors of CVD. Modifiable risk factors play a major role in the pathogenesis of CVD because they activate the endothelium and stimulate the release of proinflammatory mediators and cell surface adhesion molecules. Because modifiable risk factors account for up to 90% of population-attributable cardiac risk, regulation of these factors has a beneficial effect on the primary and secondary prevention of CVD [11; 12]. In addition to modifiable risk factors, non-modifiable risk factors of CVD, such as family history of CVD (in men younger than 55 years of age and women younger than 65 years of age), gender (men have a greater incidence of CVD than women), and age, also play a major role in atherogenesis and CVD [11; 12; 27; 31; 35; 36].
Experimental studies in animals with genetic abnormalities identical to human familial hypercholesterolemia (absence or 50% reduction in LDL receptors in homozygous or heterozygous individuals, respectively) as well as epidemiological studies of human populations have established that high levels of LDL cholesterol are atherogenic [22; 37; 38; 39]. A number of clinical studies, including the Framingham Heart Study, the Multiple Risk Factor Intervention Trial, and the Lipid Research Clinics, have also reported a direct relationship between elevated concentrations of LDL cholesterol (or total cholesterol) and an increase in cardiovascular morbidity and mortality [1; 17; 18; 19; 20; 21; 24; 25; 40; 41]. Lipid management with a combination of pharmacotherapy and lifestyle changes aimed at the reduction of cholesterol levels effectively slows the progression of atherosclerosis and plays a pivotal role in the primary and secondary prevention of CVD [1; 17; 18; 19; 20; 21; 22; 23; 24; 25; 39; 41; 42; 43].

Chronically high levels of CRP, and high sensitivity CRP (hsCRP) in particular, are biomarkers of CVD, regardless of whether they play a causal role in atherogenesis or if they are the result of underlying atherosclerosis [12; 27; 44]. The American Heart Association (AHA) and the Centers for Disease Control and Prevention have issued guidelines for hsCRP values. Concentrations of hsCRP less than 1 mg/L are associated with low risk, and 1–3 mg/L is correlated with moderate risk for CVD. Patients with levels greater than 3 mg/L are at high risk for CVD. Ongoing clinical studies suggest that lowering the plasma levels of both hsCRP and LDL may be a main goal in the secondary prevention of CVD [44].

High homocysteine blood levels (greater than 15 mcmol/L) are associated with increased oxidative stress and secretion of proinflammatory factors. Both mechanisms stimulate smooth cell proliferation and accelerate atherosclerosis [27; 45].

Numerous clinical studies have also revealed that high levels of lipoprotein(a) are associated with significant increases in CVD [12; 27; 31; 35; 46; 47]. Lipoprotein(a) is a subtype of LDL that includes apoprotein A (Apo A) in its structure. The role of lipoprotein(a) in atherogenesis relates to a variety of mechanisms including inhibition of fibrinolysis by preventing the transformation of plasminogen to plasmin, enhanced capacity to traverse the arterial endothelium, and low affinity for the LDL-receptor mediated clearance from circulation [46]. High lipoprotein(a) concentrations (greater than 30 mg/dL) in patients with an elevated total cholesterol:HDL ratio (greater than 5.5) or other major risk factors indicates the need for a more aggressive therapy to further lower LDL [24; 48].

AN OVERVIEW OF LIPIDS

PHYSIOLOGIC ROLES

Lipids play a crucial role in living organisms as a source of energy and as structural constituents of cell membranes and complex molecules such as steroids and eicosanoids (e.g., prostaglandins, thromboxane A2, leukotrienes) and lipid-soluble vitamins [30; 49; 50]. In brief, the most important lipids are phospholipids, cholesterol, fatty acids, and triglycerides.

Phospholipids are structural components of cell membranes, myelin, lipoproteins, and blood clotting factors. Cholesterol is a structural component of cell membranes and a precursor of other steroids, namely steroid hormones, bile acids, and signaling molecules. Cholesterol is mainly synthesized in the liver but is also absorbed in the intestine from dietary sources and enterohepatic circulation.
Fatty acids are a source of energy. Their general structure is represented as R-COOH, where R represents a hydrocarbon chain. More than 100 fatty acids have been identified, and they differ on length of the hydrocarbon chain and number of carbon-carbon double bonds. Fatty acids without carbon-carbon double bonds are known as saturated; those with carbon-carbon double bonds are known as unsaturated. These fats are further classified as either monounsaturated or polyunsaturated based on the number of carbon-carbon double-bonds. Saturated fatty acids are waxy solids at room temperature, while unsaturated fatty acids are liquids.

In living cells, free fatty acids are only present in trace amounts. They are esterified with glycerol and form more complex lipids, including triglycerides. Most double bonds in unsaturated fatty acids are in the cis form. Some edible fats, including hydrogenated vegetable products such as oils, margarines, and shortenings, are rich in trans fatty acids. Trans fatty acids (also known as partially hydrogenated fats) have physical properties similar to saturated fats and are solid at room temperature. They are inexpensive to produce, give foods a desirable texture and taste, have a long shelf-life, and can be reused to deep-fry foods. These properties make trans fats particularly attractive to commercial enterprises and fast food restaurants. However, their increased dietary intake is associated with increased CVD. Awareness of this link has led to the concerted effort to decrease or eliminate their availability and dietary intake. Clear information on trans fats, particularly useful for patients and the general population, is readily available from the American Heart Association (Resources).

Triglycerides are a combination of three fatty acids attached to a single glycerol molecule. They are the main source of dietary fat and can also be synthesized in the liver from intermediary metabolites of excess carbohydrates. Triglycerides accumulate in adipose tissue and muscle cells and can later be mobilized as non-esterified free fatty acids as a source of energy when dietary sources are not readily available.

Cholesterol and triglycerides have significant roles in the process of atherogenesis. They are virtually insoluble in water, and to facilitate their transport in plasma and lymph, they are packaged in larger spherical macromolecules known as lipoproteins.

**ABSORPTION, SYNTHESIS, AND METABOLISM**

Circulating lipids have two separate, although interrelated, origins and metabolic pathways: the exogenous pathway (i.e., dietary source) and the endogenous pathway (i.e., hepatic synthesis) [51].

**Exogenous Pathway**

Dietary lipids provide 30% to 40% of calories in Western diets. With the exception of the essential fatty acids (e.g., linoleic, linolenic), most lipids can also be synthesized by humans. Triglycerides, specifically, account for more than 95% of dietary lipid intake. Cholesterol from animal sources and small amounts of plant sterols comprise the majority of dietary lipid intake. Free fatty acids, phospholipids, and fat-soluble vitamins account for the remaining lipids from dietary sources [35; 49; 52].

Dietary fat is digested by enzymes produced in the mouth, stomach, and pancreas. The small intestine is the main site of lipid transformation and absorption. In the small intestine, triglycerides are hydrolyzed by gastric and pancreatic lipases, phospholipids are transformed by phospholipase A2 into lysophospholipids and fatty acids, and cholesterol is hydrolyzed by bile salts and pancreatic hydrolase (also known as cholesterol esterase).

Studies have shown that cholesterol absorption in the small intestine is regulated by selective transporters, such as the Niemann-Pick C1 like 1 (NPC1L1). Selective inhibition of NPC1L1 prevents intestinal absorption of dietary cholesterol, a mechanism targeted by ezetimibe, a lipid-lowering drug. In the enterocyte, free cholesterol is esterified to cholesteryl esters by the enzyme acyl-CoA cholesterol acyltransferase isof orm 2 (ACAT2) and incorporated into chylomicrons [53].
In a separate pathway, after enzymatic hydrolysis, free fatty acids and monoacylglycerides are transported to the intestinal cells in bile-salt micelles. Micelles deliver the lipid molecules to the enterocyte, and bile salts remain in the lumen, where they are subsequently re-used to form new micelles.

Intracellularly, lipid molecules are re-assembled and packaged in chylomicrons. These are large lipoproteins (75–1,200 nm in diameter) rich in triglycerides and cholesterol but poor in protein content. Chylomicrons are released by exocytosis into the extracellular space, enter the lymph, and ultimately reach the bloodstream. Circulating chylomicrons are transformed by lipoprotein lipase, an enzyme expressed in endothelial cells of the capillaries in muscle and adipose tissue, and deliver triglycerides to the muscle (for energy) and adipose tissue (for storage). Chylomicron remnants deliver the cholesterol and the remaining triglycerides to the liver, where cholesterol is used in the synthesis of bile salts and triglycerides and free fatty acids are used in the production of energy by β-oxidation and synthesis of new molecules of cholesterol. The synthesis of cholesterol in hepatocytes is known as the endogenous pathway.

It is relevant to mention that unesterified cholesterol can also be transported back into the intestinal tract by selective transporters, such as the ATP-binding cassette transporters ABCG5 and ABCG8 [54]. A new generation of lipid-lowering drugs that stimulate the ATP-binding cassette transporter is being investigated [55].

Endogenous Pathway

The hepatic pathway is the major source of cholesterol in the body. Circulating free fatty acids, which are released by the action of endothelial lipoprotein lipase on the chylomicrons, are taken up by the liver, where they are oxidized and transformed into acetyl-coenzyme A (acetyl-CoA), a source of energy and the “raw material” for the intracellular synthesis of cholesterol. Alternatively, free fatty acids combine with cholesterol to form triglycerides [51].

The major regulatory step in the hepatic synthesis of cholesterol from acetyl-CoA is the transformation of hydroxymethylglutaryl-coenzyme A (HMG-CoA) to mevalonic acid. This requires the participation of a selective enzyme-HMG-CoA reductase [49; 52]. Selective inhibitors of HMG-CoA reductase, such as statins, effectively prevent the synthesis of cholesterol and are powerful hypolipemic drugs [31; 56].

Newly formed cholesterol molecules can either be transiently stored in the hepatocytes or further transformed either into bile salts, steroids, or “packaged” in lipoproteins. These lipoproteins, which carry cholesterol and triglycerides from the liver into the circulation, are known as very-low density lipoproteins (VLDL) and have a very high content in triglycerides and cholesterol. VLDLs comprise 15% to 20% of the total blood cholesterol and most of the circulating triglycerides [31; 51].

In the liver, cholesterol is also eliminated by biliary secretion in the form of bile acids. Bile acids, which are highly soluble in water, are released by the hepatocytes into the biliary canaliculi and then transported to the gallbladder, where they are stored in bile and later released into the lumen of the small intestine. Most bile acid molecules (>95%) are not excreted in the feces, but rather are reabsorbed in the ileum, enter the portal circulation, and are then extracted with high first-pass efficiency by hepatocytes. This process of recycling bile acids between liver and intestine is known as enterohepatic circulation. In fact, recycled cholesterol from bile acids is a major source of cholesterol and represents 75% of the total cholesterol that goes through the intestine; dietary cholesterol, even in patients with rich diets, accounts only for up to 25%.
AN OVERVIEW OF LIPOPROTEINS

STRUCTURE AND MOLECULAR COMPONENTS

Triglycerides and cholesterol are non-polar lipids that are virtually insoluble in water. To facilitate their transport in plasma and lymph, they are packaged as lipoproteins. These large spherical macromolecules that transport cholesterol and triglycerides in the plasma vary in size (ranging from 5–1,200 nm in diameter) and density (determined by the ratio of lipid to protein content).

Lipoproteins have a hydrophobic core of non-polar triglycerides and choleseryl ester (a form of cholesterol linked by an ester bond to a fatty acid) surrounded by a monolayered shell of more water-soluble phospholipids, non-esterified cholesterol, and amphipathic surface proteins known as apoproteins.

Apoproteins (also known as apolipoproteins) are a family of surface proteins that perform three important functions: stabilizing the structure of the lipoprotein shell, activating enzymes in the plasma and endothelial cells, and binding to selective cell receptors [27; 30; 31; 57]. Specific apoproteins regulate the metabolic fate of lipoproteins, and their physiologic role can be compared to “molecular zip codes” that determine the destination of specific lipoproteins in the body. Each type of lipoprotein contains one or more specific types of apoproteins.

There are four major classes of apoproteins: Apo A, Apo B, Apo C, and Apo E. In terms of clinical relevance, the following lipoproteins are the most important: Apo A-I, Apo A-II, Apo B-100, Apo C, and Apo E [27; 31].

CLASSES OF LIPOPROTEINS AND LIPOPROTEIN PHYSIOLOGY

Lipoproteins are classified by size and density. Because proteins are denser than lipids, the greater the protein content, the greater the density of the lipoprotein. There are five types of lipoproteins: chylomicrons, VLDLs, intermediate-density lipoproteins (IDLs), LDLs, and HDLs (Table 1).
Plasma Lipid Profiles

Prior to discussing in detail the properties of the various lipoproteins, it is important to review the most pertinent information related to plasma lipid profiles. In fasting individuals, total cholesterol in plasma is carried primarily in VLDL, LDL, and HDL. Accordingly, total cholesterol is equal to the sum of VLDL, HDL, and LDL.

Clinical laboratories measure total cholesterol, HDL, and triglycerides. Most triglycerides are found in VLDL, which has five times as much triglyceride by weight as cholesterol. Therefore, the amount of cholesterol in VLDL can be calculated as triglycerides (mg/dL) divided by 5 or triglycerides (mmol/dL) divided by 2.2.

Most clinical laboratories calculate the value of LDL cholesterol indirectly, according to the Friedewald equation [58; 59]:

\[
LDL \text{ (mg/dL)} = \text{total cholesterol (mg/dL)} - \text{HDL (mg/dL)} - \left[ \frac{\text{triglycerides (mg/dL)}}{5} \right]
\]

Or, if the International System of Units is used, total LDL may be calculated as:

\[
LDL \text{ (mmol/dL)} = \frac{\text{total cholesterol (mmol/dL)}}{\text{HDL (mmol/dL)}} - \left[ \frac{\text{triglycerides (mmol/dL)}}{2.2} \right]
\]

A modified Friedewald equation is also used and has been suggested to have a higher level of accuracy in calculating LDL values [60; 61]. This equation is:

\[
LDL \text{ (mg/dL)} = \left[ \frac{\text{non-HDL cholesterol (mg/dL)} \times 0.9}{\text{triglycerides (mg/dL)} \times 0.1} \right] - \left[ \frac{\text{triglycerides (mg/dL)}}{5} \right]
\]

The ratio of total cholesterol to HDL and the ratio of LDL to HDL (LDL:HDNI) are clinically relevant predictors of coronary heart disease (CHD) risk. The lower the ratio value, the better the predicted outcome [62; 63; 64; 65]. The Apo B:Apo I-A lipoprotein ratio has also been used as a predictor for CHD. However, comparative studies have concluded that Apo B:Apo A-I ratio for prediction of CHD “does not provide incremental value for CHD risk prediction over established traditional lipid ratios” [62].

Chylomicrons

Chylomicrons are large lipoproteins 75–1,200 nm in diameter that are very rich in lipids (98% content), mainly triglycerides (83%) and cholesterol (8%), and have the lowest protein content (2%) of all lipoproteins. Chylomicrons are only synthesized in the intestine and are produced in large amounts during fat ingestion [52]. In normolipidemic individuals they are present in the plasma for 3 to 6 hours after fat ingestion and are absent after 10 to 12 hours fasting [14].

Original chylomicrons secreted by intestinal cells are also known as “incomplete” chylomicrons and only express Apo B-48. They enter the lymph and later reach the bloodstream. They interact with circulating HDL, from which they receive Apo C-II and Apo E and become “complete” chylomicrons. In the capillaries of muscle and adipose tissue, chylomicrons are transformed by the enzyme lipoprotein lipase, a process that requires Apo C-II as a cofactor. As a result of this process, 90% of the triglycerides are hydrolyzed to free fatty acids and glycerol that will be used either as a source of energy in the muscle or stored in the adipose tissue. Individual chylomicrons have a short half-life of 15 to 20 minutes [66]. After interaction with lipoprotein lipase, these cholesterol-rich chylomicron remnants deliver cholesterol and triglycerides to the liver. This process of endocytosis is mediated by a protein, the LDL receptor, expressed on the surface of hepatocytes and requires Apo E and Apo B as cofactors [67].

The concentration of chylomicrons can only be lowered by reduction of dietary fat consumption or drugs that inhibit the intestinal absorption of cholesterol. However, drugs specifically targeting the step of chylomicron secretion have not yet been developed [14]. Although rare, individuals with a genetic deficiency that results in low lipoprotein lipase activity may present with abnormally high concentrations of circulating triglycerides (1,000–5,000 mg/dL) [31].
Very-Low-Density Lipoproteins
VLDLs are smaller than chylomicrons (80 nm in diameter) and have a very high triglyceride and cholesterol content—five times as much triglycerides by weight as cholesterol. As noted, VLDL makes up 15% to 20% of the total blood cholesterol and most of the circulating triglycerides [68].

In the muscle and adipose tissue capillaries, lipoprotein lipase interacts with circulating VLDL, from which it removes triglycerides in a process that requires Apo C-II as a cofactor, as described for chylomicrons. VLDL also expresses Apo E and Apo B-100. Apo B-100 plays a fundamental role in the regulation of circulating cholesterol.

From a metabolic viewpoint, both chylomicrons and VLDL deliver triglycerides to muscle and adipose tissue [30]. However, whereas chylomicrons are an integral part of the exogenous pathway and carry dietary lipids, VLDL transport triglycerides and cholesterol synthesized in the liver as a part of the endogenous pathway. From a clinical perspective, it is particularly relevant to point out that the hepatic synthesis of VLDL is increased when the concentration of free fatty acids in the liver is increased (e.g., in high-fat diets) as well as when adipose tissue releases high amounts of free fatty acids in the circulation (e.g., as a result of obesity or diabetes) [35]. Genetic deficiencies that result in either total (abetalipoproteinemia) or partial liver failure to produce Apo B-100 (familial hypobetalipoproteinemia) inhibit the release of VLDL by hepatocytes and results in fatty liver [69].

Intermediate-Density Lipoproteins
IDLs, also known as VLDL remnants, are created when VLDL is depleted in triglycerides as a result of the hydrolysis by the enzyme lipoprotein lipase. IDL have a short half-life (less than 30 minutes) and undergo liver absorption by selective uptake mainly by binding to the LDL receptor, with Apo B-100 and Apo E as required cofactors. Genetic variants of Apo E are responsible for low binding to the LDL receptor, which results in high concentrations of circulating VLDL and IDL, a condition clinically known as type III hyperlipoproteinemia [14; 70].

Low-Density Lipoproteins
LDLs play a central role in atherogenesis and are often called “bad cholesterol” [22]. The discovery of the LDL receptor by Goldstein and Brown and their work elucidating its role in cholesterol homeostasis is one of the most important advances in cardiovascular research. Their studies have been a major contribution to the understanding of the mechanisms underlying hyperlipidemias [67]. The proatherogenic role of LDL on the release of pro-inflammatory cytokines (e.g., IL-1, TNF-α) and adhesion molecules (e.g., LAM, ICAM-1) is well established.

LDLs are the product of VLDL and IDL metabolism by lipoprotein lipase. LDL is the most cholesterol-rich of all lipoproteins, and even in healthy individuals, LDLs carry two-thirds of the circulating cholesterol [14]. LDL has a half-life of 1.5 to 2 days, which accounts for a plasma concentration higher than VLDL and IDL [14; 35; 52; 56].

There are several subtypes, also known as subfractions, of LDL, and it has been proposed that smaller, denser LDL particles are more atherogenic than larger and less dense LDL. However, research suggests that the use of clinically available LDL subfractions to estimate the risk of CVD is premature [71; 72].

Plasma clearance of LDL is primarily mediated by the LDL receptor expressed on the cell surface. Although LDL receptors are expressed in various cell types, approximately 75% of all LDL receptors are expressed in hepatocytes [73]. The uptake of LDL in hepatocytes is mediated by the interaction between the LDL receptor and Apo B-100 (the only apoprotein expressed in LDL), which acts as a ligand at the LDL receptor. This selective and highly effective mechanism accounts for the extraction of approximately 75% of all LDL from plasma [74]. Hepatic LDL receptors are downregulated by the high delivery of cholesterol by chylomicrons or dietary saturated fat and upregulated by decreased cholesterol and saturated fat intake [35; 75].
The crucial role of LDL in atherogenesis results from it being oxidized in the arterial subendothelium. Oxidized LDL has a high affinity for the scavenger receptor expressed in macrophages undergoing endocytosis, which leads to intracellular accumulation and the transformation of lipid-rich macrophages into foam cells.

Genetic mutations of either the LDL receptor or Apo B-100 alter the effectiveness of the binding and increase the plasma concentration of LDL. Familial hypercholesterolemia and familial defective Apo B-100 are examples of clinical conditions that result from these genetic mutations [36; 76]. Homozygotes for familial hypercholesterolemia inherit two mutant LDL receptor genes and present with a 6- to 10-fold elevation in plasma LDL from birth. These patients suffer from advanced CHD starting in early childhood [67; 77].

The expression of LDL receptors in the liver is also regulated by the intracellular enzyme HMG-CoA reductase. Inhibition of HMG-CoA reductase, for example by the administration of statins, not only results in direct inhibition of the intracellular synthesis of cholesterol but indirectly increases the expression of LDL receptors and therefore promotes the LDL-receptor-mediated removal of circulating cholesterol.

The LDL receptor is also relevant from a clinical perspective because both thyroid hormones and estrogens stimulate its expression in the liver [74; 78]. Consequently, deficiencies of these hormones decrease the availability of LDL receptors and result in increased concentrations of circulating LDL and increased risk of CVD [14; 74].

The subtype of lipoprotein(a) is associated with increased risk for CVD [12; 27; 31; 35; 46]. Lipoprotein(a) has a similar lipid composition to more typical LDL but has a higher protein content [79]. The atherogenic role of lipoprotein(a) relates to its unique molecular properties and results in the inhibition of fibrinolysis, enhanced capacity to traverse the arterial endothelium, and low affinity for the LDL-receptor-mediated clearance from circulation [46]. Lipoprotein(a) also exhibits platelet activating and pro-inflammatory properties that further contribute to atherogenesis [80]. Patients with high levels of lipoprotein(a) (greater than 30 mg/dL) and an elevated total cholesterol:HDL ratio (>5.5) or other major risk factors require a more aggressive therapy to lower LDL [24; 48]. Lowering circulating LDL remains the primary goal in the treatment and prevention of atherosclerosis and CVD [15; 22; 23].

**High-Density Lipoproteins**

HDLs are the smallest (5–12 nm in diameter) but the densest lipoproteins (33% protein content). HDL removes cholesterol from the periphery and transports it to the liver [52]. HDLs are a heterogeneous population classified based on size, density, and apoprotein content. The two most important subclasses of HDL express either Apo A-I alone or both Apo A-I and A-II, but the clinical relevance of the various subtypes is unknown [81].

HDL concentration in the plasma is inversely related to the risk of CVD, and for this reason HDL is also known as “good cholesterol.” The role played by HDL in the transport of cholesterol from the periphery to the liver, known as reverse cholesterol transport, and subsequent excretion in bile is a very well understood mechanism through which HDL protects against atherosclerosis [81; 82].
Two main factors are involved in cholesterol removal from the periphery. First, a cell membrane protein (ABCA1) promotes the efflux of cholesterol from cell membranes; second, ABCA1 interacts with Apo A-I from HDL and captures cholesterol. Cholesterol, in the form of cholesteryl esters, is subsequently transferred to LDL, which will carry it to the liver. In the liver, hepatic extraction requires binding to the LDL receptor. Genetic mutations that cause loss of function of ABCA1 result in extremely low levels of HDL and cholesterol accumulation in the liver, spleen, tonsils, and central and peripheral nervous systems. This results in early-life coronary and peripheral artery disease, a condition known as Tangier disease or familial alpha-lipoprotein deficiency [83; 84].

In vitro and in vivo studies have revealed that HDL has anti-inflammatory and antioxidant properties and inhibits atherogenesis. It has been suggested that high levels of HDL have a protective effect on the development of atherosclerosis and CVD [81; 85].

However, authors of a systematic review of clinical studies concluded that “simply increasing the amount of circulating HDL does not necessarily confer cardiovascular benefits” and that reduction of LDL should remain “the primary goal for lipid-modifying interventions” [86]. Other researchers concluded that raising endogenous HDL levels in humans to reduce the development of atherosclerosis “has yet to be established conclusively” [81]. Together, these studies further support the recommendation that lowering LDL should remain the target goal for patients with hyperlipidemia and/or at risk for CVD-related conditions [22; 23].

CLASSIFICATION AND CLINICAL RELEVANCE OF HYPERLIPIDEMIAS

Hyperlipidemias, also known as dyslipidemias, are elevations of LDL cholesterol either alone or in conjunction with triglycerides. As noted, they may also be associated with low HDL.

In 2013, the National Heart, Lung, and Blood Institute (NHLBI) discontinued its publication of clinical practice guidelines, instead choosing to provide its systemic evidence reviews to professional organizations, who will then publish guidelines based on these and other findings [203]. This change affected five cardiovascular disease-related documents that were in the process of being crafted, including those addressing cholesterol, blood pressure, risk assessment, lifestyle interventions, and obesity. The AHA and the American College of Cardiology (ACC) published guidelines intended to update the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) recommendations in 2013, but these guidelines focused primarily on optimal statin use and do not address specific risk factors or lifestyle changes [204].

In the 2013 ACC/AHA update to the NCEP-ATP III, one major change in the treatment recommendations was the removal of specific LDL and non-HDL-cholesterol target values. The NCEP-ATP III guidelines indicated that the target goal for LDL should be <100 mg/dL; however, the Expert Panel determined that there was not sufficient evidence to support treatment to a specific target goal [206; 207]. It should be noted, however, that some controversy exists regarding removal of target goal values, and for the purposes of this course, treatment using ATP III guidelines will primarily be discussed, with frequent mention of ACC/AHA guidelines [206; 207; 208]. According to the NCEP, the risk of CVD is organized into four categories based on assessment of the plasma concentrations of LDL (Table 2) [22; 23; 87; 88; 208].
In patients with CVD, a complete lipid profile (total cholesterol, HDL, triglyceride levels) should be obtained after an overnight fast as a screening test. In patients with initial moderately elevated LDL, it is recommended that the lipid test be repeated, considering that lipids values may vary by up to 10% in the same individual [63]. From a clinical perspective, the primary goal of lipid therapy in high-risk patients, including lifestyle changes and pharmacotherapy, is aimed at reducing LDL cholesterol to at least less than 100 mg/dL (2.58 mmol/dL) or optimally to less than 70 mg/dL (1.80 mmol/dL) [22; 23; 63; 87; 88; 206; 207]. Baseline cholesterol values also vary by geography and among ethnic minority populations. For example, in the Western population cholesterol values are about 20% higher than in the Asian population [63].

Hyperlipidemias are classified by etiology as primary or secondary, or by phenotype according to identification of lipoprotein patterns, as with Fredrickson phenotypic classification (Table 3). In practice, a combination of both classifications is used, as the patient’s condition is first identified based on clinical evidence and lipid profile, providing the data required for classification based on etiology [31; 35; 63; 73; 89].

Advances in genetics, genomics, and proteomics have contributed to a better understanding of the pathophysiology of numerous diseases and to the development of new and selective therapies. However, their contribution to the study of primary hyperlipidemias is still limited [90]. While gene therapy is being developed to treat patients with known genetic abnormalities, the genetic profile and precise molecular basis of primary hypertriglyceridemia is known for only 5% to 10% of cases; this percentage is even lower for secondary hyperlipidemia [88; 91; 92].

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL Goal (mg/dL)</th>
<th>LDL Level (mg/dL) at Which to Initiate Lifestyle Changes</th>
<th>LDL Level (mg/dL) at Which to Consider Drug Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk: CHD* or CHD risk equivalents (10-year risk** &gt;20%)</td>
<td>&lt;100 (optimal goal: &lt;70 mg/dL)</td>
<td>&gt;100</td>
<td>&gt;100 (&lt;100: consider drug options)</td>
</tr>
<tr>
<td>Moderately high risk: 2+ risk factors (10-year risk 10% to 20%)</td>
<td>&lt;130</td>
<td>&gt;130</td>
<td>&gt;130 (100–129: consider drug options)</td>
</tr>
<tr>
<td>Moderate risk: 2+ risk factors (10-year risk &lt;10%)</td>
<td>&lt;130</td>
<td>&gt;130</td>
<td>&gt;160 (160–189: LDL-lowering drug optional)</td>
</tr>
<tr>
<td>Low risk: 0–1 risk factors</td>
<td>&lt;160</td>
<td>&gt;160</td>
<td>&gt;190 (160–189: LDL-lowering drug optional)</td>
</tr>
</tbody>
</table>

*CHD includes myocardial infarction, unstable angina, angioplasty, bypass surgery, or evidence of clinically significant myocardial ischemia.


Source: [23]
PRIMARY HYPERLIPIDEMIAS

Primary hyperlipidemias result from single or multiple genetic mutations that target any of the molecules that participate in the endogenous and exogenous lipid pathways. These mutations result in increased plasma concentrations of cholesterol (pure or isolated hypercholesterolemia), triglycerides (pure or isolated hypertriglyceridemia), or both (mixed or combined hyperlipidemia) and are the result of either increased synthesis or decreased clearance. HDL concentrations may be lower than normal, either from decreased synthesis or increased clearance.

At the early stages, primary hyperlipidemias are asymptomatic. However, as the disease progresses, a constellation of signs and symptoms develop, such as eruptive xanthomas (located on the trunk, back, buttocks, elbows, knees, hands, and feet), severe hypertriglyceridemia (greater than 2,000 mg/dL), lipemis plasma (i.e., plasma develops a creamy supernatant when incubated overnight), and lipemia retinalis (i.e., creamy white-colored blood vessels in the fundus) often associated with premature CHD or peripheral vascular disease [35; 88; 93].

Familial hypercholesterolemia and familial defective Apo B-100 are examples of clinical conditions that result from LDL receptor and Apo B-100 deficiencies, respectively [36; 76; 94]. Other genetic mutations cause familial hypertriglyceridemia, familial combined hyperlipidemia, familial chylomicronemia, and familial dysbetalipoproteinemia [31; 35; 87; 88; 95].

Polygenic hypercholesterolemia, also known as nonfamilial hypercholesterolemia, is the most common form of hyperlipidemia, with a prevalence of more than 25% in the American population [95]. Polygenic hypercholesterolemia is a typical example of the combination of multiple genetic deficiencies that result in decreased activity of the LDL receptor and reduction of LDL clearance. This underlying genetic susceptibility, not yet completely understood, becomes apparent with dietary intake of saturated fats, obesity, and sedentary lifestyle. Twenty percent of polygenic hypercholesterolemia patients have a family history of CHD. Patients present with mild-to-high increases in total cholesterol (250–350 mg/dL or 6.5–9.0 mmol/L) and LDL (130–250 mg/dL or 3.33–6.45 mmol/L). A combination of lifestyle changes (e.g., reduction in saturated fat) and lipid-lowering drugs (e.g., statins, bile acid sequestrants, ezetimibe, niacin) effectively control the condition [31; 96].

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Elevated Lipoproteins</th>
<th>Elevated Lipids</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Chylomicrons</td>
<td>Triglycerides</td>
</tr>
<tr>
<td>IIa</td>
<td>LDL</td>
<td>Cholesterol</td>
</tr>
<tr>
<td>IIb</td>
<td>LDL and VLDL</td>
<td>Triglycerides and cholesterol</td>
</tr>
<tr>
<td>III</td>
<td>VLDL and chylomicron remnants</td>
<td>Triglycerides and cholesterol</td>
</tr>
<tr>
<td>IV</td>
<td>VLDL</td>
<td>Triglycerides</td>
</tr>
<tr>
<td>V</td>
<td>Chylomicrons and VLDL</td>
<td>Triglycerides and cholesterol</td>
</tr>
</tbody>
</table>

Source: [35; 89] Table 3
Familial hypercholesterolemia is an autosomal dominant disease responsible for defective LDL receptors that results in either reduction in receptor synthesis or inability of the receptor to bind and/or efficiently remove LDL. The heterozygous form (caused by a single abnormal copy of the gene) has a prevalence of 1 per every 500 in the United States, and the homozygous form (from two abnormal copies) occurs in 1 of every 1 million Americans [96; 97]. Patients typically present with tendon xanthomas, premature myocardial infarction (5% by 30 years of age and 50% by 50 years of age in untreated heterozygotes), elevated total cholesterol (275–500 mg/dL in heterozygotes and 700–1,200 mg/dL in homozygotes), and elevated triglycerides (250–500 mg/dL in heterozygotes and >500 mg/dL in homozygotes) [96; 97]. Familial hypercholesterolemia heterozygotes respond to lifestyle changes and drug therapy that combines statins with other drugs that upregulate the LDL receptors, such as bile acid sequestrants, ezetimibe, or niacin. Due to the high risk of CHD and myocardial infarction in homozygous patients, the clinical management requires early treatment in medical centers specialized in lipid treatment and often requires LDL apheresis (i.e., extracorporeal removal of LDL) and liver transplantation [30; 31; 35; 96; 97]. Two drugs have been FDA-approved for homozygous familial hypercholesterolemia since 2012, a microsomal triglyceride transfer protein inhibitor (lomitapide) and an antisense oligonucleotide inhibitor (mipomersen). A box warning for risk of hepatotoxicity was added to the latter in 2016. Both of these drugs inhibit the synthesis of Apo B–100 [214; 215]. Familial hypertriglyceridemia is a common autosomal dominant disease characterized by high triglycerides (200–500 mg/dL or 2.3–5.7 mmol/L) and normal LDL. Lipid-lowering drugs (e.g., fibrates, niacin, statins) combined with diet and weight loss are the most appropriate therapy [30].

**SECONDARY HYPERLIPIDEMIAS**

Secondary hyperlipidemias are associated with primary underlying conditions such as obesity (increased triglycerides and decreased HDL), diabetes (increased triglycerides and increased total cholesterol), alcohol abuse (increased triglycerides and increased HDL), chronic renal insufficiency (increased total cholesterol and increased triglycerides), and hypothyroidism (increased total cholesterol). It has been postulated that these events expose an underlying genetic or metabolic deficiency that increases the individual’s susceptibility to develop hyperlipidemia [31; 88].

Along with polygenic hypercholesterolemia, atherogenic dyslipidemia is one of the most common forms of hyperlipidemias. Atherogenic dyslipidemia is found in approximately 25% of patients with dyslipidemias and is usually diagnosed in patients with metabolic syndrome. In atherogenic dyslipidemia patients there is increased mobilization of triglycerides and cholesterol from adipose tissue to the circulation. This results in increased concentrations of triglycerides and VLDL rich in Apo C-III. Apo C-III inhibits lipoprotein lipase and prevents extraction of triglycerides from the circulation.
VLDL. Moderate-to-high increases in triglycerides (150–500 mg/L or 1.69–5.65 mmol/dL) result from high fat intake and mobilization from adipose tissue and VLDL secretion by the liver. These patients are treated with lifestyle changes aimed at weight reduction and increasing physical activity (which stimulates lipoprotein lipase activity). Statins (to lower VLDL) and fibrates (to lower triglycerides) are the most appropriate drugs to complement lifestyle changes [31; 99]. Studies support the use of antioxidants as well as newer fibrates in the treatment of atherogenic dyslipidemia based on their agonism at the peroxisome proliferator-activated receptor α (PPAR-α) [100; 101].

Secondary hyperlipidemias can also be associated with a number of drug-induced conditions such as estrogen therapy (increased triglycerides and increased total cholesterol), atypical antipsychotics (increased triglycerides), corticosteroids (increased total cholesterol), selective β-blockers without intrinsic sympathetic activity or α-antagonism (increased total cholesterol and decreased HDL), and thiazides (modest increase in total cholesterol and LDL) [63; 102].

In summary, secondary hyperlipidemias with elevated triglycerides are the primary lipid abnormality in patients with obesity, diabetes, alcohol abuse, hormone replacement therapy, and atypical antipsychotic therapy. Secondary hyperlipidemias with elevated cholesterol are the main dyslipidemia in patients with chronic renal failure, hypothyroidism, and typical β-blocker use (e.g., propranolol, atenolol).

From a clinical perspective, identification of the lipid profile, classification of the hyperlipidemia, and management of comorbidity are particularly relevant to help patients lower cholesterol and triglyceride levels necessary to reduce CVD risk [22; 23; 25; 35; 87; 88].

**APPROACHES TO CLINICAL MANAGEMENT OF HYPERLIPIDEMIAS**

Management of existing hyperlipidemia is a cornerstone in the prevention and management of CVD. The NCEP-ATP III has developed evidence-based guidelines for the assessment of cardiovascular risk, treatment goals, lifestyle changes, and pharmacotherapy [1; 22]. The primary target in the treatment of hyperlipidemias is to lower LDL, and the secondary targets are treating high triglycerides, low HDL, and metabolic syndrome.

The primary goal to reduce the risk associated with LDL is to achieve levels less than 100 mg/dL (2.58 mmol/L) (Table 4). This is considered beneficial because LDL levels maintained at less than 100 mg/dL throughout life are associated with a very low risk for CHD. When LDL concentrations are between 100 and 129 mg/dL (2.58–3.33 mmol/L), atherogenesis occurs at a low rate, and such levels are considered above optimal. Levels between 130 and 159 mg/dL (3.36–4.11 mmol/L) are categorized as borderline high. In borderline patients, atherogenesis proceeds at a significant rate. At higher levels, categorized as high (160–189 mg/dL or 4.13–4.88 mmol/L) or very high (190 mg/dL or 4.91 mmol/L), atherogenesis progression is markedly accelerated. The direct relationship between serum cholesterol levels and CHD risk has been consistently observed in large population studies, although evidence-based research and synthesis of information led the ACC/AHA to conclude in 2013 that there was not enough evidence to continue using specific levels [1; 22; 23; 206; 207].

In addition to removal of specific LDL target goals previously discussed, another major change in the ACC/AHA guideline is expansion of persons recommended to be treated with statins. Initiation of statin therapy is recommended for all persons older than 21 years of age with known cardiovascular disease for whom the drugs are not contraindicated regardless of blood cholesterol levels [204].
In addition, statin therapy is recommended for patients with an LDL level of 190 mg/dL or greater for primary prevention of cardiovascular disease and for individuals with LDL levels ≥70 mg/dL who have diabetes or an estimated 10-year risk of atherosclerotic cardiovascular disease ≥7.5% [22]. This recommendation has been controversial, as it increases the number of adults eligible for statin therapy by nearly 13 million, with the greatest increase among older adults without cardiovascular disease [205].

The NCEP-ATP III developed an algorithm of cardiovascular risk, whereby patients are categorized according to their risk for cardiovascular events: patients with established CHD and CHD risk equivalents, patients with multiple risk factors, and patients with zero or one risk factors [22]. All individuals with a history of CHD or CHD risk equivalents, such as diabetes, and an LDL value of 160 mg/dL or greater (≥4.13 mmol/L) are considered at high risk [22; 23; 24; 63; 87; 88].

The 2013 ACC/AHA guidelines also include recommendations to calculate risk, with consideration given to systolic blood pressure, total cholesterol, HDL level, race, age, smoking history, gender, and treatment for hypertension [204]. An online risk calculator is available at http://tools.cardiosource.org/ASCVD-Risk-Estimator. As with other changes, there is controversy regarding the reliability of the online risk calculator. Some studies conducted soon after the change of recommendations noted an overestimation in risk of atherosclerosis by approximately 75% [208]. However, other independent groups that also used similar methods of reviewing evidence to revise recommendations concluded similar results with regard to those at risk [209].

Considering hypertriglyceridemia an independent risk factor for CHD is still controversial. Treatment of borderline-high to high triglyceride levels requires further cardiac risk assessment; however, lowering very-high levels reduces the risk of pancreatitis [87].
LIFESTYLE MODIFICATION

It is important for healthcare professionals to have a good understanding of the recommendations regarding lifestyle changes for lipid management before detailed discussion of pharmacotherapy is initiated. These changes include diet, weight reduction, smoking cessation, and physical activity.

The therapeutic lifestyle change guidelines developed by the NCEP-ATP III recommend a diet low in fat (a maximum of 25% of total calories versus the 35% in the average North American diet), with less than 7% of calories derived from saturated fats and 200 mg or less per day of cholesterol (compared to the 400 mg/day in the average North American diet) [22]. A successful dietary approach to lipid lowering requires instruction by a dietitian or other knowledgeable healthcare professional. In brief, there are several principles that highlight the most important instruction to be provided to patients [22]:

- Reduce intake of high-fat food, particularly foods high in saturated fats (e.g., fast food and processed food) and trans fatty acids (e.g., processed chips, cakes, cookies).
- Replace saturated fats from meat products and oils used in processed and fast foods (e.g., lard, palm oil, coconut oil) with unsaturated fats, especially mono-unsaturated fats (e.g., canola oil, olive oil).
- Replace high-fat dairy products with low-fat alternatives (e.g., skim milk, skim cottage cheese, non-fat yogurt).
- Increase intake of fish and/or poly-unsaturated fats (e.g., fish omega-3 and plant omega-6 polyunsaturated fatty acids).
- Increase intake of foods rich in complex carbohydrates and fiber (e.g., whole grains, vegetables, legumes, fruit, psyllium).
- Limit alcohol consumption to no more than two drinks per day for men and one drink per day for women. Ideally, alcohol should be consumed with meals. Higher alcohol intake increases triglycerides.
- Reduce sodium and sugar intake.
- Achieve acceptable body weight (body mass index between 18.5 and 24.9).

Instructions to patients should not be presented as a list of “foods to avoid” but rather should provide dietary alternatives and teach the patients how to make appropriate dietary choices and control portions. A balanced diet, particularly in the modality known as the Mediterranean diet, is associated with a significant reduction in cardiovascular events and mortality [103; 104; 105]. The Mediterranean diet is characterized by meals predominately consisting of vegetables/fruits, lean protein, and healthy fats (e.g., olive oil) and the moderate consumption of wine.

Physical activity stimulates the activity of lipoprotein lipase in adults as well as in children, lowers triglycerides and VLDL, and promotes cardiovascular fitness and weight loss [31; 106]. As such, patients should be encouraged to engage in moderate-intensity physical activity on most days of the week unless contraindicated.

The AACE recommends a reasonable and feasible approach to fitness therapy (i.e., exercise programs that include at least 30 minutes of moderate-intensity physical activity four to six times weekly, with an expenditure of at least 200 kcal/day). Suggested activities include brisk walking, riding a stationary bike, water aerobics, cleaning/scrubbing, mowing the lawn, and sporting activities.


**Level of Evidence:** 2 (Nonrandomized controlled trial, prospective cohort study, retrospective case-control study, or meta-analysis of nonrandomized prospective or case-controlled trials)
Although dietary changes should always be included in the treatment of hyperlipidemias, the length of time given to lifestyle changes prior to initiation of pharmacotherapy remains controversial. In patients with low cardiovascular risk, it has been proposed that the efficacy of dietary and other lifestyle changes can be assessed in two to three visits over a two- to three-month period. However, pharmacotherapy should be promptly initiated when lifestyle changes are not effective. In patients with high cardiovascular risk or very high LDL (≥200 mg/dL or ≥5.2 mmol/L) drug therapy and lifestyle changes should be initiated immediately [35; 107].

CONSIDERATIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

Because patient education is such a vital aspect of encouraging lifestyle changes in patients with elevated lipid levels, it is each practitioner’s responsibility to ensure that information and instructions are explained in such a way that allows for patient understanding. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient’s lack of proficiency in the English language, an interpreter is required.

In this multicultural landscape, interpreters are a valuable resource to help bridge the communication and cultural gap between clients/patients and practitioners. Interpreters are more than passive agents who translate and transmit information back and forth from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers, who ultimately enhance the clinical encounter.

LIPID-LOWERING MEDICATIONS

Prior to discussing specific therapeutic indications of lipid-lowering drugs in the treatment of hyperlipidemias, it is timely to summarize their relevant mechanisms of action and therapeutic properties. The subsequent sections provide updated information regarding the pharmacologic properties and clinical profile of lipid-lowering drugs and uses the pharmacologic resources and therapeutic guidelines recommended in North America, as well as current drug information [22; 23; 25; 30; 31; 35; 56; 87; 88; 109; 110; 111; 112; 113].

DRUGS THAT INHIBIT CHOLESTEROL ABSORPTION IN THE INTESTINE

Bile Acid-Binding Resins

Mechanism of Action and Clinical Pharmacology

Bile acid-binding resins, also known as bile acid sequestrants, are cationic polymers that bind to the negatively charged bile acids in the lumen of the intestine. The bile-acid complex cannot be absorbed by the intestinal mucosa and is subsequently eliminated in the feces [114]. Bile acids are the source of 75% of cholesterol in the intestine, and inhibition of their reabsorption effectively disrupts chylomicron formation and decreases the availability of cholesterol and triglycerides in the liver.

These events upregulate 7α-hydroxylase, also known as cytochrome P450 7A1 (CYP7A1), the enzyme responsible for the synthesis of bile acid in the liver. This increases the conversion of cholesterol to bile acid synthesis in hepatocytes. Consequently, the intracellular recruitment of cholesterol to bile acid synthesis both depletes its intracellular storage and upregulates the expression of LDL receptors to remove circulating cholesterol. Ultimately, the therapeutic benefit of these drugs is to lower circulating LDL by 10% to 24% [30].
The LDL-lowering benefit of bile acid-binding resins is offset in the long term by the upregulation of cholesterol and triglyceride synthesis and a possible increase in VLDL synthesis. Accordingly, these drugs should be used cautiously in patients with hypertriglyceridemia.

Bile acid-binding resins lower the incidence of coronary events in middle-aged men by about 20%, with no significant effect on total mortality [63]. Overall, bile acid-binding resins have a solid safety record, have been shown to lower LDL by 10% to 24%, and help reduce the risk of CHD [30; 31; 115; 116]. Colesevelam, the newest drug in this class, lowers glycated hemoglobin and fasting plasma glucose and is approved as add-on therapy for glycemic control in type 2 diabetes [201].

**Adverse Effects**

Bile acid-binding resins have very low potential to cause systemic adverse effects because they are not absorbed systemically. However, some patients may report gastrointestinal symptoms, including constipation (10%), dyspepsia, and bloating (1% to 8%) [117; 118].

**Drug Interactions**

The bile acid-binding resins cholestyramine, colestipol, and to a lesser extent colesevelam inhibit intestinal absorption of a variety of lipophilic drugs. This includes fat-soluble vitamins (A, D, E, and K), corticosteroids, estrogens, progestins, thyroid and thyroxine preparations, and negatively charged (i.e., acidic) compounds such as warfarin, nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, valproic acid, folic acid, furosemide and thiazide diuretics, digitalis glycosides, tetracyclines, propranolol, and the oral antidiabetic drugs glipizide, troglitazone, and glyburide. These drug interactions increase intestinal elimination of the drug-resin complexes, resulting in decreased absorption, drug bioavailability, and therapeutic efficacy.

**Cholesterol Absorption Inhibitors**

**Mechanism of Action and Clinical Pharmacology**

Cholesterol absorption inhibitors block the intestinal absorption of cholesterol of dietary and biliary origin as well as plant sterols. Plant sterols (also known as phytosterols) and ezetimibe block the absorption of cholesterol in the intestine through two different mechanisms of action. Phytosterylols are more hydrophobic than cholesterol and displace the latter from micelles, promoting its intestinal elimination. The absorption of sterols and cholesterol across cells of the intestinal lumen requires the participation of the molecular transporter NPC1L1. Sterol binding to the NPC1L1 transporter further inhibits cholesterol absorption. Sterols are available from plant sources, dietary fiber supplements, and plant sterol-enriched margarines. If absorbed in the intestine, sterols’ action against cholesterol is compromised.

Ezetimibe selectively targets and inhibits the transporter NPC1L1, preventing the uptake of cholesterol and phytosterol across the intestinal lumen. Ezetimibe is indicated as adjunctive therapy to diet for the reduction of total cholesterol, LDL, and Apo B in patients with primary (heterozygous familial and nonfamilial) hyperlipidemia [117; 118]. It lowers LDL by 15% to 20% and causes minimal increases in HDL, but its beneficial effect on prevention of CHD remains unclear. This agent is synergistic with statins and, if taken in conjunction, can lower LDL by up to 25% in addition to the results obtained by statins alone [118; 213]. Ezetimibe is available in a combination formulation with the statin simvastatin under the brand name Vytorin. A second combination formulation combining ezetimibe with the statin atorvastatin, brand name Liptruzet, received U.S. Food and Drug Administration (FDA) approval in 2013. However, Liptruzet was recalled in 2014 for packaging issues and discontinued in 2016 [117; 118; 119; 210].
Ezetimibe reduces cholesterol absorption by approximately 50%. However, quite unlike the bile acid-binding resins, it does not prevent the absorption of triglycerides or fat-soluble vitamins, and the effects of ezetimibe in the prevention of CHD have not yet been clearly established [30; 35; 63; 120; 121].

**Adverse Effects**

Upper respiratory tract infection (4%), sinusitis (3%), diarrhea (4%), arthralgia (3%), and pain in an extremity (4%) are the most commonly reported adverse events associated with these medications [118].

**Drug Interactions**

Ezetimibe interacts with cyclosporine, cholestyramine, and fibrates. The combination of ezetimibe with a statin is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases, as well as in pregnant and nursing women [117; 118].

**FIBRATES**

**Mechanism of Action and Clinical Pharmacology**

Fibrates, also known as fibric acid derivatives, are agonists at the PPAR-α. These nuclear receptors are expressed primarily in hepatocytes and muscle cells, and their stimulation by fibrates results in activation of specific genes and subsequent changes in lipid metabolism. The lipid-lowering properties of fibrates result from multiple mechanisms of action, namely activation of lipoprotein lipase, which lowers triglycerides and VLDL; inhibition of Apo C-III synthesis in the liver, preventing the inhibitory action of Apo C-III on lipoprotein lipase activity; and stimulation of Apo A-I and Apo A-II expression, which increases HDL levels [122].

The removal of triglycerides from chylomicrons alters the size and composition of LDL from small, dense particles (which are thought to be more atherogenic due to their susceptibility to oxidation) to large, buoyant, and less atherogenic particles that have a greater affinity for LDL receptors and are rapidly cleared from the plasma. The fibrates fenofibrate, gemfibrozil, and bezafibrate decrease triglyceride levels by 20% to 50%, increase HDL 10% to 20%, and lower LDL by about 5% to 15%, although the latter result is quite variable [118].

Fibrates are indicated in the treatment of hypertriglyceridemias and dysbetalipoproteinemia and in individuals with moderately elevated triglyceride levels (150–400 mg/dL or 1.7–4.5 mmol/L), a sign often associated with metabolic syndrome. Fibrates are also indicated in the prevention of pancreatitis in patients with severely high triglyceride levels (greater than 1,000 mg/dL or 11.3 mmol/L) [118].

Fibrates are one of the most prescribed lipid-lowering drugs, second only to statins, and it is clinically relevant that they have been shown to reduce fatal and non-fatal CVD by about 20%, although their effect on LDL, as mentioned previously, is limited and variable.

In summary, fibrates lower triglycerides by 20% to 50% and are the drug of choice for the treatment of primary and secondary hypertriglyceridemias. As such, they are indicated for the prevention of pancreatitis in patients with very high triglycerides and for the prevention of CHD in patients with low HDL.

**The AACE recommends fibrates for treatment of severe hypertriglyceridemia (triglycerides >500 mg/dL). Adjunct use of 2–4 g of omega-3 fish oil can be used, if necessary, to achieve satisfactory triglyceride lowering.**


**Level of Evidence**: 1 (Randomized controlled trials or meta-analysis of randomized controlled trials)
Adverse Effects

Fibrates are usually well tolerated. Gastrointestinal side effects such as diarrhea, nausea, dyspepsia, and abdominal pain, are reported by 5% of patients. Even less common adverse effects include skin rash, myalgias, headache, and impotence [118].

Drug Interactions

Myositis occurs in up to 5% of patients taking a fibrate who are also being treated with statins. When combined with statins, fenofibrate is the preferred drug because it has less risk of rhabdomyolysis compared with gemfibrozil [123].

Fibrates potentiate the effects of oral anticoagulants (e.g., warfarin), as they compete for their binding sites to albumin. Fibrates also increase cholesterol excretion into the bile, leading to a risk of cholelithiasis. In patients with suspected cholelithiasis, diagnostic studies should be conducted; if gallstones are found, fibrate therapy should be discontinued [118].

STATINS

Mechanism of Action and Clinical Pharmacology

HMG-CoA reductase inhibitors, usually known as statins, are the most effective and the most prescribed class of lipid-lowering drugs. Statins selectively inhibit HMG-CoA reductase, the enzyme responsible for the conversion of HMG-CoA to mevalonate, the rate-limiting step in cholesterol synthesis in the liver [118].

The first statin to be tested and approved for clinical use, lovastatin, was isolated from the mold Aspergillus terreus, and pravastatin and simvastatin are chemically modified derivatives of the original molecule. Atorvastatin, fluvastatin, and rosuvastatin are synthetic compounds with distinct molecular structures. Lovastatin, pravastatin, and simvastatin are inactive prodrugs that require hydroxylation in the liver into their active forms. Although all statins are clinically very effective, rosuvastatin, atorvastatin, and simvastatin have the highest drug efficacy in this class (Table 5).

<table>
<thead>
<tr>
<th>Agent</th>
<th>Percent Reduction in LDL Necessary to Reach Goal</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>20% to 25%</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>—</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>—</td>
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<tr>
<td>Simvastatin</td>
<td>—</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>10 mg</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>10 mg</td>
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<tr>
<td>Fluvastatin</td>
<td>20 mg</td>
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</tbody>
</table>

*Increasing to 80 mg is not routinely recommended. Reserve for patients who have been taking this dose for more than 12 consecutive months without evidence of myopathy.

Source: [14; 118; 124] Table 5

**Table 5**
The selective inhibition of hepatic HMG-CoA reductase initiates a cascade of events that results in decreased synthesis of cholesterol; decreased liver release of VLDL; and activation of the transcription factor SREBP2, which upregulates the LDL receptor and consequently increases the clearance of plasma LDL. As 60% to 70% of serum cholesterol is synthesized in the liver by HMG-CoA reductase, inhibition of this enzyme drastically lowers circulating LDL [125].

In addition to the lipid-lowering actions of statins, studies suggest that the drugs are also implicated in a number of additional actions known as pleiotropic effects. This includes modulation of endothelial function, decrease in vascular inflammation, neuroprotection, and immunomodulation by inhibition of major histocompatibility complex II expression, which is upregulated in patients with myocarditis, multiple sclerosis, and rheumatoid arthritis [126; 127; 128]. Statins have been linked to a reduction in the risk of developing Alzheimer disease independent of the drugs' lipophilicity [128].

The primary therapeutic effect of statins is to lower LDL in a dose-dependent manner. They also lower triglycerides by 15% to 45% in patients with high hypertriglyceridemia (>250 mg/dL or 2.83 mmol/L). However, when the baseline triglyceride levels are less than 250 mg/dL, reductions do not exceed 25% irrespective of the dose or statin used [129].

The lowest recommended starting dose for all statins is set with the goal to decrease LDL by 20% to 30%. Dyslipidemic patients, however, often remain undertreated because the initial dose is not titrated to achieve their target LDL goal. Several sources advise that the initial dosage should be determined based on the target LDL goal for that patient [14]. As an example, for a patient with an LDL level of 170 mg/dL (4.52 mmol/L) to reach the 100 mg/dL (2.58 mmol/L) desirable baseline, a 41% reduction is required. Accordingly, rosuvastatin 10 mg or atorvastatin 40 mg would be appropriate choices. However, higher doses of statins are associated with higher incidence of adverse effects, and the patient should be adequately monitored. Administration of statins with short half-lives (≤4 hours), which would include all but atorvastatin (13 to 16 hours) and rosuvastatin (19 hours), should be taken in the evening because the synthesis of cholesterol in the liver is maximal between midnight and 2 a.m. [14].

In addition to efficacy and therapeutic goals, the clinical choice of a statin also considers cost and drug safety. Lovastatin, simvastatin, and pravastatin have all been shown to be safe in clinical trials involving thousands of subjects for five or more years. This should be particularly taken into account when treating younger patients.

The combination of statins with other lipid-lowering drugs further improves the lipid-lowering outcome. The combination of simvastatin with ezetimibe lowers LDL by an additional 18% to 20% compared with simvastatin alone [130]. Administration of a statin with a bile acid-binding resin (e.g., cholestyramine, colestipol) produces 20% to 30% greater reductions in LDL than statins alone [131; 132].

Statins are well absorbed through the gastrointestinal system and are metabolized in the liver by cytochrome P450. Metabolites are eliminated through the bile and excreted in the feces and, to a much lesser extent, by the kidneys. These drugs should not be used in patients with active liver disease and should be used cautiously at lower doses in patients with kidney disease [118].

Statins are effective in the prevention of CVD [63; 133; 134]. In a 2009 review and meta-analysis, these drugs are referred to as “the most important advance in stroke prevention since the introduction of aspirin and antihypertensive treatments” [135]. Analysis of the risk-benefit ratio of statins after one year of treatment reveals that an estimated 1,587 cases of fatal and non-fatal cases of CVD were prevented against 3.4 cases of rhabdomyolysis [123; 136; 137].
Adverse Effects

Dizziness (7%), diarrhea (4.5%), nausea/vomiting (3%), and abdominal cramps (3%) are among the most frequently reported adverse effects. Statins are contraindicated during pregnancy and lactation [113].

Statins are associated with hepatotoxicity and elevated transaminases in 1% to 2% of patients [113]. However, in 2014, the FDA concluded that the rate of liver injury associated with statin use is rare enough that routine liver enzyme screening while using statins is not needed. It is recommended that liver enzyme tests be performed before statin use begins and then only if there are symptoms of liver damage, including extreme fatigue, loss of appetite, right upper abdominal discomfort, dark urine, or jaundice [138; 211].

The FDA has also noted a small increase in the risk for type 2 diabetes while taking statins. It is noted that there may be a need to assess blood sugar levels after beginning statin use, especially in those with other risk factors [211].

The incidence of myopathy, characterized by muscle pain, weakness, and grossly elevated creatine kinase levels (>10 times the upper limit of normal), with the use of a statin alone is reported in 0.1% to 0.2% of patients [113]. Yet, studies have indicated that the occurrence of statin-induced myopathy may be much higher than originally reported, as high as 10% to 15% of patients treated with statins [123; 139].

A deficiency in coenzyme Q10 (CoQ10), a product of the HMG-CoA reductase pathway selectively inhibited by statins, has been proposed as a possible mechanism of statin-related myotoxicity. Although CoQ10 serum levels are below normal in patients taking statins, there is no direct correlation between myotoxicity and CoQ10 levels in muscle cells. Furthermore, studies of supplementation with CoQ10 to prevent myopathy in patients taking statins have not found conclusive evidence of effectiveness [123; 140]. Alternatively, other studies have shown that the inhibition of HMG-CoA reductase by statins inhibits mitochondrial function, increases intracellular calcium, and activates apoptosis (i.e., programmed cell death) [141]. This latter mechanism is being further investigated and may play a crucial role in the development of lipid-lowering drugs with an even higher safety profile [123].

The occurrence of rhabdomyolysis, defined as skeletal muscle necrosis with release of potentially toxic muscle cell components into the general circulation, has been rarely reported. Possible complications of rhabdomyolysis include myoglobinuric acute renal failure, disseminated intravascular coagulation, hyperkalemia, and cardiac arrest.

The risk of myopathy or rhabdomyolysis increases with higher statin plasma levels, which can be the result of higher doses, decreased hepatic clearance, or drug interactions [118; 142; 211].

Drug Interactions

Statins have pharmacokinetic interactions with drugs that inhibit their metabolism and increase their bioavailability, such as CYP3A4 inhibitors (e.g., azole antifungals, erythromycin, protease inhibitors, amiodarone, grapefruit) and CYP2C9 inhibitors (e.g., NSAIDs, phenytoin, warfarin), as well as drugs that potentiate statins’ therapeutic and adverse effects (e.g., fibrates, niacin). These interactions increase statin toxicity [63; 113; 143]. Interaction between statins and fibrates, particularly with gemfibrozil, increases the risk of rhabdomyolysis. For this reason, fenofibrate is preferred when the two classes are combined [123].

Clinical Outcome

Statins, the most potent lipid-lowering drugs, are indicated in a variety of clinical conditions and are effective in the prevention of CVD and stroke. They lower LDL in a dose-dependent manner by 20% to 55% and are accepted as the drug of choice in the treatment of elevated LDL. They are also effective in the treatment of hypertriglyceridemias when levels are greater than 250 mg/dL, although fibrates remain the drug of choice for hypertriglyceridemias. When elevation of HDL is required, niacin remains the drug of choice, although co-administration of statins and niacin may be considered in patients who also have an elevated LDL.
Co-administration of statins and niacin, fibrates, or ezetimibe increases the lipid-lowering benefit but also increases the risk for adverse effects. These patients should be carefully monitored.

In patients taking statins who develop myopathy and creatine kinase levels 10 or more times higher than normal, immediate discontinuation of the drug is recommended. Dietary therapy and lifestyle changes should be implemented and other lipid-lowering drugs, such as niacin, fibrates, and bile-acid sequestrants, should be considered. The National Lipid Association Muscle Expert Panel guidelines recommend considering the reintroduction of low doses of statins in conjunction with ezetimibe in cases in which the lipid-lowering benefit of statins outweighs the risk of myopathy [123; 144].

NICOTINIC ACID DERIVATIVES

Mechanism of Action and Clinical Pharmacology

Niacin, also known as nicotinic acid or vitamin B3, is a water-soluble vitamin that at physiologic levels is a substrate for nicotinamide adenine dinucleotide (NAD) and NAD phosphate (NADP), important cofactors in intermediary metabolism. Niacin is available in normal- or extended-release formulation as well as in conjunction with lovastatin (as Advicor).

The lipid-lowering and vasodilatory effects of niacin are not related to its vitamin properties. The discovery that the vasodilatory properties of niacin result from its binding to a G protein-coupled receptor (GPR109A) expressed in blood vessels has allowed for better understanding of the mechanisms underlying its metabolic and vascular effects [145]. In addition, further evidence suggests that the lipid-lowering effects result from niacin binding to another G protein-coupled receptor on adipocytes that inhibits lipoprotein lipase and prevents triglyceride release from chylomicrons. The vasodilatory effect of niacin, on the other hand, involves the release of vasodilatory prostaglandins D2 and E2 [30].

It is relevant to emphasize that niacinamide, a nicotinic acid derivative usually preferred as a vitamin supplement, has neither lipid-lowering nor vasodilatory properties [30; 146]. The lipid-lowering effects of niacin require a dose of 1,500–3,000 mg/day, whereas the recommended vitamin dose is 50 mg/day.

Niacin has low cost, a long history of clinical trials, and extensive use as a safe lipid-lowering drug, supported by evidence that it is effective in the prevention of CVD [31]. Niacin lowers LDL by 15% to 25% and triglycerides by 30% to 60% and raises HDL by 20% to 35%. Niacin should be initiated at low doses (250 mg/day) to minimize the occurrence of adverse effects. The dose may be slowly increased every four days to four weeks until the desired effect is achieved or a maximum dose of 3,000 mg/day is attained. The dose should not exceed 4.5–6 g/day due to the risk of possible toxicity [118].

Niacin is the most effective drug available for raising HDL and is considered the drug of choice for patients with borderline to moderate increases in LDL and low HDL [30]. Niacin is a safe and cost-effective drug, and it is indicated as an adjunct to diet in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Frederickson phenotypes IIa and IIb) when the response to an appropriate diet and other nonpharmacologic measures has been inadequate [113].

Adverse Effects

As noted, niacin has a good safety profile, and potential adverse effects are non-life-threatening and promptly reverse upon discontinuation. Flushing is the most common side effect of niacin, occurring in up to 60% of patients. Its occurrence can be significantly decreased by slowly increasing the dose, administration with meals, or treatment with NSAIDs. Flushing often disappears after chronic administration of the drug. Typically, other possible adverse effects include vasodilation, pruritus (6%), rash (5%), headache (11%), dizziness (11%), and
gastrointestinal events such as diarrhea (11%), nausea (10%), vomiting (8%), and activation of pre-existing gastric ulcer. The incidence of flushing is lower with use of the extended-release formulation than with the immediate-release version and can be further minimized by avoiding hot or spicy foods near the time of ingestion. Although rare, the most serious side effect of niacin is hepatotoxicity, which is almost exclusively associated with the extended-release formulation (<1%) [147].

**Drug Interactions**

The vasodilatory properties of niacin account for the most common interaction with hypotensive drugs and can result in hypotension, palpitations, tachycardia, and dizziness. Alcohol or hot drinks taken at the time of niacin administration may worsen the flushing response and pruritus. Bile acid sequestrants may decrease niacin absorption. Niacin doses of 1 g or more daily may enhance the adverse/toxic effect of statins [118].

**FISH OIL DERIVATIVES**

**Mechanism of Action and Clinical Pharmacology**

A 1975 study conducted by Danish scientists showed that the composition of plasma lipids (e.g., cholesterol esters, triglycerides, phospholipids) varied considerably in the Inuit population of Greenland when compared both to the European Danish and to Inuit living in Denmark [148]. Interestingly, epidemiological studies showed that Inuit living in Greenland following a traditional diet rich in fat had a lower mortality from CVD than Inuit living in Denmark who followed a Western diet. This puzzling observation is known as the “Eskimo paradox” [149]. It is now well established that, although individual genetic background plays an important role in the development of CVD, the answer is the type of dietary fat consumed. Greenland Inuit consume a traditional diet rich in omega-3 fatty acids from fish and fish-eating mammals (seal and whale) rather than a diet poor in omega-3 sources such as the traditional Western diet [150].

Omega-3 polyunsaturated fatty acids are considered essential fatty acids because humans, as well as other mammals, are unable to synthesize these compounds efficiently. Eicosapentaenoic (EPA) and docosahexaenoic acids (DHA) are omega-3 polyunsaturated fatty acids derived from alpha-linolenic acid (ALA). Although humans are able to transform negligible amounts of ALA into EPA and DHA (<1%), dietary supplementation is the only physiologically relevant source [151]. Omega-3 fatty acids EPA and DHA are abundant in fatty fish, such as salmon, mackerel, sardines, trout, and herring, and other seafood sources, as well as in walnuts and canola, flaxseed, and linseed oils. Vegetable oils such as soybean, corn, sunflower, safflower, and cotton seed oils are good dietary sources of omega-6 fatty acids, which will be discussed in detail later in this course [56; 152; 153; 154].

Although the mechanism of action of omega-3 fatty acids is not yet completely understood, both preclinical and clinical studies provide solid evidence that EPA and DHA both reduce the synthesis and secretion of VLDL and increase triglyceride removal from VLDL and chylomicrons through the upregulation of lipoprotein lipase [155]. The distinct mechanisms of action of omega-3 fatty acids differ from other lipid-lowering drugs, which helps to explain why they have complementary lipid benefits when administered with statins [151]. Omega-3 fatty acids also have well established anti-arrhythmic, antihypertensive, anti-atherogenic, and antithrombotic properties [151; 156; 157; 158; 159; 160; 161].

Omega-3 fatty acids are effective in primary and secondary prevention of CHD, reduce the risk of sudden cardiovascular mortality by 45%, and provide a 20% relative risk reduction in overall mortality [153; 158; 162; 163; 164; 165; 212]. EPA and DHA omega-3 fatty acids lower triglycerides by 20% to 50% and were approved by the FDA in 2004 as adjunct to the diet for the treatment of very high triglyceride levels (≥500 mg/dL or 5.65 mmol/L) [166]. The effects on LDL seem to vary...
among studies from moderate dose-dependent increases to decreases in LDL. A moderate increase in HDL (5% to 10%) is more consistently reported [151; 167; 168]. As a result, omega-3 fatty acids are used in the treatment of hypertriglyceridemias, either alone or in conjunction with other lipid-lowering drugs.

Omega-3 fatty acids are readily available as dietary supplements and as prescription medications in the United States. One prescription medication is comprised of 900 mg of ethyl esters of omega-3 fatty acids, a combination of EPA (approximately 500 mg) and DHA (approximately 400 mg) [166]. A second available medication consists of 1000 mg omega-3 in free fatty acid form, which is intended to improve the bioavailability [202]. This drug contains approximately 500–600 mg EPA, 150–250 mg DHA, and 150–350 mg other omega-3 fatty acids. Drug labeling dosage information indicates a dose of 4 g/day, taken as a single 4-g dose (four capsules) or as two 2-g doses (two capsules twice daily) [166]. In one study, a minimum dose of 500 mg per day of combined EPA/DHA was recommended for individuals without underlying overt CVD, and 800-1,000 mg/day was recommended for individuals with CHD and heart failure [169]. A 2009 review validated the beneficial effects of EPA/DHA alone or in conjunction with fibrates in the reduction of triglycerides. It also further corroborated the safety profile of omega-3 polyunsaturated fatty acids [170].

The omega-3 fatty acids EPA and DHA are safe and cost effective and are indicated as an adjunct to diet in patients with hypertriglyceridemias [166]. They may be administered alone or in conjunction with other lipid-lowering drugs, such as statins when a reduction in LDL is also required or niacin when an increase in HDL is also a therapeutic goal. Omega-3 fatty acids are effective in the prevention of CVD. Their effect on cardiovascular morbidity and mortality has not been determined [166].

### Adverse Effects

Omega-3 fatty acids are remarkably well tolerated. Minor gastrointestinal symptoms (e.g., fishy aftertaste, eructation, diarrhea) may be observed in a dose-related manner [166]. Clinical trials have concluded that omega-3 fatty acids do not have adverse effects on plasma glucose levels, bleeding, levels of muscle or liver enzymes, or kidney or nerve function.

Contaminants such as methylmercury, polychlorinated biphenyls, and dioxins may be concentrated in certain species of fish, such as shark, swordfish, king mackerel, and golden snapper. The FDA and the Environmental Protection Agency have issued a statement advising women who are or may become pregnant, breastfeeding mothers, and young children to avoid eating some types of fish and to eat fish and shellfish that are lower in mercury [171]. However, the levels of contaminants in omega-3 fatty acids, either as generic supplements or in the ethyl ester formulation, are well below acceptable levels of toxicity due to extensive purification processes. In April 2009, the FDA posted a warning regarding the ethyl ester formulations of omega-3 fatty acids reporting anaphylactic or severe allergic reactions (i.e., rash, hives, itching, difficulty breathing, tightness in the chest, swelling of the mouth, face, lips, or tongue) and hemorrhagic diathesis [172].

### Drug Interactions

Due to their antiplatelet effect, omega-3 fatty acids may increase bleeding time in a dose-dependent manner [166]. However, no cases have been reported, even when administered at high doses alone or in combination with anticoagulant medications. In patients receiving anticoagulant medication, it has been recommended that bleeding times be monitored during the first three to six months, the time normally required for omega-3 fatty acids to reach their maximum clinical effect.
STEROLS AND STANOLS

Mechanism of Action and Clinical Pharmacology

Plant sterols and stanols, also known as phytosterols, are bioactive compounds structurally and physiologically similar to cholesterol. Sterols are present naturally in small quantities in many fruits, vegetables, nuts, seeds, cereals, legumes, vegetable oils, and other plant sources, and stanols occur in even smaller quantities in many of the same sources [56; 151; 152; 153; 154; 173; 174].

Omega-6 polyunsaturated fatty acids such as gamma-linoleic acid (GLA) are derived from linoleic acid. Omega-9 polyunsaturated fatty acids, unlike omega-3 and omega-6, are non-essential because they can be synthesized in humans. The most relevant omega-9 fatty acid is oleic acid, which is present in olive oil, and supplementation is not required.

The lipid-lowering properties of omega-6 polyunsaturated fatty acids, and linoleic acid in particular, are related to their ability to alter various steps of the intestinal absorption of cholesterol. Specifically, they downregulate the intestinal expression of the cholesterol transporter NPC1L1, compete with cholesterol for binding to NPC1L1, lower the cholesterol esterification rate by ACAT2, decrease the amount of cholesterol secreted via the chylomicrons, and upregulate the expression of ATP-binding cassette-transporters ABCG5 and ABCG8 in intestinal cells, which may result in an increased excretion of cholesterol by the enteroocyte back into the lumen [174].

The beneficial role played by omega-6 polyunsaturated fatty acids in the prevention of CHD results from their transformation into anti-inflammatory and vasodilatory eicosanoids, such as prostacyclin and lipoxin A4. Some studies, however, have recommended dietary reductions in omega-6 intake, based on the potential risk of increased transformation of omega-6 into pro-inflammatory, vasoconstrictive, pro-platelet aggregation eicosanoids, such as prostaglandin E2, thromboxane A2, and leukotriene B4. An advisory of the AHA has concluded that [175]:

Aggregate data from randomized trials, case-control and cohort studies, and long-term animal feeding experiments indicate that the consumption of at least 5% to 10% of energy from omega-6 polyunsaturated fatty acids reduces the risk of CHD relative to lower intakes. The data also suggest that higher intakes appear to be safe and may be even more beneficial (as part of a low-saturated-fat, low-cholesterol diet). In summary, the AHA supports an omega-6 polyunsaturated fatty acid intake of at least 5% to 10% of energy in the context of other AHA lifestyle and dietary recommendations. To reduce omega-6 polyunsaturated fatty acid intakes from their current levels would be more likely to increase than to decrease risk for CHD.

Adverse Effects

No serious side effects have been reported with omega-6 fatty acids. Some minor gastrointestinal effects may resemble those described for the omega-3 polyunsaturated fatty acids. Plant sterols and stanols lower plasma levels of beta-carotene by 25% and vitamin E by 8% [176].

Drug Interactions

Bile acid sequestrants and additives and drugs that impair the absorption of fat and soluble nutrients, such as olestra and orlistat, have the potential to significantly impair absorption of omega-3, 6, and 9 polyunsaturated fatty acids.

NOVEL PHARMACOTHERAPIES FOR HYPERLIPIDEMIAS

The discovery of lipid-lowering drugs has been a major contribution to the clinical management of hyperlipidemias and the prevention of CVD. However, the incidence of lipid disorders and resultant cardiovascular pathology continues to increase worldwide.
Existing available therapies are generally effective. Statins are the most prescribed lipid-lowering drugs because of their therapeutic efficacy and beneficial effects on the prevention of CVD, although the potential for the occurrence of serious adverse effects in a small number of patients requires monitoring. Other therapies, including bile acid-binding resins, ezetimibe, fibrates, niacin, and omega-3 polyunsaturated fatty acids, either alone or co-administered with other lipid-lowering drugs, including statins, can further lower LDL and triglycerides or raise HDL. However, patients with severe hypercholesterolemia or those intolerant to statins may not attain the recommended targets with available regimens. In fact, it is estimated that 10% of patients are not able or cannot tolerate available therapies to achieve recommended LDL goals [123]. So, continued research for globally effective pharmacotherapy is underway.

Advances in pharmacologic research have provided new molecular insights on lipid metabolism, and translational knowledge is being applied to the development of novel therapies including squalene synthase inhibitors (e.g., lapaquistat), new generation cholesterol absorption inhibitors, ATP-binding cassette transporter activators/cholesterol excretion stimulators, a new generation of nicotinic acid analogs, microsomal triglyceride transfer protein inhibitors, antisense oligonucleotides against Apo B-100 (e.g., mipomersen), and proprotein convertase subtilisin/kexin type 9 (PCSK9), a serine protease synthesized in the liver, being investigated for its regulatory effect on LDL receptors [55; 177; 178; 179; 180; 181].

Squalene synthase modulates the first committed step of hepatic cholesterol biosynthesis. Its inhibition results in a reduction in cholesterol synthesis in the liver and upregulation of the LDL receptor. Inhibition of squalene synthase activity occurs downstream from HMG-CoA reductase inhibited by statins. Theoretically, squalene synthase inhibitors reduce LDL cholesterol without causing the myopathy side effect seen with upstream inhibition of HMG-CoA. As of 2013, only one synthase inhibitor, lapaquistrate (TAK-475), has undergone extensive development in clinical trials as a mono-therapy; however, two cases of severe liver enzyme elevations among more than 5100 study participants exposed to the drug resulted in termination of the development program [182; 183].

New generation cholesterol absorption inhibitors (e.g., AVE5530) share some mechanistic properties with ezetimibe, a NPC1L1 transporter inhibitor. However, rather than being partially absorbed in the intestine, they remain in the lumen where they can exert their pharmacologic actions more effectively than ezetimibe. As a result, these agents can inhibit cholesterol absorption for up to 24 hours [184]. These drugs have been subjected to clinical trials. To date, four trials have been terminated and one completed, with results not yet available [185].

The process of cholesterol being transported back into the intestinal tract by selective transporters, such as the ATP-binding cassette transporters, has also been a target for potential treatments [54]. A new generation of drugs that is able to stimulate the ATP-binding cassette transporter and promote cholesterol elimination by enterocytes is being investigated [55].

The discovery of a G protein-coupled receptor for nicotinic acid has provided new insights on its lipid-lowering properties. This has raised the possibility of developing selective agonists that will not share its flush-inducing side effects [145; 178].

Microsomal triglyceride transfer protein catalyzes the assembly of cholesterol, triglycerides, and Apo B-100. Microsomal triglyceride transfer protein inhibitors (e.g., AEGR-733, lomitapide) inhibit intestinal assembly of chylomicrons and hepatic synthesis of VLDL, consequently lowering LDL. Initial clinical results showed a dose-dependent reduction of LDL by 19% to 30% when administered alone, or by 46% when administered in combination with ezetimibe [186]. Research is ongoing.
Antisense oligonucleotides (e.g., mipomersen) are single-stranded DNA that bind to matching mRNA and induce its selective degradation. Preclinical studies and small clinical trials have shown a 30% to 50% reduction in LDL with the use of these agents. Increases in transaminases and injection site reactions have been observed, and larger clinical trials are being conducted [185; 187].

Down-regulation of the LDL receptor by proprotein convertase subtilisin/kexin 9 (PCSK9) has emerged as a regulatory mechanism that controls plasma LDL cholesterol concentrations. Studies have demonstrated that PCSK9, by enhancing hepatic LDL receptor degradation, decreases the availability of the LDL receptor for LDL uptake, resulting in increased plasma LDL cholesterol levels. However, PCSK9 may have much broader roles than initially thought. For example, when human PCSK9 is injected into LDL receptor-deficient mice, it is still rapidly cleared by the liver, suggesting that it is physiologically also cleared by receptors other than the LDL receptor [188; 189; 190; 191]. In 2015, the FDA approved two PCSK9 inhibitors, alirocumab and evolocumab, to be used in conjunction with diet and statin therapy to reduce LDL cholesterol. A third PCSK9, bococizumab, is seeking FDAapproval [209].

ROLE OF LIPID-LOWERING DRUGS IN THE PREVENTION OF CVD MORBIDITY AND MORTALITY

As discussed, the clinical approach to hyperlipidemias is aimed at the primary and secondary prevention of CVD. As the evidence has shown, it is clear that lipid-lowering strategies play a fundamental role in the primary prevention of CVD. Primary prevention is defined as the long-term management of individuals at increased risk for but without clinical evidence of CVD and who have not undergone revascularization procedures [192]. Secondary prevention is defined as the clinical management of individuals with a history of CVD. Primary prevention of hyperlipidemias aims to avert new onset CHD and is considered an important aspect of the societal approach to the promotion of cardiovascular health [25]. The goal of primary prevention is to reduce risk factors for CHD and includes two complementary approaches: population strategies and clinical “individual” strategies [22]. The multidisciplinary team of healthcare providers plays a pivotal role in bridging the gap between public health and patient management and should support and advocate for continued public health approaches to improved nutrition, physical activity, and weight control [22; 25]. The effectiveness of primary prevention on the cholesterol levels of aging patients has been validated by the slower rate of increase in cholesterol levels associated with aging in patients for whom primary prevention strategies have been implemented [24; 25; 193]. Attaining lower LDL and triglyceride plasma concentrations can be achieved by a combination of lifestyle changes and drug therapy. However, because the role of lifestyle changes is often minimized, or simply neglected by the clinician or patient, it is relevant to note that the NCEP-ATP III emphasized that interventions should not be limited to drug therapy. They state [22]:

It must be emphasized that the ATP III clinical guidelines do not advocate the attainment of LDL goals exclusively through drug therapy. The aim of therapy is to achieve the LDL goals that are set according to absolute risk criteria. ATP III recommendations call for achieving the goals of therapy by the safest and most cost-effective means. Use of dietary therapy to attain the targets of therapy is emphasized, and if drugs are required, cost-effective agents should be used in the lowest doses needed to achieve the recommended goals of therapy.
Secondary prevention should be initiated in patients with previous CHD. These patients are at very high risk for recurrent CHD, and LDL-lowering therapy prior to the introduction of statins has been shown to reduce recurrent coronary events and cardiovascular mortality; however, these interventions had no effect on non-cardiovascular death. Clinical trials with statins reported a reduction in cardiovascular morbidity and mortality as well as a reduction in total mortality [22]. Lifestyle changes provide only moderate improvement of the lipid profile in patients with previous CHD, so although they should be implemented, pharmacotherapy is required to attain therapeutic goals [24].

The complexity of health status in patients with a history of CVD requires an approach of multifac-torial risk reduction. Multifactorial risk reduction has a synergistic effect on disease progression and clinical outcomes and should be associated with a case management approach [24; 194]. Case management allows for collaborative and effective expert evaluation, systematic intervention, and regular follow-up. Management should focus not only on the appropriate drug choices but also on patient education and counseling [24; 195].

CLINICAL GUIDELINES FOR THE ASSESSMENT OF RISK FACTORS ASSOCIATED WITH HYPERLIPIDEMIAS

The clinical guidelines for the assessment of cardiovascular risk take into account a number of factors including gender, age, family history of premature CVD (myocardial infarction or sudden cardiac death before 55 years of age in a first-degree male relative or before 65 years of age in a first-degree female relative), hypertension (whether treated or not), cigarette smoking (10 or more cigarettes per day), and plasma lipid profile indicating high LDL (>130 mg/dL) or low HDL (<40 mg/dL).

The NCEP-ATP III, the European Atherosclerosis Society, and many other trials use the risk assessment tables developed from the Framingham Heart Study in an attempt to match the intensity of treatment to the severity of CHD risk in patients (Table 6 and Table 7) [22; 23; 196; 197]. The scores from these risk assessment tables can be used to determine the 10-year risk for myocardial infarction in men (Table 8) and women (Table 9). Although the Framingham risk tables are quite comprehensive, they do not take into account the risk associated with a family history of premature CHD or obesity. Consequently, the risk of CHD is seriously underestimated in these patients and may result in inappropriate therapy [14; 198].

CLINICAL GUIDELINES FOR THE TREATMENT OF HYPERLIPIDEMIAS

Treatment guidelines for hyperlipidemias were developed by the NCEP-ATP III [22]. These guidelines were partially updated by the 2013 ACC/AHA guideline; however, as discussed, the recommendations in the newer guideline were controversial, and for the purposes of this course, the treatment guidelines provided by the NCEP-ATP III will be presented.

According to the NCEP-ATP III, patients are classified in three groups according to the presence of risk factors. High-risk patients have established CHD or CHD equivalents, while moderate-risk patients present multiple risk factors. Patients with zero or one risk factor are considered at low risk.

Patients within each risk category are then matched with appropriate therapy to meet target lipid goals, which include lifestyle changes and drug therapy (Table 10). Patients classified as intermediate risk are further categorized by evaluating their 10-year risk of developing CHD using additional information collected by using the Framingham risk scores.
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*Source: [22]*

### Calculated Risk Based on Framingham Scores: Women

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*Source: [22]*

### NCEP-ATP III Guidelines for Treatment of Hyperlipidemia

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<th>Consider Drug Therapy If:</th>
<th>LDL Goal</th>
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<td>LDL &gt;100 mg/dL (2.58 mmol/L)</td>
<td>LDL &gt;100 mg/dL (2.58 mmol/L) (drug optional if &lt;100 mg/dL [&lt; 2.58 mmol/L])</td>
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<td>Moderate high: &gt;2 risk factors with 10-year risk 10 to 20%</td>
<td>LDL &gt;130 mg/dL (3.36 mmol/L)</td>
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<td>LDL &gt;130 mg/dL (3.36 mmol/L)</td>
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<td>Lower: 0–1 risk factor</td>
<td>LDL &gt;160 mg/dL (4.13 mmol/L)</td>
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*Source: [22; 23]*

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**CALCULATED RISK BASED ON FRAMINGHAM SCORES: MEN**

**CALCULATED RISK BASED ON FRAMINGHAM SCORES: WOMEN**

**NCEP-ATP III GUIDELINES FOR TREATMENT OF HYPERLIPIDEMIA**
The NCEP-ATP III treatment guidelines are related to both population-based and patient-based approaches. The population-based approach to reduce CHD risk involves promoting lifestyle changes in the community. Outreach programs emphasize the importance of increasing exercise and reducing total calories from fat to less than 30% and from saturated and trans fats to less than 10%. Other dietary recommendations include consuming less than 300 mg of cholesterol per day; eating a variety of oily fish twice a week and foods rich in α-linolenic acid (e.g., canola, flaxseed, soybean, walnuts); and maintaining a desirable body weight [199].

The patient-based approach focuses on the primary goal of lowering individuals’ LDL levels. Instruction on lifestyle changes and dietary and nutritional counseling should be provided to patients [14]. Patients with CHD or a CHD equivalent (e.g., symptomatic peripheral or carotid vascular disease, abdominal aortic aneurysm, >20% 10-year CHD risk, diabetes) should immediately start suitable lipid-lowering drug therapy irrespective of their baseline LDL level [23; 98; 200].

Patients without CHD or CHD equivalent should be managed with lifestyle changes for three to six months before drug therapy is implemented. During the period before drug therapy is initiated, secondary causes of hyperlipidemia should be excluded [14; 63].

In high-risk patients (CHD or CHD equivalent with 10-year risk greater than 20%), drug therapy is initiated when LDL is ≥100 mg/dL. This should also be accompanied by lifestyle changes.

Patients in the moderate risk group (2 or more risk factors with 10-year risk less than 10%) are selected for therapeutic lifestyle changes when LDL cholesterol is greater than 130 mg/dL. Pharmacologic treatment is indicated for these patients if LDL is greater than 160 mg/dL. In patients in the moderate-high-risk category (2 or more risk factors with 10-year risk 10% to 20%) drug treatment is recommended if LDL is greater than 130 mg/dL.

Low-risk individuals with one or no risk factors and estimated 10-year CHD risk less than 10% are candidates for lifestyle interventions if LDL cholesterol is greater than 160 mg/dL. If these patients have an LDL level greater than 190 mg/dL, drug therapy may be initiated [63].

**CONCLUSION**

Cardiovascular diseases are a leading cause of death in developed countries. Although the prevalence of CVD in developed countries has increased in the past 40 years, the mortality rate has declined as the result of advances in the diagnosis and medical and surgical treatments.

The complex interaction between modifiable and non-modifiable risk factors underlies the etiology of CVD. It is now well established that hyperlipidemias, and high concentrations of LDL in particular, are implicated in the etiology of atherosclerosis and increased incidence of CVD such as coronary artery disease, peripheral vascular disease, and ischemic cerebrovascular disease. Hyperlipidemias are also associated with primary hypertension and metabolic syndrome. As a result, prevention, early diagnosis, and appropriate clinical management of hyperlipidemias have become a public health priority.
Effective lipid management slows the progression of atherosclerosis and lowers morbidity and mortality associated with CVD. This requires not only a change in general perceptions but also a multidisciplinary approach to prevention that involves all members of the healthcare team, including physicians, nurses, pharmacists, dietitians, counselors, and physiotherapists.

The evidence-based guidelines for the assessment of cardiovascular risk, treatment goals, lifestyle changes, and pharmacotherapy developed by the NCEP-ATP III should be followed as the gold standard in clinical practice [22; 23]. The primary target in the treatment of hyperlipidemias is to lower LDL; the secondary targets are treating high triglycerides, low HDL, and metabolic syndrome. A variety of lipid-lowering drugs with a favorable risk-benefit profile, in conjunction with implementation of lifestyle changes, is available to meet these goals.

A better understanding of the molecular elements and physiology of the exogenous and endogenous lipid pathways has played a fundamental role in the development of the most potent lipid-lowering drugs. Scientific advances have led to the development of a newer generation of drugs, now undergoing several stages of clinical evaluation, with the potential to improve on existing drugs’ risk-benefit profiles. The important role played by the implementation of lifestyle changes, including a balanced diet, in achieving a healthy lipid profile and decreasing the incidence of CVD cannot be overstated and should be an integral part of disease management.

RESOURCES

The following resources are provided for those clinicians in need of additional information or as patient education sources.

**American Heart Association (AHA)**
http://www.heart.org

**MyAmericanHeart for Professionals**
(A service provided by the AHA)
http://my.americanheart.org/professional

**My Life Check: Life’s Simple 7**
http://www.heart.org/HEARTORG/Conditions/My-Life-Check---Lifes-Simple-7_UCM_471453_Article.jsp#.V4Au_rgrLIU

**Heart and Stroke Foundation of Canada**
http://www.heartandstroke.com

**Centers for Disease Control and Prevention Cholesterol Homepage**
http://www.cdc.gov/cholesterol

**National Center for Health Statistics**
http://www.cdc.gov/nchs

**National Heart, Lung, and Blood Institute**
http://www.nhlbi.nih.gov
FACULTY BIOGRAPHY

A. José Lança, MD, PhD, received his Medical Degree at the University of Coimbra in Coimbra, Portugal, and completed his internship at the University Hospital, Coimbra. He received his PhD in Neurosciences from a joint program between the Faculties of Medicine of the University of Coimbra, Portugal, and the University of Toronto, Toronto, Canada. He was a Gulbenkian Foundation Scholar and received a Young Investigator Award by the American Brain & Behavior Research Foundation.

Dr. Lança participated in international courses and conferences on neurosciences. He has contributed to a better understanding of the mechanisms underlying the ontogenetic development of the brain opiate system. As a research scientist at the Addiction Research Foundation (ARF) in Toronto, he initiated research on the functional role played by dopaminergic cell transplants on alcohol consumption, leading to the publication of the first research reports on cell transplantation and modulation of an addictive behavior. Subsequently, he also investigated the role played by other neurotransmitter systems in the limbic system and mechanisms of reward, co-expression of classical neurotransmitters and neuropeptides and potential role in neuropsychiatric disorders.

He is an Assistant Professor in the Department of Pharmacology at the Faculty of Medicine and at the Faculty of Dentistry at the University of Toronto, where he lectures and directs several undergraduate and postgraduate pharmacology and clinical pharmacology courses. He was the Program Director for Undergraduate Studies in the Department of Pharmacology of the University of Toronto. He has developed clinical pharmacology courses for the Medical Radiation Sciences and Chiropody Programs of The Michener Institute for Health Sciences at the University of Toronto.

Dr. Lança’s commitment to medical education started while a medical student, teaching in the Department of Histology and Embryology, where he became cross-appointed after graduation. In Toronto, he has contributed extensively to curriculum development and teaching of pharmacology to undergraduate, graduate, and medical students.

He has authored research and continuing education in peer-reviewed publications and is the author of six chapters in pharmacology textbooks. Dr. Lança has conducted research in various areas including neuropharmacology, pharmacology of alcoholism and drug addiction, and herbal medications.

He has developed and taught courses and seminars in continuing medical education and continuing dental education. His commitment to continuing education emphasizes an interdisciplinary approach to clinical pharmacology.
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**Evidence-Based Practice Recommendations Citations**

