COURSE #90844 — 10 CONTACT HOURS/CREDITS RELEASE DATE: 08/01/22 EXPIRATION DATE: 07/31/25

# Hyperlipidemias and Atherosclerotic Cardiovascular Disease

## HOW TO RECEIVE CREDIT

- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. (If you are a physician or Florida nurse, please return the included Answer Sheet/Evaluation.) Your postmark or facsimile date will be used as your completion date.
- Receive your Certificate(s) of Completion by mail, fax, or email.

***Faculty***

**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 was awarded a Young Investigator Award by the American National Association for the Research of Schizophrenia and Depression (NARSAD). (A complete biography appears at the end of this course.)

***Faculty Disclosure***

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

***Division Planners***

John V. Jurica, MD, MPH
Jane C. Norman, RN, MSN, CNE, PhD
Randall L. Allen, PharmD

***Director of Development and Academic Affairs***

Sarah Campbell

***Division Planners/Director Disclosure***

The division planners and director 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 pharmacy professionals who may intervene to limit the effects of hyperlipidemias in their patients, promoting better long-term health and preventing cardiovascular disease.

***Accreditations & Approvals***

JOINTLY ACCREDITED PROVIDER™ INTERPROFESSIONAL CONTINUING EDUCATION

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.

***Designations of Credit***

NetCE designates this enduring material for a maximum of 10 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 10 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit. Completion of this course constitutes permission to share the completion data with ACCME.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the learner to earn credit toward the CME and Self-Assessment requirements of the American Board of Surgery's Continuous Certification program. It is the CME activity provider's responsibility to submit learner completion information to ACCME for the purpose of granting ABS credit.

This activity has been designated for 10 Lifelong Learning (Part II) credits for the American Board of Pathology Continuing Certification Program.

Through an agreement between the Accreditation Council for Continuing Medical Education and the Royal College of Physicians and Surgeons of Canada, medical practitioners participating in the Royal College MOC Program may record completion of accredited activities registered under the ACCME's "CME in Support of MOC" program in Section 3 of the Royal College's MOC Program.

*Copyright © 2022 NetCE*

*A complete Works Cited list begins on page 40.*

***Mention of commercial products does not indicate endorsement.***

NetCE designates this continuing education activity for 10 ANCC contact hours.


This activity was planned by and for the healthcare team, and learners will receive 10 Interprofessional Continuing Education (IPCE) credits for learning and change.

NetCE designates this continuing education activity for 12 hours for Alabama nurses.

NetCE designates this continuing education activity for 7 pharmacotherapeutic/pharmacology contact hours.

AACN Synergy CERP Category A.

NetCE designates this activity for 10 hours ACPE credit(s). ACPE Universal Activity Numbers: JA4008164-0000-22-011-H01-P and JA4008164-0000-22-011-H01-T.

### *Individual State Nursing Approvals*

In addition to states that accept ANCC, NetCE is approved as a provider of continuing education in nursing by: Alabama, Provider #ABNP0353 (valid through 07/29/2025); Arkansas, Provider #50-2405; California, BRN Provider #CEP9784; California, LVN Provider #V10662; California, PT Provider #V10842; District of Columbia, Provider #50-2405; Florida, Provider #50-2405; Georgia, Provider #50-2405; Kentucky, Provider #7-0054 (valid through 12/31/2025); South Carolina, Provider #50-2405; West Virginia, RN and APRN Provider #50-2405.

### *Special Approvals*

This activity is designed to comply with the requirements of California Assembly Bill 1195, Cultural and Linguistic Competency.

### *About the Sponsor*

The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

Our contributing faculty members have taken care to ensure that the information and recommendations are accurate and compatible with the standards generally accepted at the time of publication. The publisher disclaims any liability, loss or damage incurred as a consequence, directly or indirectly, of the use and application of any of the contents. Participants are cautioned about the potential risk of using limited knowledge when integrating new techniques into practice.

### *Disclosure Statement*

It is the policy of NetCE not to accept commercial support. Furthermore, commercial interests are prohibited from distributing or providing access to this activity to learners.

### *Course Objective*

The purpose of this course is to provide a review of hyperlipidemia in the pathogenesis of cardiovascular disease, as well as the therapeutic benefits of pharmacologic and nonpharmacologic approaches to treatment. The objectives are to promote team-based care, foster patient awareness and shared provider-patient decision-making, and promote implementation of lifestyle changes and compliance with guideline-directed therapy for prevention of cardiovascular disease.

### *Learning Objectives*

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

1. Discuss the incidence of cardiovascular disorders, expected epidemiologic 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.

### *Pharmacy Technician Learning Objectives*

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

1. Discuss the incidence, relevance, and risk factors for atherosclerotic cardiovascular disorders and hyperlipidemia.
2. Describe lipid synthesis and metabolism, types of lipoproteins, and various lipid profiles
3. Outline approaches to assessing patient risk and managing hyperlipidemias.


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 ATHEROSCLEROTIC CARDIOVASCULAR DISEASES

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death in developing countries and accounts for 25.7% of all deaths in the United States and 45% of deaths in Europe [1; 2]. According to the World Health Organization (WHO), 17.9 million people die each year from cardiovascular disease, an estimated 32% of all deaths worldwide [3]. It has been estimated that by 2030, ASCVD will account for approximately 23 million annual deaths worldwide, an increase of more than 5 million from current estimates [3].

In developed countries, both the prevalence of ASCVD and the rate of mortality have declined. In the United States, from 2006 to 2016, the number of heart-related deaths declined by 18.6%. 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 ASCVD, 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 2014–2015, the estimated direct and indirect cost of ASCVD was $351.2 billion [1]. This figure is projected to increase to $1.1 trillion by 2035 [1]. As a comparison, the estimated 2011 annual direct cost of all cancer and benign neoplasms combined is $84 billion, versus $213.8 billion for direct costs of ASCVD [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 ASCVD 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 ASCVD 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 ASCVD such as coronary artery disease, peripheral vascular disease, and ischemic cerebrovascular disease. Hyperlipidemias are also associated with primary hypertension and metabolic syndrome [13; 14].

American Heart Association data from 2015 to 2018 show unfavorable lipid measures of LDL cholesterol >130 mg/dL were present in 27.8% of adults 20 years of age and older, and total blood cholesterol concentrations >240 mg/dL (6.2 mmol/L) were present in 11.5% of adults [234]. Both lipid parameters are associated with excess 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, a disorder characterized by abdominal obesity, hypertension, insulin resistance, low levels of high-density lipoprotein (HDL), and increased risk of ASCVD [13]. Hypertriglyceridemia is also associated with pancreatitis, and severe hypertriglyceridemia has been established as the etiology of up to 7% of pancreatitis. Hypertriglyceridemia-induced pancreatitis rarely occurs unless levels exceed 1,700 mg/dL (20 mmol/L) [16].

Effective lipid management has been shown to slow the progression of atherosclerosis and lower morbidity and mortality of ASCVD [17; 18; 19; 20; 21; 22; 23]. As a result, early diagnosis and appropriate clinical management of hyperlipidemias has become a public health priority in the primary and secondary prevention of ASCVD [24]. Guidelines for the management of hyperlipidemias focus not only on the administration of lipid-lowering drugs but also the implementation of lifestyle changes [24]. Together, these interventions assist with patient adherence and improve clinical outcomes [22; 23]. 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 results from a chronic inflammatory process that targets medium- and large-sized arteries. This process begins in 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 ASCVD [14; 17; 18; 19; 20; 21; 22]. The causative role of hyperlipidemia has been supported by the finding that decreasing the plasma levels of LDL and triglycerides has a beneficial effect on primary and secondary prevention of ASCVD by reversing, to some extent, the underlying pathology of atherosclerosis [23].

Atherosclerotic vascular disease develops in 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 continuing infiltration by smooth muscle cells, which migrate from the underlying muscular layer and accumulate oxidized LDL, and infiltration by T-lymphocytes, which synthesize and release inflammatory cytokines. These changes increase the number of foam cells and exacerbate local inflammation. In time, extracellular accumulation of LDL, collagen, elastic fibers, and calcium deposits contribute to the formation of larger and thicker atherosclerotic vascular plaques. Histology shows that atherosclerotic plaques consist of a large lipid core surrounded by a fibrous cap. After decades of development, the plaque grows in size and exhibits features of a chronic inflammatory process within the vessel wall [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, further increasing 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 [MI], 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 discussed, hyperlipidemia has been established as a main risk factor in the development of atherosclerosis and ASCVD. Together with obesity, hypertension, diabetes, smoking, and physical inactivity, hyperlipidemia is a known modifiable risk factor of ASCVD. Additionally, several biomarkers, including C-reactive protein (CRP), hyperhomocysteinemia, and lipoprotein(a), are also considered modifiable risk factors of ASCVD. Modifiable risk factors play a major role in the pathogenesis of ASCVD 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 ASCVD [11; 12].

| AHA/ACC RISK-ENHANCING FACTORS |
|---|
| • Family history of premature ASCVD (men: age younger than 55 years; women: age younger than 65 years)<br>• Primary hypercholesterolemia (LDL 160–189 mg/dL; non-HDL 190–219 mg/dL[a])<br>• Metabolic syndrome<br>• Chronic kidney disease (i.e., eGFR 15–59 mL/min/1.73 $m^2$ with or without albuminuria, not treated with dialysis or kidney transplantation)<br>• Chronic inflammatory conditions (e.g., psoriasis, rheumatoid arthritis, HIV/AIDS)<br>• History of premature menopause (before 40 years of age) and history of pregnancy-associated conditions that increase later ASCVD risk (e.g., pre-eclampsia)<br>• High-risk race/ethnicity (e.g., South Asian ancestry)<br>• Persistently[a] elevated, primary hypertriglyceridemia (≥175 mg/dL) and/or other lipid/biomarkers associated with increased ASCVD risk, including (if measured):<br>– Elevated hsCRP (≥2.0 mg/L)<br>– Elevated Lp(a): a relative indication for its measurement is family history of premature ASCVD. Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor, especially at higher levels of Lp(a).<br>– Elevated Apo B ≥130 mg/dL: a relative indication for its measurement is triglyceride ≥200 mg/dL. A level ≥130 mg/dL corresponds to an LDL >160 mg/dL and constitutes a risk-enhancing factor<br>– ABI <0.9 |
| [a]Optimally, three determinations.<br>ABI = ankle-brachial index; Apo B = Apolipoprotein B; eGFR = estimated glomerular filtration rate; HIV/AIDS = human immunodeficiency virus/acquired immunodeficiency syndrome; hsCRP = high-sensitivity C-reactive protein; Lp(a) = lipoprotein(a). |
| *Source: [24]* *Table 1* |

In addition to modifiable risk factors, the American Heart Association (AHA) and the American College of Cardiology (ACC) have included "risk-enhancing factors" in their 2018 guideline on the management of blood cholesterol (***Table 1***). Projections of future risk derived from primary risk factors and risk-enhancing factors can be used to adjust the intensity of LDL-lowering therapy and enhance clinician-patient risk discussion [24]. When risk is uncertain, a coronary artery calcium score can help facilitate decision-making in adults 40 years of age and older. The identification of familial hypercholesterolemia is a priority in children, adolescents, and young adults. Across all age groups, the emphasis is on reducing lifetime ASCVD risk through a heart-healthy lifestyle [24].

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 epidemiologic studies of human populations have established that high levels of LDL cholesterol are atherogenic [35; 36; 37]. 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; 23; 25; 38; 39]. 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 ASCVD [1; 17; 18; 19; 20; 21; 22; 23; 25; 37; 39; 40; 41].

Chronically high levels of CRP, and high sensitivity CRP (hsCRP) in particular, are biomarkers of ASCVD, regardless of whether they play a causal role in atherogenesis or if they are the result of underlying atherosclerosis [12; 27; 42]. The AHA and the Centers for Disease Control and Prevention have issued a joint statement regarding hsCRP values [43]. Concentrations of hsCRP less than 1 mg/L are associated with low risk, and 1–3 mg/L is correlated with moderate risk for ASCVD. Patients with levels greater than 3 mg/L are at high risk for ASCVD [43]. An hsCRP level >10 mg/L has been observed in acute plaque rupture, which may lead to thrombosis [44]. Ongoing clinical studies suggest that lowering the plasma levels of both hsCRP and LDL may be a main goal in the secondary prevention of ASCVD [42].

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 ASCVD [12; 27; 31; 46; 47; 48]. 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 [47]. 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 [23; 49].

## 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; 50; 51]. 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 classified as saturated; those with carbon-carbon double bonds are classified unsaturated. Unsaturated fatty acids are further differentiated into 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.

Intracellular free fatty acids are present in trace amounts and esterified with glycerol to 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 ASCVD. 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 distinct but interrelated origins and metabolic pathways: the exogenous (i.e., dietary source) and the endogenous pathways (i.e., hepatic synthesis) [52].

### 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 [46; 50; 53].

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 established 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 isoform 2 (ACAT2) and incorporated into chylomicrons [54].

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 lymphatics, 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 [55]. A new generation of lipid-lowering drugs that stimulate the ATP-binding cassette transporter is being investigated [56].

**Endogenous Pathway**

The hepatic pathway is the major source of cholesterol in the body. It is well-established that daily cholesterol synthesis in the liver has a circadian pattern, with lowest levels in the day (30% to 35%) and highest levels at night (65% to 70%). This diurnal rhythm in cholesterol synthesis is regulated by HMG-CoA activity [240]. Selective inhibitors of HMG-CoA reductase, such as statins, effectively prevent the synthesis of cholesterol and are powerful hypolipidemic drugs [31; 57].

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; 52].

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 cholesteryl 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 in lipid physiology: stabilize the structure of the lipoprotein shell, activate enzymes in the plasma and endothelial cells, and bind to selective cell receptors [27; 30; 31; 58]. Specific apoproteins regulate the metabolic fate of lipoproteins; their 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].

| PLASMA LIPOPROTEINS | | | | | |
|---|---|---|---|---|---|
| **Characteristic** | **Chylomicrons** | **Very-Low-Density Lipoprotein (VLDL)** | **Intermediate-Density Lipoprotein (IDL)** | **Low-Density Lipoprotein (LDL)** | **High-Density Lipoprotein (HDL)** |
| Density | <0.95 g/mL | 0.95–1.006 g/mL | 1.006–1.019 g/mL | 1.019–1.063 g/mL | 1.063–1.210 g/mL |
| Diameter | 75–1,200 nm | 30–80 nm | 25–35 nm | 18–25 nm | 5–12 nm |
| Protein | 2% | 10% | 18% | 25% | 33% |
| Total lipid | 98% | 90% | 82% | 75% | 67% |
| Triglycerides | 83% | 50% | 31% | 10% | 8% |
| Cholesterol | 8% | 22% | 29% | 45% | 30% |
| Phospholipid | 7% | 18% | 22% | 20% | 29% |
| Major apoproteins | Apo B-48 Apo C-II Apo E | Apo B-100 Apo C-II Apo E | Apo B-100 Apo C-II | Apo B-100 | APO A-I APO A-II Apo C-II Apo E |

*Source: Compiled by Author* *Table 2*

## 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 2***).

### Plasma Lipid Profiles

Prior to discussing 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.

For more than 50 years, most clinical laboratories have calculated the value of LDL cholesterol indirectly, according to the Friedewald equation [59; 60]:

LDL (mg/dL) = total cholesterol (mg/dL) – HDL (mg/dL) – [triglycerides (mg/dL) / 5]

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

LDL (mmol/dL) = total cholesterol (mmol/dL) – HDL (mmol/dL) – [triglycerides (mmol/dL) / 2.2]

A modified Friedewald equation is also used and has been suggested to have a higher level of accuracy in calculating LDL values [61; 62]. This equation is:

LDL (mg/dL) = [non-HDL cholesterol (mg/dL) x 0.9] – [triglycerides (mg/dL) x 0.1]

It is known that in hypertriglyceridemia, LDL calculated using the Friedewald equation can be unreliable, particularly at levels <70 mg/dL. The increased prevalence of high triglyceride states (e.g., diabetes, obesity) and the use of novel lipid lowering medications (e.g., proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors) have provided an impetus for finding improved methods for estimating LDL.

Direct LDL assays are not standardized and can be even less accurate than the Friedewald equation. In one study of seven direct methods for measuring LDL, total assessment errors ranged from 13.3% to 13.5% across assays in healthy individuals and from -26.6% to 31.9% in individuals with known ASCVD or dyslipidemias. The National Cholesterol Education Program has a target total error goal of ≤13%, meaning that all seven direct assays failed standard accuracy goals [63; 64].

Several prior equations have attempted to improve upon the Friedewald equation, but most used the same fixed ratio between triglycerides and VLDL. In a study of more than 1.3 million fasting and nonfasting patients, Martin and colleagues derived and validated a novel equation that replaced the fixed ratio with one of 180 adaptable ratios based on the patient's individual non-HDL and triglyceride values. The overall accuracy of the Martin/Hopkins approach compared with direct measurement was 92% for HDL and 85% for triglycerides. LDL estimation accuracy with the Martin/Hopkins equation was 94%, compared with 77% with the Friedewald method [65]. The 2018 AHA/ACC guideline acknowledges the importance of accurate LDL estimation and recommends measuring LDL either directly or with an alternative method (e.g., the Martin/Hopkins equation) [24; 63].

The ratio of total cholesterol (TC) to HDL (TC:HDL) and the ratio of LDL to HDL (LDL:HDL) are clinically relevant predictors of coronary heart disease (CHD) risk. The lower the ratio value, the better the predicted outcome [66; 67; 68; 69]. The Apo B:Apo A-I 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" [66]. However, the ratio may be useful for evaluating the severity of CHD [70]. A cross-sectional study enrolled 792 patients with angiographically defined CHD following hospital admission. The patients were placed into three groups based on the degree of angiographic atherosclerosis or the number of stenotic coronary branches. Demographic and biochemical data were collected, and lipoprotein ratios were calculated. According to the results, the ratios of LDL:HDL and Apo B:Apo A-I increased with increasing degree of angiographic atherosclerosis, and the ratios of triglyceride:HDL, TC:HDL, LDL:HDL and Apo B:Apo A-I increased with the number of stenotic coronary branches. The ratios of TC:HDL, LDL:HDL, and Apo B:Apo A-I were positively associated with both the degree of atherosclerosis and the number of stenotic vessels, and the ratio of triglyceride:HDL was positively associated with the number of stenotic vessels. The Apo B:Apo A-I ratio was also shown to be a direct mediator between the risk factors of age, BMI, HDL, LDL, and severity of CHD [70].

EVIDENCE-BASED PRACTICE RECOMMENDATION

In adults who are 20 years of age or older and not on lipid-lowering therapy, the ACC/AHA assert measurement of either a fasting or a nonfasting plasma lipid profile is effective in estimating ASCVD risk and documenting baseline LDL. If an individual has ingested an extremely high-fat meal in the preceding eight hours, it may be prudent to assess lipids on another day after counseling the patient to avoid such meals.

(http://www.onlinejacc.org/content/73/24/e285?_ga=2.118995977.141815126.1563751668-1264536891.1558548868. Last accessed July 25, 2022.)

**Level of Evidence**: Expert Opinion/Consensus Statement

## 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 [53]. 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].

Chylomicrons secreted by intestinal cells are known as "incomplete" chylomicrons because they only express Apo B-48. After entering the lymph and later reaching the bloodstream, chylomicrons interact with circulating HDL, from which they receive Apo C-II and Apo E and then referred to as "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 [71]. 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 [72].

The concentration of chylomicrons can only be lowered by reducing dietary fat consumption or by 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 [73].

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) [46]. 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 result in fatty liver [74].

**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. IDLs 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; 75].

**Low-Density Lipoproteins**

LDLs play a central role in atherogenesis and are often called "bad cholesterol." 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 [72]. 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; 46; 53; 57].

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 ASCVD is premature [76; 77; 78].

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 [79]. 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 [80]. 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 [46; 81].

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 [82; 83]. 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 [72; 84].

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 [80; 85]. Consequently, deficiencies of these hormones decrease the availability of LDL receptors and result in increased concentrations of circulating LDL and increased risk of ASCVD [14; 80].

The subtype of lipoprotein(a) is associated with increased risk for ASCVD [12; 27; 31; 46; 47]. Lipoprotein(a) has a similar lipid composition to more typical LDL but has a higher protein content [86]. 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 [47]. Lipoprotein(a) also exhibits platelet activating and pro-inflammatory properties that further contribute to atherogenesis [87]. 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 [23; 49]. Lowering circulating LDL remains the primary goal in the treatment and prevention of atherosclerosis and ASCVD [15; 22; 24].

### 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 [53]. 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 [88].

HDL concentration in the plasma is inversely related to the risk of ASCVD, 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 [88; 89].

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 [90; 91].

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 ASCVD [88; 92]. 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" [93]. Other researchers concluded that raising endogenous HDL levels in humans to reduce the development of atherosclerosis "has yet to be established conclusively" [88]. Together, these studies further support the recommendation that lowering LDL should remain the target goal for patients with hyperlipidemia and/or at risk for ASCVD-related conditions [22; 24].

## CLASSIFICATION 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 then publish guidelines based on these and other findings [94]. 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 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 did not address specific risk factors or lifestyle changes [95].

| LIPOPROTEIN PATTERNS OF HYPERLIPIDEMIAS (FREDRICKSON PHENOTYPES) | | |
|---|---|---|
| **Phenotype** | **Elevated Lipoproteins** | **Elevated Lipids** |
| I | Chylomicrons | Triglycerides |
| IIa | LDL | Cholesterol |
| IIb | LDL and VLDL | Triglycerides and cholesterol |
| III | VLDL and chylomicron remnants | Triglycerides and cholesterol |
| IV | VLDL | Triglycerides |
| V | Chylomicrons and VLDL | Triglycerides and cholesterol |

*Source: [46; 98]* *Table 3*

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 [96; 97]. The 2018 AHA/ACC update to the 2013 guideline includes a limited restoration of LDL treatment targets, particularly in higher-risk groups, based on the results of U.S. population studies and randomized controlled trials confirming the general principle that for LDL, "lower is better" [24]. For the purposes of this course, the 2018 AHA/ACC guideline recommendations will be discussed.

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; 46; 67; 79; 98].

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 [99]. While gene therapy is being developed to treat some patients with known genetic abnormalities, the genetic profile and molecular basis of primary hypertriglyceridemia has been determined in only 5% to 10% of cases, and the percentage is even lower for secondary hyperlipidemia [100; 101; 102].

## 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), lipemic 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 [46; 100; 103].

Familial hypercholesterolemia and familial defective Apo B-100 are examples of clinical conditions that result from LDL receptor and Apo B-100 deficiencies, respectively [82; 83; 104]. Other genetic mutations cause familial hypertriglyceridemia, familial combined hyperlipidemia, familial chylomicronemia, and familial dysbetalipoproteinemia [31; 46; 100; 105; 106].

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 [106]. 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; 107].

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 [107; 108]. Patients typically present with tendon xanthomas, premature MI (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) [107; 108]. 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 MI 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; 46; 107; 108]. Three drugs have been approved by the U.S. Food and Drug Administration (FDA) for homozygous familial hypercholesterolemia since 2012, a microsomal triglyceride transfer protein inhibitor (lomitapide), an antisense oligonucleotide inhibitor (mipomersen), and an adenosine triphosphate-citrate lyase inhibitor (bempedoic acid). A box warning for risk of hepatotoxicity was added to mipomersen in 2016. Lomitapide and mipomersen inhibit the synthesis of Apo B–100, while bempedoic acid inhibits renal tubular organic anion transporter 2 [109; 110; 233]. 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; 100].

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 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; 111]. 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) [112; 113].

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 α-blockers without intrinsic sympathetic activity or α-antagonism (increased total cholesterol and decreased HDL), and thiazides (modest increase in total cholesterol and LDL) [67; 114].

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, identifying the lipid profile, classifying the hyperlipidemia, and managing comorbidity are each necessary in order for patients to achieve lower cholesterol and triglyceride levels required to reduce ASCVD risk [22; 25; 46; 100; 105].

## APPROACHES TO CLINICAL MANAGEMENT OF HYPERLIPIDEMIAS

Management of existing hyperlipidemia is a cornerstone in the prevention and management of ASCVD. In large randomized controlled trials, LDL lowering has been consistently shown to reduce the risk of ASCVD. However, in clinical practice, absolute responses in LDL levels to statin therapy depend on baseline LDL levels and the intensity of lipid-lowering therapy. Furthermore, it is important to bear in mind that as cardiovascular risk increases, so does the absolute benefit of therapeutic interventions proven to lower LDL cholesterol levels; both the absolute risk and the magnitude of LDL cholesterol level reduction achieved are important

[235]. A given dose of statins produces a similar percentage reduction in LDL levels across a broad range of baseline levels; therefore, percentage reduction is a more reliable indicator of statin efficacy. The 2018 AHA/ACC guideline uses percentage reduction to estimate the efficacy of statin therapy, with the primary goal being a ≥50% reduction in LDL levels [24].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The U.S. Preventive Services Task Force (USPSTF) recommends that adults without a history of cardiovascular disease (CVD) use a low- to moderate-dose statin for the prevention of cardiovascular events and mortality when all of the following criteria are met:

- They are 40 to 75 years of age.
- They have one or more CVD risk factors.
- They have a calculated 10-year risk of a cardiovascular event of 10% or greater.

Identification of dyslipidemia and calculation of 10-year CVD event risk requires universal lipids screening in adults 40 to 75 years of age.

(https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/statin-use-in-adults-preventive-medication. Last accessed July 25, 2022.)

**Strength of Recommendation/Level of Evidence:** B (There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.)

Hypertriglyceridemia is associated with an increased risk of ASCVD events and acute pancreatitis, and lowering triglyceride levels in high-risk patients (e.g., those with ASCVD or diabetes) is associated with decreased cardiovascular morbidity and mortality. The management of mixed dyslipidemia remains controversial, so treatment should focus primarily on lowering LDL levels [105].

Baseline levels are used to estimate risk of ASCVD, guide treatment decisions, and accurately evaluate response to therapy. It is important to note that baseline cholesterol levels may vary by geography and among ethnic minority populations. For example, cholesterol values are about 20% higher in the Western population than in the Asian population [67]. The 2018 AHA/ACC guideline provides recommendations for the accurate measurement of baseline LDL levels (***Table 4***) [24; 63].

## LIFESTYLE MODIFICATION

Management of hyperlipidemia is but one component of a general strategy for reducing the risk of ASCVD. It is important that healthcare professionals have a good understanding of other measures required for effective risk reduction, including lifestyle changes that may facilitate lipid management before there is need of pharmacotherapy. The 2019 AHA/ACC Guideline on the Primary Prevention of Cardiovascular Disease presents recommendations related to lifestyle modification (e.g., diet and physical activity), patient comorbidities (e.g., obesity, diabetes, hypertension), and patient-centered approaches (e.g., team-based care, shared decision-making, assessment of social determinants of health) to management [236]. The recommendations for management of hyperlipidemia in the AHA/ACC 2018 Cholesterol Clinical Practice Guidelines have been included in the 2019 AHA/ACC guideline.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The ACC/AHA recommend a diet emphasizing intake of vegetables, fruits, legumes, nuts, whole grains, and fish decrease ASCVD risk factors.

(http://www.onlinejacc.org/content/73/24/e285?_ga=2.118995977.141815126.1563751668-1264536891.1558548868. Last accessed July 25, 2022.)

**Level of Evidence:** I (Strong)

| AHA/ACC RECOMMENDATIONS FOR ASSESSMENT OF BASELINE LEVELS OF LDL AND NON-HDL |
|---|
| In adults 20 years of age or older not on lipid-lowering therapy, measurement of either a fasting or a nonfasting plasma[a] lipid profile is effective in estimating ASCVD risk and documenting baseline LDL (Class I, based onmoderate-quality evidence). |
| In adults 20 years of age or older in whom an initial nonfasting lipid profile reveals a triglyceride level of ≥400 mg dL (≥4.5 mmol/L), perform a repeat lipid profile in the fasting state for assessment of fasting triglyceride levels and baseline LDL (Class I, based on moderate-quality evidence). |
| For patients with an LDL level <70 mg/dL (<1.8 mmol/L), measurement of direct LDL or modified LDL estimate is reasonable to improve accuracy over the Friedewald formula (Class IIa, based on limited data). |
| In adults 20 years of age or older without a personal history of ASCVD but with a family history of premature ASCVD or genetic hyperlipidemia, measurement of a fasting plasma lipid profile is reasonable as part of an initial evaluation to aid in the understanding and identification of familial lipid disorders (Class IIa, based on limited data). |
| [a]Both fasting and nonfasting total cholesterol and HDL levels appear to have similar prognostic value and associations with ASCVD outcomes. Therefore, nonfasting samples can be used for risk assessment in primary prevention and for assessment of baseline LDL levels prior to initiation of a statin. If more precision is necessary, fasting lipids can be measured, but a nonfasting sample is reasonable for most situations. |
| *Source: [24]* *Table 4* |

Modifiable lifestyle factors for cardiovascular disease risk reduction include diet, weight reduction, physical activity (exercise), and smoking cessation [24; 236]. The 2018 AHA/ACC guideline on management of blood cholesterol and 2019 guideline on primary prevention of cardiovascular disease concur on the recommendations for good nutrition, diet, and exercise [24; 236]. All adults should consume a healthy diet that [236]:

- Emphasizes the intake of fruits, vegetables, nuts, and whole grains
- Includes low-fat dairy products, poultry, fish, legumes, and nontropical vegetable oils
- Limits the intake of sweets, sugar-sweetened beverages, refined carbohydrates, red meat, and processed meats
- Replaces saturated fat (no more than 5% to 6% of calories from saturated fat) with dietary monounsaturated and polyunsaturated fats
- Avoids the intake of trans fat

It is important to adapt the dietary pattern to the patient's calorie requirements, personal and cultural food preferences, and nutrition therapy for other medical conditions, including diabetes. For adults with obesity, counseling and caloric restriction are recommended for achieving and maintaining weight reduction [236]. A successful dietary approach to lipid lowering requires instruction by a dietitian or other knowledgeable healthcare professional.

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 [116; 117; 118]. 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. Plans such as those offered by the USDA's Dietary Guidelines for Americans, the AHA Diet and Lifestyle Recommendations, and the DASH Eating Plan can also help the patient achieve recommended lifestyle changes [119; 120; 121].

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; 122]. Adults should engage in 150 minutes per week of accumulated moderate-intensity or 75 minutes per week of vigorous-intensity aerobic physical activity to reduce ASCVD risk [236]. An example of moderate exercise is brisk walking; examples of vigorous exercise are swimming, biking, and playing tennis. Combining moderate and vigorous physical activity allows for a proportionate reduction in time allotted to exercise each week.

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. Drug therapy is recommended only in select patients with moderately-high LDL (≥160 mg/dL) or patients with very-high LDL (190 mg/dL). High-intensity or maximal statin therapy plus ezetimibe and/or a PCKS9 inhibitor is recommended for the patient at very-high risk (i.e., history of multiple major ASCVD events) [24].

### 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 [25; 30; 31; 46; 57; 105; 100; 123; 124; 125; 126; 127; 128].

### 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 [129]. 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.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Under certain circumstances, the ACC/AHA assert that nonstatin medications (i.e., ezetimibe, bile acid sequestrants, and PCSK9 inhibitors) may be useful in combination with statin therapy.

(http://www.onlinejacc.org/content/73/24/e285?_ga=2.118995977.141815126.1563751668-1264536891.1558548868. Last accessed July 25, 2022.)

**Level of Evidence**: Expert Opinion/Consensus Statement

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 [67]. 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; 130; 131]. 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 select patients with type 2 diabetes [109; 132].

### *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%) [109; 133].

### *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. Phytosterols 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. Inhibition of cholesterol absorption increases the expression of hepatic LDL receptors and enhances clearance of LDL from the circulation. 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 [109; 133]. 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 [109; 134]. 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 FDA approval in 2013. However, Liptruzet was recalled in 2014 for packaging issues and discontinued in 2016 [109; 133; 135; 136].

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; 46; 67; 137; 138].

### *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 [109].

### *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 [109; 133].

## 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 [139].

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 [109].

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) [109].

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 ASCVD by about 20%, although their effect on LDL, as mentioned previously, is limited and variable.

### 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 [109].

### 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 [140].

| STATIN DOSES REQUIRED TO REDUCE LDL TO BASELINE GOAL | | | | | | |
|---|---|---|---|---|---|---|
| **Agent** | **Percent Reduction in LDL Necessary to Reach Goal** | | | | | |
| | **20% to 25%** | **26% to 30%** | **31% to 35%** | **36% to 40%** | **41% to 50%** | **51% to 55%** |
| Rosuvastatin | – | – | – | 5 mg | 10 mg | 20–40 mg |
| Atorvastatin | – | – | 10 mg | 20 mg | 40 mg | 80 mg |
| Simvastatin | – | 10 mg | 20 mg | 40 mg | 80 mg[a] | – |
| Lovastatin | – | 20 mg | 40 mg | 80 mg | – | – |
| Pravastatin | 10 mg | 20 mg | 40 mg | 80 mg | – | – |
| Fluvastatin | 20 mg | 40 mg | 80 mg | – | – | – |
| Pitavastatin | – | 1–4 mg | – | – | – | – |
| [a]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; 24; 109; 141]* | | | | | | *Table 5* |

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 [109].

## 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 [109]. Inhibition of HMG-CoA reductase leads to increased expression of the hepatic LDL receptor and increased clearance of LDL from the circulation [235]. Statins are the primary pharmacotherapeutic agents used to lower LDL cholesterol levels.

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***).

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 [142].

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 [143; 144; 145]. Statins have been linked to a reduction in the risk of developing Alzheimer disease independent of the drugs' lipophilicity [145; 146].

As stated, the percentage reduction in LDL levels is used to estimate the efficacy of statin therapy, with the primary goal being a ≥50% reduction [24]. In clinical practice, absolute responses in LDL levels to statin therapy depend on baseline levels and the intensity (i.e., low, moderate, or high) of lipid-lowering therapy [24].

In addition to efficacy, therapeutic goals, and patient preferences, 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 [147]. 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 [148; 149].

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 [109].

Statins are effective in the prevention of ASCVD [67; 150; 151]. 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" [152]. 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 ASCVD were prevented against 3.4 cases of rhabdomyolysis [140; 153; 154]. Randomized controlled trials across differing risk categories of patients have shown that statins confer significant relative risk reductions in cardiovascular events and all-cause mortality [235].

**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 [128].

Statins are associated with hepatotoxicity and elevated transaminases in 1% to 2% of patients [128]. 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 [155; 156].

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 [156].

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 [128]. 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 [140; 157].

| AHA/ACC RECOMMENDATIONS FOR STATIN SAFETY AND MANAGEMENT OF STATIN-ASSOCIATED SIDE EFFECTS |
|---|
| In patients with nonsevere statin-associated side effects, reassess and rechallenge to achieve maximal LDL lowering by modified dosing regimen, alternate statin, or in combination with nonstatin therapy (Class I, based on moderate-quality evidence). |
| In patients with increased diabetes risk or new-onset diabetes, continue statin therapy with added emphasis on adherence, net clinical benefit, and core principles of healthy lifestyle (Class I, based on moderate-quality evidence). |
| In patients treated with statins, measure creatine kinase levels in individuals with severe SAMS and objective muscle weakness. Measure liver transaminases as well as total bilirubin and alkaline phosphatase (hepatic panel) if symptoms suggest hepatotoxicity (Class I, based on limited data). |
| In patients at increased ASCVD risk with chronic, stable liver disease (including non-alcoholic fatty liver disease), when appropriately indicated, it is reasonable to use statins after obtaining baseline measurements and determining a schedule of monitoring and safety checks (Class I, based on moderate-quality evidence). |
| In patients at increased ASCVD risk with severe SAMS or recurrent SAMS despite appropriate statin rechallenge, it is reasonable to use randomized controlled trial-proven nonstatin therapy that is likely to provide net clinical benefit (Class IIa, based on moderate-quality evidence). |
| SAMS = statin-associated muscle symptoms. |
| *Source: [24]* *Table 6* |

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 [140; 158; 159; 160]. 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) [161]. 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 [140].

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 [109; 156; 162].

The AHA/ACC recommend that a clinician-patient risk discussion be conducted prior to the initiation of statin therapy to review and weigh the risk reduction benefit against the potential for adverse effects, drug-drug interactions, and safety. Patients with statin-associated muscle symptoms should be evaluated for nonstatin causes and predisposing factors. When a statin is indicated, identify predisposing factors for statin-associated side effects (e.g., new-onset diabetes mellitus, muscle symptoms) prior to initiating statin therapy (***Table 6***) [24].

**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 [67; 128; 163]. Interac-

tion between statins and fibrates, particularly with gemfibrozil, increases the risk of rhabdomyolysis. For this reason, fenofibrate is preferred when the two classes are combined [140].

### Clinical Outcome

Statins, the most potent lipid-lowering drugs, are indicated in a variety of clinical conditions and are effective in the prevention of ASCVD 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. Furthermore, randomized controlled trials do not support the use of fibrates and niacin as add-on drugs to statin therapy. However, if a fibrate is necessary in a patient being treated with a statin, it is safer to use fenofibrate than gemfibrozil due to lower risk of severe myopathy [24]. 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 re-introduction of low doses of statins in conjunction with ezetimibe in cases in which the lipid-lowering benefit of statins outweighs the risk of myopathy [140; 164].


The more LDL is reduced on statin therapy, the greater will be subsequent risk reduction. Therefore, the ACC/AHA recommend patients with clinical ASCVD be treated with a maximally tolerated statin to lower LDL levels by ≥50%.

(https://www.ahajournals.org/doi/pdf/10.1161/CIR.0000000000000677. Last accessed July 25, 2022.)

**Level of Evidence:** I (Strong)

## 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 [165]. 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; 166]. 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 ASCVD [31]. However, it is no longer recommended, except in specific clinical situations, such as a patient with triglyceride levels >500 mg/dL, a patient who is not able to achieve desired response, or a patient with intolerance to other therapies [109]. Although niacin has a mild LDL-lowering action, randomized controlled trials do not support its use as an add-on to statin therapy, and it is not listed as an LDL-lowering drug option in the 2018 AHA/ACC guideline [24]. Niacin has not been shown to reduce ASCVD outcomes beyond that achieved with statin use, and it may be associated with harm [167; 168; 169].

## 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 [170]. Interestingly, epidemiologic studies showed that Inuit living in Greenland following a traditional diet rich in fat had a lower mortality from ASCVD than Inuit living in Denmark who followed a Western diet. This puzzling observation is known as the "Eskimo paradox" [171]. It is now well established that, although individual genetic background plays an important role in the development of ASCVD, 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 [172].

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 [173]. 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 [57; 174; 175; 176].

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 [177]. 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 [173]. Omega-3 fatty acids also have well established antiarrhythmic, antihypertensive, anti-atherogenic, and antithrombotic properties [173; 178; 179; 180; 181; 182; 183].

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 [175; 180; 184; 185; 186; 187; 188]. 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) [189]. 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 [173; 190; 191]. 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 in the United States. It is important to note that dietary supplements are not FDA-required to demonstrate safety and efficacy prior to marketing, whereas prescription products are. Dietary supplements generally contain lower levels of EPA and DHA than prescription products, are not approved or intended to treat disease, and may have levels of EPA and DHA that vary widely within and between brands. Supplements should not be substituted for prescription products, as they may also contain unwanted cholesterol or fats or potentially harmful components, including toxins and oxidized fatty acids [192].

Omega-3 fatty acids also are readily available in the United States as prescription medications. 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) [189]. A second available medication consists of 1,000 mg omega-3 in free fatty acid form, which is intended to improve the bioavailability [193]. 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) [189]. In one study, a minimum dose of 500 mg per day of combined EPA/DHA was recommended for individuals without underlying overt ASCVD, and 800-1,000 mg/day was recommended for individuals with CHD and heart failure [194]. 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 [195]. In 2019, the FDA approved icosapent ethyl, a prescription omega-3 fatty acid, as an adjunctive therapy (to maximally tolerated statin therapy) to reduce the risk of cardiovascular events in adults with elevated triglyceride levels (≥150 mg/dL), cardiovascular disease and/or diabetes, and at least two additional risk factors [232].

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 [109; 189]. They may be considered for triglyceride levels >1,000 mg/dL and may be used alone or in conjunction with HMG-CoA reductase inhibitors [109]. Omega-3 fatty acids are effective in the prevention of ASCVD. Their effect on cardiovascular morbidity and mortality has not been determined [189].

**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 [189]. 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 [196]. 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 [197].

### Drug Interactions

Due to their antiplatelet effect, omega-3 fatty acids may increase bleeding time in a dose-dependent manner [109; 189]. 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 [57; 173; 174; 175; 176; 198; 199].

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 enterocyte back into the lumen [199].

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 [200]:

> 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% [201].

### 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.

## ADENOSINE TRIPHOSPHATE-CITRATE LYASE (ACL) INHIBITOR

### Mechanism of Action and Clinical Pharmacology

As noted, in 2020, the FDA approved bempedoic acid for the treatment of Heterozygous familial hypercholesterolemia or established ASCVD [233]. Bempedoic acid is the first in the class of adenosine triphosphate-citrate lyase (ACL) inhibitors. By inhibiting ACL, a hepatic enzyme involved in the synthesis of cholesterol, bempedoic acid decreases the conversion of mitochondrial-derived citrate to cytosolic ACL, creating less substrate for cholesterol and fatty acid synthesis. This ultimately decreases liver cholesterol synthesis and decreases serum LDL-C levels by upregulating LDL receptors [239].

Bempedoic acid is available as monotherapy and in a tablet with ezetimibe as combination therapy. It is an option to modify statin therapy or for patients who cannot tolerate statins. This combination has been demonstrated in clinical trials to lower LDL-C levels by 36% and, when given as monotherapy, bempedoic acid and ezetimibe have been respectively shown to lower LDL-C levels by 15% to 23% and by 13% to 20%, respectively [239]. The usual dose is 180 mg bempedoic acid and, if used, 10 mg ezetimibe once daily.

### Adverse Effects

Potential adverse effects associated with bempedoic acid include leukopenia, thrombocythemia, upper respiratory tract infection, and, most commonly, hyperuricemia and gout. Gout and hyperuricemia are more common at higher doses and related to inhibition of tubular OAT2, which may increase blood uric acid levels [109]. It usually develops within the first four weeks of treatment initiation and persists until cessation of administration.

Rupture or injury of tendon has rarely (<1%) occurred, typically involving the rotator cuff, biceps tendon, or Achilles tendon [109]. Risk factors include age older than 60 years, concomitant use of corticosteroids or fluoroquinolones, kidney failure, and prior tendon disorders.

### Drug Interactions

Bempedoic acid can increase the serum concentration of certain drugs metabolized by the liver, including elagolix, voxilaprevir, and asunaprevir and should be avoided in patients taking these medications [109]. It may also increase the serum levels of the statins simvastatin and lovastatin. If bempedoic acid is coadministered with these agents, the dose should be limited to no more than 20 mg daily for simvastatin or 40 mg daily for lovastatin [109; 239].

## 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 ASCVD. 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 ASCVD, 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 [140]. 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 PCSK9, a serine protease synthesized in the liver, being investigated for its regulatory effect on LDL receptors [56; 202; 203; 204; 205; 206].

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, lapaquistat (TAK-475), has undergone extensive development in clinical trials as a monotherapy; 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 [207; 208].

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 [209]. These drugs have been subjected to clinical trials. To date, four trials have been terminated and one completed, with results not yet available [210].

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 [55]. A new generation of drugs that is able to stimulate the ATP-binding cassette transporter and promote cholesterol elimination by enterocytes is being investigated [56].

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 [165; 203].

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 [211]. Research is ongoing [212; 213].

Antisense oligonucleotides (e.g., mipomersen) are single-stranded DNA that bind to matching mRNA and induce its selective degradation. Pre-clinical 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 [210; 214].

Downregulation of the LDL receptor by PCSK9 is one regulatory mechanism that controls plasma LDL cholesterol concentrations. Studies have demonstrated that the PCSK9 enzyme binds to the hepatic LDL receptor and promotes its degradation, which in turn decreases LDL uptake and increases 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 [215; 216; 217; 218].

PCSK9 inhibitors are monoclonal antibodies that inactivate the PCSK9 enzyme and promote clearance of LDL from the circulation. Administration of PCSK9 inhibitors can reduce serum LDL cholesterol by 60% [235]. 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. To date, clinical trials of PCSK9 inhibitor therapy as an adjunct to statins have been conducted for secondary prevention of ASCVD in high-risk patients [235]. The demonstrated benefit is modest, the cost relatively high, and the long-term safety not yet well-established.

| AHA/ACC RECOMMENDATIONS TO IMPROVE ADHERENCE TO GUIDELINE IMPLEMENTATION |
|---|
| Provide interventions focused on improving adherence to therapy (e.g., telephone reminders, calendar reminders, integrated multidisciplinary educational activities, pharmacist-led interventions) (Class I, based on high-quality evidence). |
| Identify patients not receiving guideline-directed medical therapy, and facilitate initiation of appropriate guideline-directed medical therapy using multifaceted strategies to improve guideline implementation (Class I, based on moderate-quality evidence). |
| Conduct patient-clinician discussion prior to therapy to promote shared decision-making (Class I, based on moderate-quality evidence). |
| *Source: [24]* *Table 7* |

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

As discussed, the clinical approach to hyperlipidemias is aimed at the primary and secondary prevention of ASCVD. As the evidence has shown, it is clear that lipid-lowering strategies play a fundamental role in the primary prevention of ASCVD. Primary prevention is defined as the long-term management of individuals at increased risk for but without clinical evidence of ASCVD and who have not undergone revascularization procedures [220]. Secondary prevention is defined as the clinical management of individuals with a history of ASCVD.

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 assess and reduce risk factors for CHD in each age group and to emphasize adherence to a healthy lifestyle. This is achieved through two complementary approaches: population strategies and clinical "individual" strategies [24]. Population (public health) strategies shift the distribution of risk factors of the target population to more desirable levels. For example, the 2018 AHA/ACC guideline emphasizes promotion of a heart-healthy lifestyle that improves cardiovascular health and prevents dyslipidemia and other ASCVD risk factors for all age groups. Successful implementation of these recommendations on a population level requires the multidisciplinary team of healthcare providers to help bridge the gap between public health and patient management by supporting and advocating for continued public health initiatives and by encouraging a collaborative effort among healthcare professionals, government agencies, schools, the food industry, and the media [25].

Healthcare delivery is complex, and barriers to guideline implementation can occur at both the public and individual level (***Table 7***) [24].

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 [23; 25; 221]. Attaining lower LDL and triglyceride plasma concentrations can be achieved by a combination of lifestyle changes and drug therapy. As stated, the 2018 AHA/ACC guideline continues to emphasize the adoption of a heart-healthy lifestyle from adolescence onward, as this reduces ASCVD risk at all ages. In all age groups, lifestyle therapy is the primary intervention for metabolic syndrome [24].

Secondary prevention should be initiated in patients with clinical ASCVD. A meta-analysis of randomized controlled trials conducted by the Cholesterol Treatment Trialists demonstrated that lowering LDL with statins reduces major ASCVD events and also benefits patients with stroke or peripheral artery disease [222; 223]. Compared with moderate-intensity statin therapy, high-intensity statin therapy significantly reduced major vascular events by 15% with no significant reduction in coronary deaths. High-intensity statin therapy generally reduces LDL

levels by ≥ 50%. However, as stated, absolute benefit depends on baseline levels [24]. Lifestyle changes provide only moderate improvement of the lipid profile in patients with previous ASCVD, so although they should be implemented, pharmacotherapy is required to attain therapeutic goals [23; 24].

The complexity of health status in patients with a history of ASCVD requires an approach of multifactorial risk reduction. Multifactorial risk reduction has a synergistic effect on disease progression and clinical outcomes and should be associated with a case management approach [23; 224; 225]. 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 [23; 24; 225; 226].

## CLINICAL ASSESSMENT OF RISK ASSOCIATED WITH HYPERLIPIDEMIAS

The Framingham Heart Study took the lead in creating risk-prediction equations, and previous guidelines made use of the Framingham risk score algorithm. However, the 2013 Work Group for the guideline on assessment of cardiovascular risk decided against using the Framingham algorithm due to its use of an exclusively white sample population and the limited scope of the outcome (i.e., to determine CHD alone) [227]. Instead, the Group compiled data from five community-based cohorts that were broadly representative of the U.S. population. The final pooled cohorts included participants from several large, racially and geographically diverse, NHLBI-sponsored studies. The Group validated pooled cohort equations that provided sex- and race-specific estimates of 10-year risk of first, hard ASCVD event (i.e., MI and stroke, fatal and nonfatal) for African-American and white men and women 40 to 79 years of age (***Table 8***). Variables included in the risk equation were age, total cholesterol, HDL, systolic blood pressure, diabetes, and current smoking status [227].

Data from the Women's Health Initiative initially appeared to indicate that the pooled cohort equations overestimated the risk of ASCVD, but when event surveillance was improved by data from Centers for Medicare and Medicaid Services, it was found that the equations discriminated risk well [228]. However, because the algorithms may over- or underestimate risk for individual patients, the 2013 AHA/ACC guideline on assessment of cardiovascular risk additionally introduced the clinician-patient risk discussion to facilitate decisions about appropriate therapy. This risk discussion is an integral part of the decision-making process in the 2018 AHA/ACC guideline on the management of blood cholesterol [24; 227].

As stated, the pooled cohort equations estimate risk of hard ASCVD events among patients 40 to 79 years of age who are without pre-existing disease. Because pooled cohort equations are population equations, the estimates and recommendations for therapy should be considered in the context of the patient's individual circumstances. Patients are considered to be at elevated risk if the pooled cohort equations estimate is ≥ 7.5% [24].

The 2018 and 2019 AHA/ACC guidelines concur with the recommendation that clinical management should be based on calculation of the patient's 10-year estimated risk of ASCVD, as this will influence the intensity of management, whether it be lifestyle modification, drug therapy, or both [24; 236]. In children, adolescents, and young adults, priority should be estimation of lifetime risk and promotion of lifestyle risk reduction [24]. The ACC ASCVD risk assessment tool is available (http://tools.acc.org/ASCVD-Risk-Estimator-Plus) to estimate the risk of ASCVD within 10 years. The risk calculator is intended for use in patients 40 to 75 years of age who do not have diabetes and whose LDL cholesterol is 70 – 189 mg/dL [235].

The AHA/ACC recommends that for adults 40 to 70 years of age, clinicians routinely assess traditional risk factors and calculate the estimated 10-year risk of ASCVD [24; 236]. For adults 20 to 39 years of age, clinicians should assess (monitor) ASCVD risk factor status every three to six years. For adults at

| DISTRIBUTION OF ESTIMATED 10-YEAR RISK OF FIRST HARD ASCVD EVENT IN ASCVD-FREE NONPREGNANT U.S. POPULATION, 40 TO 79 YEARS OF AGE, BY SEX AND RACE/ETHNICITY[a] | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Population** | **Predicted 10-Year Risk of ASCVD Event** | | | | | | |
| | **<2.5%** | **2.5% to 4.9%** | **5.0% to 7.4%** | **7.5% to 9.9%** | **10.0% to 14.9%** | **15.0% to 19.9%** | **≥20.0%** |
| Total | 33.4% | 21.0% | 12.7% | 7.4% | 8.9% | 6.3% | 10.2% |
| **All Races/Ethnicities** | | | | | | | |
| Men | 17.4% | 22.7% | 15.6% | 10.1% | 12.1% | 8.8% | 13.3% |
| Women | 48.0% | 19.5% | 10.0% | 5.0% | 5.9% | 4.1% | 7.5% |
| **White Race/Ethnicity** | | | | | | | |
| Men | 18.0% | 22.4% | 15.7% | 10.0% | 11.7% | 8.7% | 13.6% |
| Women | 47.1% | 20.4% | 10.7% | 5.1% | 5.5% | 4.1% | 7.1% |
| **African American Race/Ethnicity** | | | | | | | |
| Men | 1.4% | 23.9% | 20.6% | 11.8% | 17.4% | 11.1% | 13.8% |
| Women | 36.5% | 18.7% | 10.9% | 6.5% | 9.4% | 5.7% | 12.3% |
| **Hispanic Race/Ethnicity** | | | | | | | |
| Men | 24.0% | 22.1% | 13.2% | 10.6% | 11.4% | 6.2% | 12.6% |
| Women | 59.4% | 14.5% | 7.5% | 4.5% | 4.9% | 3.0% | 6.3% |
| **Other Race/Ethnicities** | | | | | | | |
| Men | 20.8% | 27.1% | 11.6% | 7.2% | 11.5% | 12.3% | 9.4% |
| Women | 59.8% | 18.6% | 4.4% | 1.7% | 6.4% | 2.4% | 6.7% |
| [a]Data derived by applying pooled cohort equations to National Health and Nutrition Examination Surveys, 2007–2010. | | | | | | | |
| *Source: [227]* | | | | | | | *Table 8* |

borderline risk (5% to <7.5% 10-year ASCVD risk) or intermediate risk (7.5% to <20% 10-year ASCVD risk), additional risk-enhancing factors can be used to guide decisions about therapeutic interventions; such factors may include family history of premature ASCVD, chronic inflammatory disease (e.g., rheumatoid arthritis, lupus), chronic kidney disease, early menopause, or metabolic syndrome. In adults at intermediate risk or borderline 10-year ASCVD risk, if risk-based decisions for preventive therapy such as statin treatment remain uncertain, it is reasonable to measure a coronary artery calcium score to guide clinician-patient risk discussion [236].

For purposes of shared clinical decision making, the AHA/ACC categorizes patients according to level of cardiovascular disease risk at 10 years and recommends routine clinician-patient ASCVD risk discussion in relation to the level of risk [24; 236]:

- Low (<5%): Risk discussion should emphasize healthy lifestyle to reduce risk.
- Borderline (5% to <7.5%): If there are risk enhancers present, then risk discussion regarding benefit of moderate-intensity statin therapy.
- Intermediate (7.5% to <20%): If risk estimate plus added risk enhancers favor statin therapy, discussion on benefit of initiating moderate-intensity statin to reduce LDL-C by 30% to 49%.
- High (≥20%): Discussion on benefit of statin therapy to reduce LDL-C by 50% or more combined with adoption of a healthy lifestyle.

A 10-year "intermediate" risk score (10% to 15%) does not automatically mandate a statin, but rather should lead to discussion and shared decision-making between the clinician and the patient [229].

Drug therapy is recommended only in select patients with moderately-high LDL (≥160 mg/dL) or patients with very-high LDL (190 mg/dL).

Two higher-risk patient categories are those with severe hypercholesterolemia (LDL ≥190 mg/dL) and older adults with diabetes. Patients with severe hypercholesterolemia and adults 40 to 75 years of age with diabetes are candidates for immediate statin therapy without further risk assessment. Adults with diabetes should start with a moderate-intensity statin (i.e., one that lowers LDL by 30% to 49%). A high-intensity statin (i.e., one that lowers LDL by ≥50%) may be indicated as the patient accrues multiple risk factors. In all other adults 40 to 75 years of age, the 10-year risk of ASCVD should guide therapeutic decision making. The higher the 10-year risk, the more likely the patient will benefit from evidence-based statin treatment [24].

## CLINICAL GUIDELINES FOR THE TREATMENT OF HYPERLIPIDEMIAS

Treatment guidelines for hyperlipidemias were developed by the NCEP-ATP III [230]. These guidelines were partially updated by the 2013 ACC/AHA guideline; however, as discussed, the recommendations provided by the 2018 AHA/ACC guideline and adapted by the 2019 AHA/ACC guideline on primary prevention of CVD will be presented [24; 236]. In 2020, the Department of Veterans Affairs and the Department of Defense (VA/DoD) also published a clinical practice guideline for the management of dyslipidemia [237]. The VA/DoD guideline is designed for the adult population older than 40 years of age and eligible for healthcare in the VA and DoD health systems. Healthcare professionals working within the VA and DoD systems, and others participating in care of patients within the systems, may wish to review the VA/DoD document, as there are differences between these guidelines and the AHA/ACC guidelines, such as the intensity of statin recommended, the risk level thresholds for statin treatment, and the use of adjunctive therapies for primary prevention in patients on statins [238].

Guidelines on management of hyperlipidemia specify four major categories of patients for whom statins may be considered (***Table 9***) [24]:

- Those with clinical ASCVD
- Those with severe hypercholesterolemia (LDL ≥190 mg/dL)
- Those 40 to 75 years of age with diabetes and LDL ≥70 mg/dL
- Those 40 to 75 years of age with no diabetes but with LDL ≥70 mg/dL and ≥7.5% 10-year ASCVD risk

In addition to the patient factors discussed, race and ethnicity inform and influence the estimates of ASCVD risk, treatment intensity, use of lipids, and other issues. For example, when evaluating ASCVD risk, it is useful for the clinician to know that risk in people of South and East Asian origin varies by country of origin. When evaluating lipid issues, it is useful to know that Hispanic/Latina women have a higher prevalence of low HDL compared with Hispanic/Latino men. When evaluating metabolic issues, it is useful to know that there is an increased prevalence of diabetes and hypertension among Black Americans. Country-specific race/ethnicity, along with the patient's socioeconomic status, may affect the estimation of risk by pooled cohort equations [24].

Other at-risk patient groups include those with moderate or severe hypertriglyceridemia, women with gender-specific history (e.g., premature menopause, history of pregnancy-associated disorders), adults with chronic kidney disease, adults with chronic inflammatory disorders and HIV, older adults (≥75 years of age), young adults (20 to 39 years of age), and children and adolescents. The 2018 AHA/ACC guideline provides recommendations and considerations for clinical decision-making for these unique patient populations [24]. Additionally, the guideline continues to emphasize adherence to a heart-healthy lifestyle from adolescence onward; promote assessment of lifetime ASCVD risk for young adults 20 to 40 years of age; and emphasize comprehensive lifestyle improvements to prevent development of metabolic syndrome [231].

| AHA/ACC RECOMMENDATIONS FOR STATIN THERAPY | | | |
|---|---|---|---|
| **Age** | **Patient Factors** | **Recommendation** | **Target % LDL** |
| **Patients with ASCVD** | | | |
| ≤75 years | Clinical ASCVD | High-intensity statin (initiate or continue) | ≥50% |
| | Clinical ASCVD and contraindication to high-intensity statin | Moderate-intensity statin (initiate or continue) | 30% to 49% |
| | Clinical ASCVD, at very high risk, being considered for PCKS9 inhibitor therapy | Maximally-tolerated LDL-lowering therapy (with maximally tolerated statin and ezetimibe) | |
| | Clinical ASCVD, at very high risk, on maximally tolerated LDL-lowering therapy, with LDL ≥70 mg/dL or non-HDL ≥100 mg/dL | It is reasonable to add PCSKP-I following clinician-patient discussion | |
| | Clinical ASCVD, on maximally tolerated statin therapy, at very high risk, with LDL ≥70 mg/dL | It is reasonable to add ezetimibe | |
| ≥75 years | Clinical ASCVD and evaluated for ASCVD risk reduction, statin adverse effects, drug-drug interactions, patient frailty and preferences | It is reasonable to initiate moderate- or high-intensity statin | 30% to 49% |
| | Currently tolerating high-intensity statin therapy and evaluated for ASCVD risk reduction, statin adverse effects, drug-drug interactions, patient frailty and preferences | It is reasonable to continue high-intensity statin | |
| | Clinical ASCVD, currently receiving maximally tolerated statin therapy but LDL level remains ≥70 mg/dL | It may be reasonable to add ezetimibe | |
| | Heart failure and reduced ejection fraction attributable to ischemic heart disease and reasonable life expectancy (3 to 5 years), not on statin therapy due to ASCVD | May consider initiation or moderate-intensity statin therapy | |
| | Clinical ASCVD, on maximally tolerated statin therapy, at very high risk, with LDL ≥70 mg/dL | It is reasonable to add ezetimibe | |
| **Patients with Severe Hypercholesterolemia** | | | |
| 20 to 75 years | LDL ≥190 mg/dL | Maximally-tolerated statin therapy | ≥50% |
| | LDL ≥190 mg/dL, achieves <50% reduction in LDL while receiving maximally tolerated statin and/or have LDL ≥100 mg/dL | Ezetimibe therapy is reasonable | |
| | Baseline LDL ≥190 mg/dL, achieves <50% reduction in LDL levels and has fasting triglycerides ≤300 mg/dL while taking maximally tolerated statin and ezetimibe therapy | Consider adding a bile acid sequestrant | |
| 30 to 75 years | Heterozygous FH with LDL ≥100 mg/dL while taking maximally tolerated statin and ezetimibe therapy | Consider adding a PCSK9 inhibitor | ≥50% |
| 40 to 75 years | Baseline LDL ≥220 mg/dL, achieves on-treatment LDL ≥130 mg/dL while receiving maximally tolerated statin and ezetimibe therapy | Consider adding a PCSK9 inhibitor | ≥50% |

*Table 9 continues on next page.*

| AHA/ACC RECOMMENDATIONS FOR STATIN THERAPY | | | |
|---|---|---|---|
| **Age** | **Patient Factors** | **Recommendation** | **Target % LDL** |
| **Patients with Diabetes** | | | |
| 40 to 75 years | Diabetes | Moderate-intensity statin, regardless of estimated 10-year ASCVD risk | — |
| | Diabetes and LDL 70–189 mg/dL | Reasonable to assess 10-year risk of first ASCVD event using race-, sex-specific pooled cohort equations | — |
| | Diabetes with multiple ASCVD risk factors | Reasonable to prescribe high-intensity statin | ≥50% |
| ≥75 years | Diabetes and on statin therapy | Reasonable to continue statin therapy | |
| | Diabetes and 10-year ASCVD risk ≥20% | May be reasonable to add ezetimibe to maximally tolerated statin | ≥50% |
| >75 years | Diabetes | May be reasonable to initiate statin therapy after clinician-patient risk discussion | — |
| 20 to 39 years | Diabetes with specific risk enhancers[a] | May be reasonable to initiate statin therapy | — |
| **Patients with No Diabetes But Other Risk Factors** | | | |
| 40 to 75 years | LDL ≥70 mg/dL and 10-year ASCVD risk ≥7.5% | Moderate-intensity statin, if favored by clinician-patient risk discussion | — |
| [a]Diabetes of long duration (≥10 years type 2, ≥20 years type 1), albuminuria, eGFR <60 mL/min/1.73 $m^2$, retinopathy, neuropathy, ankle-brachial index <0.9 | | | |
| *Source: [24]* | | | *Table 9* |

Adherence to changes in lifestyle and effects of LDL-lowering medication should be assessed by measuring fasting lipids 4 to 12 weeks after initiation of statin therapy or dose adjustment, and every 3 to 12 months thereafter to assess adherence and safety indicators. Good adherence to an LDL-lowering diet will reduce LDL levels by 10% to 15%. Moderate-intensity statins may reduce LDL levels by another 30% to 40%, and high-intensity statins by ≥50%. The intensity of statin therapy will vary according to the patient's age and risk category [24].

The 2022 AHA/ACC/HFSA Guidelines for the management of Heart Failure recommend the use of sodium-glucose cotransporter-2 inhibitors (SGLT2is) in the treatment of heart failure with reduced ejection fraction [241]. Numerous randomized controlled trials have found that patients with diabetes and ASCVD without heart failure have improved survival and reduced hospitalizations when treated with SGLT2is. SGLT2i therapy prevents heart failure hospitalizations in patients with type 2 diabetes and improves outcomes in patients with heart failure with reduced ejection fraction whether or not they also have diabetes [242]. The mechanism of action of SGLT2i on the improvement in heart failure events is still not clearly elucidated, but it seems to be independent of glucose lowering effects. Proposed mechanisms include [242]:

- Promotion of osmotic diuresis and reductions in plasma volume in patients with and without diabetes, therefore reducing cardiac preload
- Improvements in endothelial function and promotion of peripheral vasodilation, therefore reducing cardiac afterload
- Improvements in myocardial metabolism, reduction of arterial stiffness, and interaction with the Na+/H+ exchanger, improving cardiac efficiency

The recommendations in the 2022 AHA/ACC/HFSA guidelines are also in agreement with the Heart Failure Guidelines Update of the Canadian Cardiovascular Society, published in 2021 [243].

## CONCLUSION

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

The complex interaction between modifiable, nonmodifiable, and risk-enhancing risk factors underlies the etiology of ASCVD. 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 ASCVD 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 ASCVD. 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 AHA/ACC should be followed as the gold standard in clinical practice [24; 95; 115; 120; 227]. 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 ASCVD 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)**
https://www.heart.org

**Professional Heart Daily**
**(A service provided by the AHA)**
https://professional.heart.org

**My Life Check: Life's Essential 8**
https://www.heart.org/en/healthy-living/healthy-lifestyle/lifes-essential-8

**Heart and Stroke Foundation of Canada**
https://www.heartandstroke.ca

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

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

**National Heart, Lung, and Blood Institute**
https://www.nhlbi.nih.gov

**Implicit Bias in Health Care**

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

## 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 opiatergic 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 and Toxicology 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 and Toxicology 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.

## Works Cited


1. Benjamin EJ, Muntner P, Alonso A et al. Heart disease and stroke statistics—2019 update: a report from the American Heart Association. *Circulation*. 2019;139(10):e56-e528.
2. European Heart Network. European Cardiovascular Disease Statistics 2017. Available at https://ehnheart.org/cvd-statistics.html. Last accessed July 11, 2022.
3. World Health Organization. Cardiovascular Diseases. Available at https://www.who.int/cardiovascular_diseases/en/. Last accessed July 11, 2022.
4. Rosamond WD, Chambless LE, Heiss G, et al. Twenty-two Year Trends in the incidence of myocardial infarction, CHD mortality, and case-fatality in four US communities, 1987 to 2008. *Circulation*. 2012;125(15):1848-1857.
5. Fuster V, Kelly BB (eds). *Institute of Medicine (US) Committee on Preventing the Global Epidemic of Cardiovascular Disease: Meeting the Challenges in Developing Countries; Promoting Cardiovascular Health in the Developing World: A Critical Challenge to Achieve Global Health*. Washington, DC: National Academies Press; 2010.
6. American College of Cardiology. Heart Disease Remains Top Killer in the United States. Available at https://www.cardiosmart.org/news/2016/1/heart-disease-remains-top-killer-in-united-states. Last accessed July 11, 2022.
7. World Health Organization. WHO Report on the Global Tobacco Epidemic 2021. Available at https://www.who.int/teams/health-promotion/tobacco-control/global-tobacco-report-2021. Last accessed July 11, 2022.
8. Institute for Health Metrics and Evaluation. *The Global Burden of Disease: Generating Evidence, Guiding Policy*. Seattle, WA: Institute for Health Metrics and Evaluation; 2013.
9. Foley KA, Vasey J, Alexander CM, Markson LE. Development and validation of the Hyperlipidemia Attitudes and Beliefs in Treatment (HABIT) survey for physicians. *J Gen Intern Med*. 2003;18(12):984-990.
10. Foley KA, Vasey J, Alexander CM, Markson LE. The Hyperlipidemia: Attitudes and Beliefs in Treatment (HABIT) survey for patients: results of a validation study. *J Cardiovasc Nurs*. 2005;20(1):35-42.
11. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364(9438):937-952.
12. Lilly LS (ed). *Pathophysiology of Heart Disease: A Collaborative Project of Medical Students and Faculty*. 7th ed. Philadelphia, PA: Lippincott Williams &Wilkins; 2020.
13. Moller DE, Kaufman KD. Metabolic syndrome: a clinical and molecular perspective. *Annu Rev Med*. 2005;56:45-62.
14. Gurgle HE, Blumenthal DK. Drug therapy for dyslipidemias. In: Brunton L, Hilal-Dandan R, Knollman B (eds). *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 13th ed. New York, NY: McGraw-Hill; 2018: 605-618.
15. Centers for Disease Control and Prevention. Total high-density lipoprotein cholesterol in adults: National Health and Nutrition Examination Survey, 2011–2014. *NCHS Data Brief*. 2015;226:1-8.
16. Gan SI, Edwards AL, Symonds CJ, Beck PL. Hypertriglyceridemia-induced pancreatitis: a case-based review. *World J Gastroenterol*. 2006;12(44):7197-7202.
17. The Lipid Research Clinics Coronary Primary Prevention. Trial results: I. Reduction in incidence of coronary heart disease. *JAMA*. 1984;251(3):351-364.
18. The Lipid Research Clinics Coronary Primary Prevention. Trial results: II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. *JAMA*. 1984;251(3):365-374.
19. Stamler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA*. 1986;256(20):2823-2828.
20. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation*. 1998;97(18):1837-1847.
21. Wong ND, Wilson PW, Kannel WB. Serum cholesterol as a prognostic factor after myocardial infarction: the Framingham Study. *Ann Intern Med*. 1991;115(9):687-693.
22. Grundy SM, Cleeman JI, Merz CNB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation*. 2004;110(2):227-239.
23. Dembowski E, Davidson MH. A review of lipid management in primary and secondary prevention. *J Cardiopulm Rehabil Prev*. 2009;29(1):2-12.
24. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;139(25):e1082-e1143.
25. Fletcher B, Berra K, Braun LT, et al. Managing abnormal blood lipids: a collaborative approach. *Circulation*. 2005;112(20):3184-3209.
26. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med*. 2005;352(16):1685-1695.
27. Porth CM, Matfin G. *Pathophysiology: Concepts of Altered Health States*. 8th ed. Philadelphia, PA: Lippincott Williams &Wilkins; 2009.

28. Glass CK, Witzum JL. Atherosclerosis: the road ahead. *Cell*. 2001;104(4):503-516.
29. Hammer GD, McPhee SJ. *Pathophysiology of Disease: An Introduction to Clinical Medicine*. 8th ed. New York, NY: McGraw-Hill; 2019.
30. Krisko TI, Armstrong EJ, Cohen DE. Pharmacology of cholesterol and lipoprotein metabolism. In: Golan DE, Armstrong EJ, Armstrong AW (eds). *Principles of Pharmacology. The Pathophysiological Basis of Drug Therapy*. 4th ed. Philadelphia, PA: Wolters Kluwer Health; 2016: 336-357.
31. Ito MK. Dyslipidemias, atherosclerosis, and coronary heart disease. In: Alldredge BK, Corelli RL, Ernst ME, et al. (eds). *Koda-Kimble and Young's Applied Therapeutics: The Clinical Use of Drugs*. 10th ed. Philadelphia, PA: Lippincott Williams &Wilkins; 2013: 252-290.
32. Nissen SE, Tuzcu EM, Schoenhagen P, et al. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. *N Engl J Med*. 2005;352(1):29-38.
33. Colles SM, Irwin KC, Chisolm GM. Roles of multiple oxidized LDL lipids in cellular injury: dominance of 7 beta-hydroperoxycholesterol. *J Lipid Res*. 1996;37(9):2018-2028.
34. Colles SM, Maxson JM, Carlson SG, Chisolm GM. Oxidized LDL-induced injury and apoptosis in atherosclerosis: potential roles for oxysterols. *Trends Cardiovasc Med*. 2001;11(3-4):131-138.
35. Bilheimer DW, Watanabe Y, Kita T. Impaired receptor-mediated catabolism of low density lipoprotein in the WHHL rabbit, an animal model of familial hypercholesterolemia. *Proc Natl Acad Sci U S A*. 1982;79(10):3305-3309.
36. Ravnskov U. Is atherosclerosis caused by high cholesterol? *QJM*. 2002;95(6):397-403.
37. Schuck RN, Mendys PM, Simpson RJ Jr. Beyond statins: lipid management to reduce cardiovascular risk. *Pharmacotherapy*. 2013;33(7):754-764.
38. Green PP, Namboodiri KK, Hannan P, et al. The Collaborative Lipid Research Clinics Program Family Study. III: Transformations and covariate adjustments of lipid and lipoprotein levels. *Am J Epidemiol*. 1984;119(6):959-974.
39. Lloyd-Jones DM, Larson MG, Beiser A, Levy D. Lifetime risk of developing coronary heart disease. *Lancet*. 1999;353(9147):89-92.
40. Ridker PM, Danielson E, Fonseca FAH, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359(21):2195-2207.
41. Heart Protection Study Collaborative Group, Bulbulia R, Bowman L, et al. Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20,536 high-risk individuals: a randomised controlled trial. *Lancet*. 2011;378(9808):2013-2020.
42. Mora S, Musunuru K, Blumenthal RS. The clinical utility of high-sensitivity C-reactive protein in cardiovascular disease and the potential implication of JUPITER on current practice guidelines. *Clin Chem*. 2009;55(2):219-228.
43. Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation*. 2003;107(3):499-511.
44. Hong YJ, Mintz GS, Kim SW, et al. Impact of plaque rupture and elevated C-reactive protein on clinical outcome in patients with acute myocardial infarction: an intravascular ultrasound study. *J Invasiv Cardiol*. 2008;20(9):428-435.
45. Zhou J, Austin RC. Contributions of hyperhomocysteinemia and atherosclerosis: causal relationship and potential mechanisms. *Biofactors*. 2009;35(2):120-129.
46. Porter RS. *The Merck Manual of Diagnosis and Therapy*. 20th ed. Whitehouse Station, NJ: Merck Research Laboratories; 2018.
47. Ellington AA, Kullo IJ. Atherogenic lipoprotein subprofiling. *Adv Clin Chem*. 2008;46:295-317.
48. Nordestgaard BG, Chapman MJ, Ray K. Lipoprotein(a) as a cardiovascular risk factor: current status. *Eur Heart J*. 2010;31(23):2844-2853.
49. Genest J, Frohlich J, Fodor G, Mcpherson R, the Working Group on Hypercholesterolemia and Other Dyslipidemias. Recommendations for the management of dyslipidemia in the prevention of cardiovascular disease: summary of the 2003 update. *CMAJ*. 2003;169(9):921-924.
50. Nelson DL, Cox MM. *Lehninger Principles of Biochemistry*. 8th ed. New York, NY: W.H. Freeman and Company; 2021.
51. Waller DG, Sampson AP, Hitchings AW. *Medical Pharmacology and Therapeutics*. 6th ed. London: Saunders Elsevier; 2022.
52. Kingsbury KJ, Bondy G. Understanding the Essentials of Blood Lipid Metabolism. Available at http://www.medscape.com/viewarticle/451762_5. Last accessed July 11, 2022.
53. Rhoades RA, Bell DR. *Medical Physiology: Principles for Clinical Medicine*. 5th ed. Philadelphia, PA: Lippincott Williams &Wilkins; 2017.
54. Lee RG, Willingham MC, Davis MA, Skinner KA, Rudel LL. Differential expression of ACAT1 and ACAT2 among cells within liver, intestine, kidney, and adrenal of nonhuman primates. *J Lipid Res*. 2000;41(12):1991-2001.
55. Duan L-P, Wang HH, Wang DQH. Cholesterol absorption is mainly regulated by the jejunal and ileal ATP-binding cassette sterol efflux transporters Abcg5 and Abcg8 in mice. *J Lipid Res*. 2004;45(7):1312-1323.
56. Velamakanni S, Wei SL, Janvilisri T, van Veen HW. ABCG transporters: structure, substrate specificities and physiological roles: a brief overview. *J Bioenerg Biomembr*. 2007;39(5-6):465-471.

57. Cheng A, Leiter LA. Dyslipidemias and antihyperlipidemic drugs. In: Kalant H, Grant DM, Mitchell J (eds). *Principles of Medical Pharmacology*. 7th ed. Toronto: Elsevier Canada; 2007.
58. Blasiole DA, Davis RA, Attie AD. The physiological and molecular regulation of lipoprotein assembly and secretion. *Mol Biosyst*. 2007;3(9):608-619.
59. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18(6):499-502.
60. Fukuyama N, Homma K, Wakana N, et al. Validation of the Friedewald equation for evaluation of plasma LDL-cholesterol. *J Clin Biochem Nutr*. 2008;43(1):1-5.
61. Chen Y, Zhang X, Baishen P, et al. A modified formula for calculating low-density lipoprotein cholesterol values. *Lipids Health Dis*. 2010;21;9:52.
62. Puavilai W, Laorugpongse D, Deerochanawong C, Muthapongthavorn N, Srilert P. The accuracy in using modified Friedewald equation to calculate LDL from non-fast triglyceride: a pilot study. *J Med Assoc Thai*. 2009;92(2):182-187.
63. Ferraro RA, Sathiyakumar V, Blumenthal RS. Understanding Strengths and Limitations of Different Methods of LDL-C Estimation. Available at https://www.acc.org/latest-in-cardiology/articles/2019/04/02/13/21/understanding-strengths-and-limitations-of-different-methods-of-ldl-c-estimation. Last accessed July 11, 2022.
64. Miller WG, Myers GL, Sakurabayashi I, et al. Seven direct methods for measuring HDL and LDL cholesterol compared with ultracentrifugation reference measurement procedures. *Clin Chem*. 2010;56(6):977-986.
65. Martin SS, Blaha MJ, Elshazly MB, et al. Comparison of a novel method vs the Friedewald equation for estimating low-density lipoprotein cholesterol levels from the standard lipid profile. *JAMA*. 2013;310(19):2061-2068.
66. Ingelsson E, Schaefer EJ, Contois JH, et al. Clinical utility of different lipid measures for prediction of coronary heart disease in men and women. *JAMA*. 2007;298(7):776-785.
67. Baron RB. Lipid disorders. In: McPhee SJ, Papadakis MA (eds). *Current Medical Diagnosis & Treatment 2016*. New York, NY: McGraw-Hill; 2016.
68. Lemieux I, Lamarche B, Couillard C, et al. Total cholesterol/HDL cholesterol ratio vs. LDL cholesterol/HDL cholesterol ratio as indices of ischemic heart disease risk in men: the Quebec Cardiovascular Study. *Arch Intern Med*. 2001;161(22):2685-2692.
69. Fernandez ML, Webb D. The LDL to HDL cholesterol ratio as a valuable tool to evaluate coronary heart disease risk. *J Am Coll Nutr*. 2008;27(1):1-5.
70. Yongyan S, Yang Y, Zhang J, et al. The apoB100/apoAI ratio is independently associated with the severity of coronary heart disease: a cross sectional study in patients undergoing coronary angiography. *Lipids Health Dis*. 2015;14:150.
71. César TB, Oliveira MRM, Mesquita CH, Maranhão RC. High cholesterol intake modifies chylomicron metabolism in normolipidemic young men. *J Nutr*. 2006;136(4):971-976.
72. Goldstein JL, Brown MS. The LDL receptor. *Arterioscler Thromb Vasc Biol*. 2009;29(4):431-438.
73. Alldredge BK, Corelli RL, Ernst ME, et al. (eds). *Koda-Kimble and Young's Applied Therapeutics: The Clinical Use of Drugs*. 10th ed. Philadelphia, PA: Lippincott Williams &Wilkins; 2013.
74. Tarugi P, Averna M, Di Leo E, et al. Molecular diagnosis of hypobetalipoproteinemia: an ENID review. *Atherosclerosis*. 2007;195(2):e19-e27.
75. Genest J. Lipoprotein disorders and cardiovascular risk. *J Inherit Metab Dis*. 2003;26(2-3):267-287.
76. Ip S, Lichtenstein AH, Chung M, Lau J, Balk EM. Systematic review: association of low-density lipoprotein subfractions with cardiovascular outcomes. *Ann Intern Med*. 2009;150(7):474-484.
77. Prado KB, Shugg S, Backstrand JR. Low-density lipoprotein particle number predicts coronary artery calcification in asymptomatic adults at intermediate risk of cardiovascular disease. *J Clin Lipidol*. 2011;5(5):408-413.
78. Kjellmo CA, Hovland A, Lappegard KT. CVD risk stratification in the PCSK9 era: is there a role for LDL subfractions? *Diseases*. 2018;6(2):pii:E45.
79. Matfin G. Disorders of blood flow in the systemic circulation. In: Porth CM, Matfin G (eds). *Pathophysiology: Concepts of Altered Health States*. 8th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2009: 477-504.
80. Shin DJ, Osborne TF. Thyroid hormone regulation and cholesterol metabolism are connected through Sterol Regulatory Element-Binding Protein-2 (SREBP-2). *J Biol Chem*. 2003;278(36):34114-34118.
81. Nachimuthu S, Raggi P. Novel agents to manage dyslipidemias and impact atherosclerosis. *Cardiovasc Hematol Disord Drug Targets*. 2006;6(3):209-217.
82. Soutar AK, Naoumova RP. Mechanisms of disease: genetic causes of familial hypercholesterolemia. *Nat Clin Pract Cardiovasc Med*. 2007;4(4):214-225.
83. Rader DJ, Cohen J, Hobbs HH. Monogenic hypercholesterolemia: new insights in pathogenesis and treatment. *J Clin Invest*. 2003;111(12):1795-1803.
84. Goldstein JL, Hobbs HH, Brown MS. Familial hypercholesterolemia. In: Scriver CR, Beaudet AL, Sly WS, Valle D (eds). *The Metabolic and Molecular Bases of Inherited Disease*. 8th ed. New York, NY: McGraw-Hill; 2001: 2863-2913.

85. Klouche M. Estrogens in human vascular diseases. *Ann N Y Acad Sci*. 2006;1089:431-443.
86. MBewu AD, Durrington PN. Lipoprotein (a): structure, properties and possible involvement in thrombogenesis and atherogenesis. *Atherosclerosis*. 1990;85(1):1-14.
87. Tsimikas S, Tsironis LD, Tselepis AD. New insights into the role of lipoprotein(a)-associated lipoprotein-associated phospholipase A2 in atherosclerosis and cardiovascular disease. *Arterioscler Thromb Vasc Biol*. 2007;27(10):2094-2099.
88. Tabet F, Rye KA. High-density lipoproteins, inflammation and oxidative stress. *Clin Sci (Lond)*. 2009;116(2):87-98.
89. Lewis GF, Rader DJ. New insights into the regulation of HDL metabolism and reverse cholesterol transport. *Circ Res*. 2005;96: 1221-1232.
90. Kolovou GD, Mikhailidis DP, Anagnostopoulou KK, Daskalopoulou SS, Cokkinos DV. Tangier disease four decades of research: a reflection of the importance of HDL. *Curr Med Chem*. 2006;13(7):771-782.
91. Sampietro T, Puntoni M, Bigazzi F, et al. Images in cardiovascular medicine: Tangier disease in severely progressive coronary and peripheral artery disease. *Circulation*. 2009;119(20):2741-2742.
92. Navab M, Yu R, Gharavi N, et al. High-density lipoprotein: antioxidant and anti-inflammatory properties. *Curr Atheroscler Rep*. 2007;9(3):244-248.
93. Briel M, Ferreira-Gonzalez I, You JJ, et al. Association between change in high density lipoprotein cholesterol and cardiovascular disease morbidity and mortality: systematic review and meta-regression analysis. *BMJ*. 2009;338(b92):1-8.
94. Gibbons GH, Shurin SB, Mensah GA, Lauer MS. Refocusing the agenda on cardiovascular guidelines: an announcement from the National Heart, Lung, and Blood Institute. *Circulation*. 2013;128(15):1713-1715.
95. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63(25 Pt B):2889-2934.
96. O'Riordan M. New Cholesterol Guidelines Abandon LDL Targets. Available at https://www.medscape.com/viewarticle/814152. Last accessed July 11, 2022.
97. Ben-Yehuda O, DeMaria AN. LDL-cholesterol targets after the ACC/AHA 2013 guidelines: evidence that lower is better? *J Am Coll Cardiol*. 2014;64(5):495-497.
98. The Merck Manual. Dyslipidemia (Hyperlipidemia). Available at https://www.merckmanuals.com/professional/endocrine-and-metabolic-disorders/lipid-disorders/dyslipidemia. Last accessed July 11, 2022.
99. Plump AS, Lum PY. Genomics and cardiovascular drug development. *J Am Coll Cardiol*. 2009;53(13):1089-1100.
100. Yuan G, Al-Shali KZ, Hegele RA. Hypertriglyceridemia: its etiology, effects and treatment. *CMAJ*. 2007;176(8):1113-1120.
101. Hegele RA. Monogenic dyslipidemias: window on determinants of plasma lipoprotein metabolism. *Am J Hum Genet*. 2001;69(6):1161-1177.
102. Filippatos TD, Elisaf MS. Recommendations for severe hypertriglyceridemia treatment, are there new strategies? *Curr Vasc Pharmacol*. 2014;12(4):598-616.
103. Leaf DA. Chylomicronemia and the chylomicronemia syndrome: a practical approach to management. *Am J Med*. 2008;121(1): 10-12.
104. Ejarque I, Real JT, Martinez-Hervas S, et al. Evaluation of clinical diagnosis criteria of familial ligand defective apoB 100 and lipoprotein phenotype comparison between LDL receptor gene mutations affecting ligand-binding domain and the R3500Q mutation of the apoB gene in patients from a South European population. *Transl Res*. 2008;151(3):162-167.
105. Oh RC, Lanier JB. Management of hypertrygliceridemia. *Am Fam Physician*. 2007;75(9):1365-1371.
106. Aguilar-Salinas C, Gomez-Diaz R, Tusie-Luna MT. Fifty years studying hyperlipidemias: the case of familial combined hyperlipidemia. *Invest Clin*. 2010;51(2):145-158.
107. July M. Familial Hypercholesterolemia. Available at https://emedicine.medscape.com/article/121298-overview. Last accessed July 11, 2022.
108. Yuan G, Wang J, Hegele RA. Heterozygous familial hypercholesterolemia: an underrecognized cause of early cardiovascular disease. *CMAJ*. 2006;174(8):1124-1129.
109. Lexi-Comp Online. Available at https://online.lexi.com. Last accessed July 11, 2022.
110. U.S. Food and Drug Administration. Archived News Release: FDA Approves New Orphan Drug Kynamro to Treat Inherited Cholesterol Disorder. Available at https://wayback.archive-it.org/7993/20170112023906/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm337195.htm. Last accessed July 11, 2022.
111. Krauss RM, Blanche PJ, Rawlings RS, Fernstrom HS, Williams PT. Separate effects of reduced carbohydrate intake and weight loss on atherogenic dyslipidemia. *Am J Clin Nutr*. 2006;83(5):1025-1031.
112. Nissen SE, Nicholls SJ, Wolski K, et al. Effects of a potent and selective PPAR-α agonist in patients with atherogenic dyslipidemia or hypercholesterolemia: two randomized controlled trials. *JAMA*. 2007;297(12):1362-1373.
113. Rizzo M, Kotur-Stevuljevic J, Berneis K, et al. Atherogenic dyslipidemia and oxidative stress: a new look. *Transl Res*. 2009;153(5):217-223.
114. Brook RD. Mechanism of differential effects of antihypertensive agents on serum lipids. *Curr Hypertens Rep*. 2000;2(4):370-377.

115. Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(Suppl 2):S76-S99.
116. de Lorgeril M, Salen P, Martin J-L, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation*. 1999;99(6): 779-785.
117. Leaf A. Dietary Prevention of coronary heart disease: the Lyon Diet Heart Study. *Circulation*. 1999;99(6):733-735.
118. de Lorgeril M, Salen P. The Mediterranean diet: rationale and evidence for its benefit. *Curr Atheroscler Rep*. 2008;10(6):518-522.
119. Dietary Guidelines for Americans 2020-2025. Available at https://www.dietaryguidelines.gov/resources/2020-2025-dietary-guidelines-online-materials. Last accessed July 11, 2022.
120. The American Heart Association Diet and Lifestyle Recommendations. Available at https://www.heart.org/en/healthy-living/healthy-eating/eat-smart/nutrition-basics/aha-diet-and-lifestyle-recommendations. Last accessed July 11, 2022.
121. National Heart, Lung, and Blood Institute. DASH Eating Plan. Available at https://www.nhlbi.nih.gov/health-topics/dash-eating-plan. Last accessed July 11, 2022.
122. Seip RL, Semenkovich CF. Skeletal muscle lipoprotein lipase: molecular regulation and physiological effects in relation to exercise. *Exerc Sport Sci Rev*. 1998;26:191-218.
123. Aminoff MJ, Basbaum AI, Beauduy CE, et al. *Basic and Clinical Pharmacology*. 15th ed. New York, NY: McGraw-Hill; 2020.
124. Ritter JM, Flower RJ, Henderson G, et al. *Rang and Dale's Pharmacology*. 9th ed. Philadelphia, PA: Elsevier; 2019.
125. Papadakis MA, McPhee SJ (eds). *Current Medical Diagnosis and Treatment*. 61st ed. New York, NY: McGraw-Hill; 2021.
126. U.S. Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. Available at https://www.accessdata.fda.gov/scripts/cder/daf/. Last accessed July 11, 2022.
127. Thomson. *Physicians' Desk Reference*. 71st ed. Toronto: Thomson Reuters; 2017.
128. Compendium of Pharmaceuticals and Specialties. *The Canadian Drug Reference for Health Professionals*. Ottawa: Canadian Pharmacists Association; 2013.
129. Einarsson K, Ericsson S, Ewerth S, et al. Bile acid sequestrants: mechanisms of action on bile acid and cholesterol metabolism. *Eur J Clin Pharmacol*. 1991;40(Suppl 1):S53-S58.
130. Gilardi F, Mitro N, Godio C, et al. The pharmacological exploitation of cholesterol 7alpha-hydroxylase, the key enzyme in bile acid synthesis: from binding resins to chromatin remodelling to reduce plasma cholesterol. *Pharmacol Ther*. 2007;116(3):449-472.
131. Hou R, Goldberg AC. Lowering low-density lipoprotein cholesterol: statins, ezetimibe, bile acid sequestrants, and combinations: comparative efficacy and safety. *Endocrinol Metab Clin North Am*. 2009;38(1):79-97.
132. Bays HE. Long-term (52-78 weeks) treatment with colesevelam HCl added to metformin therapy in type 2 diabetes mellitus patients. *Diabetes Metabl Syndr Obes*. 2012;5:125-134.
133. Daily Med. Available at https://dailymed.nlm.nih.gov/dailymed/index.cfm. Last accessed July 11, 2022.
134. Cannon CP, Blazing MA, Giugliano RP. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015; 372:2387-2397.
135. Nordqvist C. Liptruzet Approved by FDA to Cut Cholesterol, Despite Criticism by Cardiologists. Available a22https://www.medicalnewstoday.com/articles/260088. Last accessed July 11, 2019.
136. Drugs.com. Ezetimibe and Atorvastatin Tablets. Available at https://www.drugs.com/drug-shortages/ezetimibe-and-atorvastatin-tablets-169. Last accessed July 11, 2022.
137. Davis HR Jr, Basso F, Hoos LM, Tetzloff G, Lally SM, Altmann SW. Cholesterol homeostasis by the intestine: lessons from Niemann-Pick C1 Like 1 (NPC1L1). *Atheroscler Suppl*. 2008;9(2):77-81.
138. Kidambi S, Patel SB. Cholesterol and non-cholesterol sterol transporters: ABCG5, ABCG8 and NPC1L1: a review. *Xenobiotica*. 2008;38(7/8):1119-1139.
139. Staels B, Auwerx J. Regulation of apo A-I gene expression by fibrates. *Atherosclerosis*. 1998;137(Suppl):S19-S23.
140. Harper CR, Jacobson TA. The broad spectrum of statin myopathy: from myalgia to rhabdomyolysis. *Curr Opin Lipidol*. 2007;18(4):401-408.
141. Jones PH. Comparing HMG-CoA reductase inhibitors. *Clin Cardiol*. 2003;26(1 Suppl 1):I15-I20.
142. Wang CY, Liu PY, Liao JK. Pleiotropic effects of statin therapy: molecular mechanisms and clinical results. *Trends Mol Med*. 2008;14(1):37-44.
143. Tang TY, Howarth SP, Miller SR, et al. The ATHEROMA (Atorvastatin Therapy: Effects on Reduction of Macrophage Activity) Study: evaluation using ultrasmall superparamagnetic iron oxide-enhanced magnetic resonance imaging in carotid disease. *J Am Coll Cardiol*. 2009;53(22):2039-2050.
144. Kwak B, Mulhaupt F, Myit S, Mach F. Statins as a newly recognized type of immunomodulator. *Nat Med*. 2000;6(12):1399-1402.
145. Haag MD, Hofman A, Koudstaal PJ, Stricker BH, Breteler MM. Statins are associated with a reduced risk of Alzheimer disease regardless of lipophilicity. *J Neurol Neurosurg Psychiatry*. 2009;80(1):13-17.

146. Hendrie HC, Hake A, Lane K, et al. Stain use, incident dementia and Alzheimer disease in elderly African Americans. *Ethn Dis*. 2015;25(3):345-354.

147. Padial LR. Ezetimibe plus simvastatin cardiovascular outcomes study program. *Expert Rev Cardiovasc Ther*. 2008;6(1):17-25.

148. Tikkanen MJ. Statins: within-group comparisons, statin escape and combination therapy. *Curr Opin Lipidol*. 1996;7(6):385-388.

149. Insull W Jr. Clinical utility of bile acid sequestrants in the treatment of dyslipidemia: a scientific review. *South Med J*. 2006;99(3):257-273.

150. Rodriguez-Yañez M, Agulla J, Rodriguez-González R, Sobrino T, Castillo J. Statins and stroke. *Ther Adv Cardiovasc Dis*. 2008;2(3):157-166.

151. Fuentes B, Martínez-Sánchez P, Díez-Tejedor E. Lipid-lowering drugs in ischemic stroke prevention and their influence on acute stroke outcome. *Cerebrovasc Dis*. 2009;27(Suppl 1):126-133.

152. Amarenco P, Labreuche J. Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention. *Lancet Neurol*. 2009;8(5):453-463.

153. Gaist D, García Rodríguez LA, Huerta C, Hallas J, Sindrup SH. Are users of lipid-lowering drugs at increased risk of peripheral neuropathy? *Eur J Clin Pharmacol*. 2001;56(12):931-933.

154. Stein EA, Ballantyne CM, Windler E, et al. A randomized, double-blind, double dummy comparison of efficacy and tolerability of fluvastatin XL 80 mg alone, ezetimibe alone, and the combination of fluvastatin XL 80 mg with ezetimibe in patients with a history of muscle related side effects with other statins. *Circulation*. 2006;101(4):490-496.

155. U.S. Food and Drug Administration. FDA Drug Safety Communication: Important Safety Label Changes to Cholesterol-Lowering Statin Drugs. Available at https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-important-safety-label-changes-cholesterol-lowering-statin-drugs. Last accessed July 11, 2022.

156. ConsumerMedSafety.org. FDA Expands Advice on Statin Risk. Available at https://www.consumermedsafety.org/latest-fda-medication-alerts/item/532-fda-expands-advice-on-statin-risks. Last accessed July 11, 2022.

157. Keating AJ, Campbell KB, Guyton JR. Intermittent nondaily dosing strategies in patients with previous statin-induced myopathy. *Ann Pharmacother*. 2013;47(3):398-404.

158. Bogsrud MP, Langlset G, Ose L, et al. No effect of combined coenzyme Q10 and selenium supplementation on atorvastatin- induced myopathy. *Scand Cardiovasc J*. 2013;47(2):80-87.

159. Qu H, Guo M, Chai H, Wang WT, Gao ZY, Shi DZ. Effects of coenzyme Q10 on statin-induced myopathy: an updated meta-analysis of randomized controlled trials. *J Am Heart Assoc*. 2018;7(19):e009835.

160. Taylor BA, Lorson L, White CM, Thompson PD. A randomized trial of coenzyme Q10 in patients with confirmed statin myopathy. *Atherosclerosis*. 2015;238(2):329-335.

161. Dirks AJ, Jones KM. Statin-induced apoptosis and skeletal myopathy. *Am J Physiol Cell Physiol*. 2006;291(6):C1208-C1212.

162. Omar MA, Wilson JP, Cox TS. Rhabdomyolysis and HMG-CoA reductase inhibitors. *Ann Pharmacother*. 2001;35(9):1096-1107.

163. Bottorff MB. Statin safety and drug interactions: clinical implications. *Am J Cardiol*. 2006;97(8A):27C-31C.

164. McKenney JM, Davidson MH, Jacobson TA, Guyton JR. Final conclusions and recommendations of the National Lipid Association Statin Safety Assessment Task Force. *Am J Cardiol*. 2006;97(8A):89C-94C.

165. Gille A, Bodor ET, Ahmed K, Offermanns S. Nicotinic acid: pharmacological effects and mechanisms of action. *Annu Rev Pharmacol Toxicol*. 2008;48:79-106.

166. Hathcock JN. Vitamin and Mineral Safety. 3rd ed. Available at http://www.crnusa.org/resources/vitamin-mineral-safety. Last accessed July 11, 2022.

167. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2017 focused update of the 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol*. 2017;70(14):1785-1822.

168. Boden WE, Sidhu MS, Toth PP. The therapeutic role of niacin in dyslipidemia management. *J Cardiovasc Pharmacol Ther*. 2014;19(2):141-158.

169. Garg A, Sharma A, Krishnamoorthy P, et al. Role of niacin in current clinical practice: a systematic review. *Am J Med*. 2017;130(2):173-187.

170. Dyerberg J, Bang HO, Hjorne N. Fatty acid composition of the plasma lipids in Greenland Eskimos. *Am J Clin Nutr*. 1975;28(9):958-966.

171. Dyerberg J. Coronary heart disease in Greenland Inuit: a paradox. Implications for western diet patterns. *Arctic Med Res*. 1989;48(2):47-54.

172. Dyerberg J, Bang HO. A hypothesis on the development of acute myocardial infarction in Greenlanders. *Scand J Clin Lab Invest*. 1982;161(Suppl):7-13.

173. Bays HE, Tighe AP, Sadovsky R, Davidson MH. Prescription omega-3 fatty acids and their lipid effects: physiologic mechanisms of action and clinical implications. *Expert Rev Cardiovasc Ther*. 2008;6(3):391-409.

174. Covington MB. Omega-3 fatty acids. *Am Fam Physician*. 2004;70(1):133-140.
175. Riediger ND, Othman RA, Suh M, Moghadasian M. A systematic review of the roles of n-3 fatty acids in health and disease. *J Am Diet Assoc*. 2009;109(4):668-679.
176. Russo GL. Dietary n-6 and n-3 polyunsaturated fatty acids: from biochemistry to clinical implications in cardiovascular prevention. *Biochem Pharmacol*. 2009;77(6):937-946.
177. Harris WS, Miller M, Tighe AP, Davidson MH, Schaefer EJ. Omega-3 fatty acids and coronary heart disease risk: clinical and mechanistic perspectives. *Atherosclerosis*. 2008;197(1):12-24.
178. Harrison N, Abhyankar B. The mechanism of action of omega-3 fatty acids in secondary prevention of myocardial infarction. *Curr Med Res Opin*. 2005;21(1):95-100.
179. Davidson MH. Mechanisms for the hypotriglyceridemic effect of marine omega-3 fatty acids. *Am J Cardiol*. 2006;98(4A):27i-33i.
180. Psota TL, Gebauer SK, Kris-Etherton P. Dietary omega-3 fatty acid intake and cardiovascular risk. *Am J Cardiol*. 2006;98(4 Suppl 1):3i-18i.
181. Reiffel JA, McDonald A. Antiarrhythmic effects of omega-3 fatty acids. *Am J Cardiol*. 2006;98(4A):50-60.
182. Robinson JG, Stone NJ. Antiatherosclerotic and antithrombotic effects of omega-3 fatty acids. *Am J Cardiol*. 2006;98(4A):39i-49i.
183. von Schacky C, Harris WS. Cardiovascular benefits of omega-3 fatty acids. *Cardiovasc Res*. 2007;73(2):310-315.
184. Jacobson TA. Secondary prevention of coronary artery disease with omega-3 fatty acids. *Am J Cardiol*. 2006;98(4A):61i-70i.
185. Biscione F, Pignalberi C, Totteri A, Messina F, Altamura G. Cardiovascular effects of omega-3 free fatty acids. *Curr Vasc Pharmacol*. 2007;5(2):163-172.
186. Boriani G, Valzania C, Diemberger I, et al. Potential of non-antiarrhythmic drugs to provide an innovative upstream approach to the pharmacological prevention of sudden cardiac death. *Expert Opin Investig Drugs*. 2007;16(5):605-623.
187. Cundiff DK, Lanou AJ, Nigg CR. Relation of omega-3 fatty acid intake to other dietary factors known to reduce coronary heart disease risk. *Am J Cardiol*. 2007;99(9):1230-1233.
188. Jain AP Aggarwal KK, Zhang PY. Omega-3 fatty acids and cardiovascular disease. *Eur Rev Med Pharmacol Sci*. 2015;19(3):441-445.
189. U.S. Food and Drug Administration. Product Monograph: Lovaza. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021654s041lbl.pdf. Last accessed July 11, 2022.
190. Yokoyama M, Origasa H, Matsuzaki M, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet*. 2007;369(9567):1090-1098.
191. Mattar M, Obeid O. Fish oil and the management of hypertriglyceridemia. *Nutr Health*. 2009;20(1):41-49.
192. Fialkow J. Omega-3 fatty acid formulations in cardiovascular disease: dietary supplements are not substitutes for prescription products. *Am J Cardiovasc Drugs*. 2016;16(4):229-239.
193. U.S. Food and Drug Administration. NDA Approval Letter: Epanova. Available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/205060Orig1s000ltr.pdf. Last accessed July 11, 2022.
194. Lavie CJ, Milani RV, Mehra MR, Ventura HO. Omega-3 polyunsaturated fatty acids and cardiovascular diseases. *J Am Coll Cardiol*. 2009;54(7):585-594.
195. Toth PP, Dayspring TD, Pokrywka GS. Drug therapy for hypertriglyceridemia: fibrates and omega-3 fatty acids. *Curr Atheroscler Rep*. 2009;11(1):71-79.
196. U.S. Food and Drug Administration. Archive: What You Need to Know about Mercury in Fish and Shellfish. Available at https://wayback.archive-it.org/7993/20170723051703/https://www.fda.gov/Food/FoodborneIllnessContaminants/Metals/ucm351781.htm. Last accessed July 11, 2022.
197. U.S. Food and Drug Administration. Archive: Safety: Lovaza (Omega-3-Acid Ethyl Esters) Capsules. Available at https://wayback.archive-it.org/7993/20170112174505/http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm186892.htm. Last accessed July 11, 2022.
198. Piironen V, Toivo J, Puupponen-Pimia R, Lampi AM. Plant sterols in vegetables, fruits, and berries. *J Sci Food Agric*. 2003;83(4):330-337.
199. Sanclemente T, Marques-Lopes I, Puzo J, García-Otín AL. Role of naturally-occurring plant sterols on intestinal cholesterol absorption and plasmatic levels. *J Physiol Biochem*. 2009;65(1):87-98.
200. Harris WS, Mozaffarian D, Rimm E, et al. Omega-6 fatty acids and risk for cardiovascular disease: a science advisory from the American Heart Association Nutrition Subcommittee of the Council on Nutrition, Physical Activity, and Metabolism; Council on Cardiovascular Nursing; and Council on Epidemiology and Prevention. *Circulation*. 2009;119(6):902-907.
201. Jones PJH, AbuMweis SS. Phytosterols as functional food ingredients: linkages to cardiovascular disease and cancer. *Curr Opin Clin Nutr Metab Care*. 2009;12(2):147-151.
202. Bays H, Stein EA. Pharmacotherapy for dyslipidaemia-current therapies and future agents. *Expert Opin Pharmacother*. 2003;4(11):1901-1938.
203. Bodor ET, Offermanns S. Nicotinic acid: an old drug with a promising future. *Br J Pharmacol*. 2008;153(Suppl 1):S68-S75.

204. Davidson MH. Novel nonstatin strategies to lower low-density lipoprotein cholesterol. *Curr Atheroscler Rep*. 2009;11(1):67-70.

205. Stein EA. Other therapies for reducing low-density lipoprotein cholesterol: medications in development. *Endocrinol Metab Clin North Am*. 2009;38(1):99-119.

206. Ferri N. Proprotein convertase subtilisin/kexin type 9: from the discovery to the development of new therapies for cardiovascular diseases. *Scientifica*. 2012;2012:1927352.

207. Seiki S, Frishman WH. Pharmacologic inhibition of squalene synthase and other downstream enzymes of the cholesterol synthesis pathway: a new therapeutic approach to treatment of hypercholesterolemia. *Cardiol Rev*. 2009;17(2):70-76.

208. Stein EA, Bays H, O'Brien D, Pedicano J, Piper E, Spezzi A. Lapaquistat acetate: development of a squalene synthase inhibitor for the treatment of hypercholesterolemia. *Circulation*. 2011;123(18):1974-1985.

209. van Heek M, Farley C, Compton DS, et al. Comparison of the activity and disposition of the novel cholesterol absorption inhibitor, SCH58235, and its glucuronide, SCH60663. *Br J Pharmacol*. 2000;129(8):1748-1754.

210. ClinicalTrials.gov. Available at https://www.clinicaltrials.gov. Last accessed July 11, 2022.

211. Samaha FF, McKenney J, Bloedon LT, Sasiela WJ, Rader DJ. Inhibition of microsomal triglyceride transfer protein alone or with ezetimibe in patients with moderate hypercholesterolemia. *Nat Clin Pract Cardiovasc Med*. 2008;5(8):497-505.

212. Liu X, Men P, Wang Y, Zhai S, Zhao Z, Liu G. Efficacy and safety of lomitapide in hypercholesterolemia. *Am J Cardiovasc Drugs*. 2017;17(4):299-309.

213. Khoury E, Brisson D, Roy N, Tremblay G, Gaudet D. Review of the long-term safety of lomitapide: a microsomal triglycerides transfer protein inhibitor for treating homozygous familial hypercholesterolemia. *Expert Opin Drug Saf*. 2019;18(5):403-414.

214. Kastelein JJ, Wedel MK, Baker BF, et al. Potent reduction of apolipoprotein B and low-density lipoprotein cholesterol by short- term administration of an antisense inhibitor of apolipoprotein B. *Circulation*. 2006;114(16):1729-1735.

215. Canuel M, Sun X, Asselin MC, Paramithiotis E, Prat A, Seidah NG. Proprotein convertase subtilisin/kexin type 9 (PCSK9) can mediate degradation of the low density lipoprotein receptor-related protein 1 (LRP-1). *PLoS One*. 2013;8(5):e64145.

216. Duff CJ, Hooper NM. PCSK9: an emerging target for treatment of hypercholesterolemia. *Expert Opin Ther Targets*. 2011;15(2):157-168.

217. Mousavi SA, Berge KE, Leren TP, The unique role of proprotein convertase subtilisin/kexin 9 in cholesterol homeostatis. *J Intern Med*. 2009;266(6):507-519.

218. Cameron J, Boqsrud MP, Tveten K, et al. Serum levels of proprotein convertase subtilisin/kexin type 9 in subject with familial hypercholesterolemia indicate that proprotein convertase subtilisin/kexin type 9 is cleared from plasma by low-density lipoprotein receptor-independent pathways. *Transl Res*. 2012;160(2):125-130.

219. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol*. 2016;68(1):92-125.

220. Fodor G. Primary prevention of CVD: treating dyslipidaemia. *BMJ Clin Evid*. 2008;pii:0215.

221. Goff DC Jr, Labarthe DR, Howard G, Russel GB. Primary prevention of high blood cholesterol concentrations in the United States. *Arch Intern Med*. 2002;162(8):913-919.

222. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376(9753):1670-1681.

223. Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet*. 2016;388(10059):2532-2561.

224. Haskell WL, Alderman EL, Fair JM, et al. Effects of intensive multiple risk factor reduction on coronary atherosclerosis and clinical cardiac events in men and women with coronary artery disease. The Stanford Coronary Risk Intervention Project (SCRIP). *Circulation*. 1994;89(3):975-990.

225. Fletcher B, Berra K, Ades P, et al. Managing abnormal blood lipids. *Circulation*. 2005;112(20):3184-3209.

226. DeBusk RF, Miller NH, Superko HR, et al. A case-management system for coronary risk factor modification after acute myocardial infarction. *Ann Intern Med*. 1994;120(9):721-729.

227. Goff DC, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines *Circulation*. 2014;129(Suppl 2):S49-S73.

228. Mora S, Wenger NK, Cook NR, et al. Evaluation of the pooled cohort risk equations for cardiovascular risk prediction in a multiethnic cohort from the Women's Health Initiative. *JAMA Intern Med*. 2018;178(9):1231-1240.

229. Stiles S. New AHA/ACC Cholesterol Treatment Guideline Expands Role of LDL Targets. Available at https://www.medscape.com/viewarticle/904736. Last accessed July 11, 2022.

230. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III): final report. *Circulation*. 2002;106(25):3143-3421.

231. Pallazola V, Cardoso R, Blumenthal RS, Martin SS. Was the Juice Worth the Squeeze? Understanding the New 2018 AHA/ACC Cholesterol Guideline. Available at https://www.acc.org/latest-in-cardiology/articles/2018/11/14/10/48/was-the-juice-worth-the-squeeze. Last accessed July 11, 2022.

232. U.S. Food and Drug Administration. FDA Approves Use of Drug to Reduce Risk of Cardiovascular Events in Certain Adult Patient Groups. Available at https://www.fda.gov/news-events/press-announcements/fda-approves-use-drug-reduce-risk-cardiovascular-events-certain-adult-patient-groups. Last accessed July 11, 2022.

233. U.S. Food and Drug Administration. Nexletol (Bempedoic Acid) Prescribing Information. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/211616s000lbl.pdf. Last accessed July 11, 2022.

234. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart disease and stroke statistics—2022 update: a report from the American Heart Association. *Circulation*. 2022;145:e153-e639.

235. Michos ED, McEvoy JW, Blumenthal RS. Lipid management for the prevention of atherosclerotic cardiovascular disease. *N Engl J Med*. 2019;381:1557-1567.

236. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;74:1376-1414.

237. U.S. Department of Veterans Affairs. Clinical Practice Guidelines: The Management of Dyslipidemia for Cardiovascular Risk Reduction. Available at https://www.healthquality.va.gov/guidelines/CD/lipids/VADoDDyslipidemiaCPGProviderSummary5087172020.pdf. Last accessed July 11, 2022.

238. Arnold MJ, O'Malley PG. Key recommendations on managing dyslipidemia for cardiovascular risk reduction: stopping where the evidence does. *Am Fam Physician*. 2021;103:456-458.

239. Marrs JC, Anderson SL. Bempedoic acid for the treatment of dyslipidemia. *Drugs Context*. 2020;9:2020-6-5.

240. Schroor MM, Sennels HP, Fahrenkrug J, Jørgensen HL, Plat J, MensinkRP. Diurnal variation of markers for cholesterol synthesis, cholesterol absorption, and bile acid synthesis: a systematic review and the Bispebjerg Study of Diurnal Variations. *Nutrients*. 2019;11(7):1439.

241. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145(18): e895-e1032.

242. Givertz MM, Colucci WS. Pharmacologic Therapy of Heart Failure with Reduced Ejection Fraction: Mechanism of Action. Available at https://www.uptodate.com/contents/pharmacologic-therapy-of-heart-failure-with-reduced-ejection-fraction-mechanisms-of-action. Last accessed July 26, 2022.

243. McDonald M, Virani S, Chan M, et al. CCS/CHFS heart failure guidelines update: defining a new pharmacologic standard of care for heart failure with reduced ejection fraction. *Can J Cardiol*. 2021;37(4):531-546.

## *Evidence-Based Practice Recommendations Citations*

Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;139(25):e1082-e1143. Available at http://www.onlinejacc.org/content/73/24/e285?_ga=2.118995977.141815126.1563751668-1264536891.1558548868. Last accessed July 25, 2022.

U.S. Preventive Services Task Force. Statin Use for the Primary Prevention of Cardiovascular Disease in Adults: Preventive Medication. Available at https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/statin-use-in-adults-preventive-medication. Last accessed July 25, 2022.

Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the primary prevention of cardiovascular disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140:e563-e595. Available at https://www.ahajournals.org/doi/pdf/10.1161/CIR.0000000000000677. Last accessed July 25, 2022.