# Clinical Lipid Management

Second Edition

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# Introduction

Cholesterol remains a fundamental causal factor in the development of atherosclerotic cardiovascular disease (ASCVD). This book provides a concise overview of the clinical management of cholesterol in adults, giving clinicians the key information needed to prevent ASCVD events and manage common lipid disorders.

The greatest emphasis is placed on treatment recommendations supported by strong to moderate evidence from randomized trials of drug therapy. Therefore, the main recommendations for evidence-based patient care come from the *2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol* (referred to as the 2018 multi-society cholesterol guideline).

Because not all clinical questions can be answered from this body of evidence, expert guidance is provided based on the evidence available from clinical trials, meta-analyses of randomized trials that were not included in the dataset considered for the 2018 multi-society cholesterol guideline, post hoc analyses of randomized trials, analyses of observational clinical datasets, and, in rare instances, epidemiologic studies.

## Historical Overview

Over 150 years ago, Virchow and colleagues described the accumulation of lipid as the hallmark of atherosclerotic plaque. Since then, an extensive body of epidemiologic evidence has shown a direct relationship between blood cholesterol levels and ASCVD, a relationship magnified in the presence of other cardiovascular risk factors. The causal role of cholesterol in atherosclerosis has been proven in numerous clinical trials showing that lowering total and low-density lipoprotein cholesterol

(LDL-C) slows the development of atherosclerosis and prevents clinical events.

In the 1970s and 1980s, the first clinical trials of lipid-modifying drug therapy (using niacin, gemfibrozil, or bile acid sequestrants) were performed in high-risk populations with ASCVD—men with severe hypercholesterolemia, with and without clinical coronary artery disease (CAD).

Statins were developed in the 1980s and have gone on to revolutionize the treatment of cholesterol to prevent ASCVD. Based on an extensive body of evidence from at least 28 randomized trials in a broad range of populations, statins are considered first-line therapy for ASCVD prevention.

The first National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP I) was published in 1988 and made recommendations regarding screening, desirable normal and high blood cholesterol levels, and dietary treatment. As results from the early randomized trials became available, updated recommendations were provided in ATP II in 1993. ATP II recommended using risk status to guide the intensity of lipid-lowering therapy, with an emphasis on setting an LDL-C goal of <100 mg/dL for those with clinical ASCVD (secondary prevention). Step I and II cholesterol-lowering diets were recommended.

Numerous primary and secondary prevention statin trials were completed in the late 1990s and early 2000s, guiding the development of ATP III, published in 2001 and updated in 2004. ATP III again used risk status to guide the intensity of therapy and added numerous LDL-C and non–high-density lipoprotein cholesterol (non–HDL-C) treatment goals, depending on the level of risk. The concept of metabolic syndrome was introduced and therapeutic lifestyle changes (diet, physical activity, and weight control) were strongly emphasized. Statins were recommended as first-line therapy, but the use of other lipid-modifying drugs was encouraged to reach LDL-C and non–HDL-C goals.

## 2013 ACC/AHA Cholesterol Guideline

In 2008, the National Heart, Lung and Blood Institute (NHLBI) convened ATP IV, and charged the Panel with developing an evidence-

based cholesterol guideline for reducing the risk of cardiovascular events using evidence from randomized, controlled trials (RCTs). The Panel undertook a rigorous systematic review and guideline development process that adhered to principles set forth by the Institute of Medicine in *Clinical Practice Guidelines We Can Trust*. These recommendations were transitioned to the American College of Cardiology/American Heart Association (ACC/AHA) for implementation, as the 2013 ACC/AHA *Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Disease (ASCVD) Risk*. This guideline was supported by accompanying ACC/AHA guidelines for the assessment of ASCVD risk, lifestyle, and obesity.

The 2013 ACC/AHA cholesterol guideline introduced a new paradigm for cholesterol treatment focused on the potential to receive a net ASCVD risk reduction benefit from drug therapy. It provides recommendations for the use of statin, as well as nonstatin, therapy in groups of patients most likely to benefit. This paradigm moves away from LDL-C and non–HDL-C treatment goals used in previous guidelines. As is typical for a new paradigm, the 2013 ACC/AHA cholesterol guideline was initially met with some criticism, primarily from lipidologists concerned by the move away from LDL-C and non–HDL-C treatment targets. However, analyses subsequent to the release of the 2013 ACC/AHA cholesterol guideline have overwhelmingly supported the 2013 ACC/AHA guideline's new paradigm focused on net benefit from drug therapy rather than cholesterol goal achievement.

## 2018 Multi-Society Cholesterol Guideline

The current guideline on cholesterol management was released in 2018, as a collaboration between the ACC, the AHA, and ten other professional societies. Importantly, the paradigm of not treating to specific LDL-C targets, first introduced in the 2013 ACC/AHA guideline, was maintained. The primary aim of the 2018 multi-society guideline was to provide guidance updated with data that became available since the release of the 2013 ACC/AHA guideline. This included primarily more information on the appropriate uses of nonstatin therapies (ezetimibe and PCSK9 inhibitors), a new ASCVD risk categorization, additional risk factor

considerations, categorization of ASCVD into very high risk and not very high risk, and more information on specific groups, including children and racial/ethnic groups. The 2018 multi-society guideline also included specific thresholds of when to consider nonstatins in addition to statin therapy.

The evidence supporting the 2018 multi-society cholesterol guideline recommendations is reviewed in subsequent chapters. The most important randomized trials, meta-analyses, and other analyses published after the 2018 multi-society cholesterol guideline are also reviewed, along with their implications for clinical practice.

## Management of Patients Beyond the 2018 Multi-Society Guideline

The 2018 multi-society cholesterol guideline focused on the strongest available evidence to guide pharmacologic treatment of cholesterol to reduce ASCVD risk. Clinicians at a minimum should be maximizing statin therapy in the patients most likely to benefit based on the evidence from clinical trials. This book will also provide clinical management recommendations for the many groups of patients who were not included in randomized cardiovascular outcomes trials, who cannot tolerate maximal statin therapy, or statin-treated patients who might benefit from additional LDL-C lowering. Expert guidance for managing hypertriglyceridemia and patients with familial hyperlipidemias is also provided.

## Evolving Role of Nonstatins in ASCVD Prevention

Statins are first-line therapy for ASCVD risk reduction, yet some patients could benefit from further LDL-C lowering with a nonstatin to reduce their ASCVD risk. Information on individual nonstatins is presented in dedicated chapters. Recommendations from the 2018 multi-society guideline and the 2022 ACC Expert Consensus Decision Pathway on nonstatins are presented. Additionally, a framework based on the potential

for a net ASCVD risk reduction benefit is provided to aid decisions on whether to initiate nonstatin therapy.

## Other Highlights

Other highlights include:

- *Bottom Line feature*: Summarizes the essential clinical take-home recommendations for the section.
- *Lipid and lipoprotein basics*: A basic introduction to lipid and lipoprotein metabolism highlighting the most important concepts for understanding familial lipid disorders.
- *Familial lipid disorders*: Clinicians should be familiar with familial hypercholesterolemia diagnosis and screening. For those who are interested and for reference, a general overview of lipoproteins and their role in atherogenesis is provided, as is a brief description of less common genetic lipid disorders.
- *Lifestyle recommendations*: Lifestyle is the foundation of ASCVD risk reduction efforts. Current recommendations for diet, physical activity, and weight control are reviewed.
- *Risk assessment for primary prevention*: Evidence-based approaches to estimating and refining a patient's ASCVD risk estimate are provided that may enhance the Clinician-Patient Discussion.
- *Special issues in women, older adults, and race/ethnicity*: Less randomized trial evidence is available for women, individuals >75 years of age, and non-Caucasian populations. Issues regarding safety and efficacy are discussed and treatment approaches based on the best available evidence are discussed.
- *Lipid management in special clinical populations*: Lipid management can be challenging in some groups of patients due to increased ASCVD risk, adverse effects of drug therapy and increased safety concerns due to drug-drug interaction. Expert guidance is based on the available evidence.
- *Comparative effectiveness of lipid drug therapy*: The comparative efficacy and safety of currently available statin and nonstatin drugs are

provided to inform drug choice decision. For easy reference, appropriate uses, mechanisms of action, lipid-modifying efficacy, cardiovascular benefits, and safety for each class of lipid-modifying drugs are reviewed.

- *Role for PCSK9 inhibitors*: Data from phase 2 and 3 trials and FDA-approved indications are reviewed and the clinical application of these drugs is discussed.
- *Management of hypertriglyceridemia*: A straightforward and evidence-based approach to triglycerides is provided.

## RECOMMENDED READINGS


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. *Circulation*. 2019;139(25):e1082-e1143.

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CHAPTER **2**

# Lipid and Lipoprotein Basics

## Normal Lipid Physiology

Lipids are critical structural components of cells and circulating plasma lipoproteins and play important regulatory roles in the body. Cholesterol and triglycerides are the lipids of greatest clinical importance.

### Cholesterol

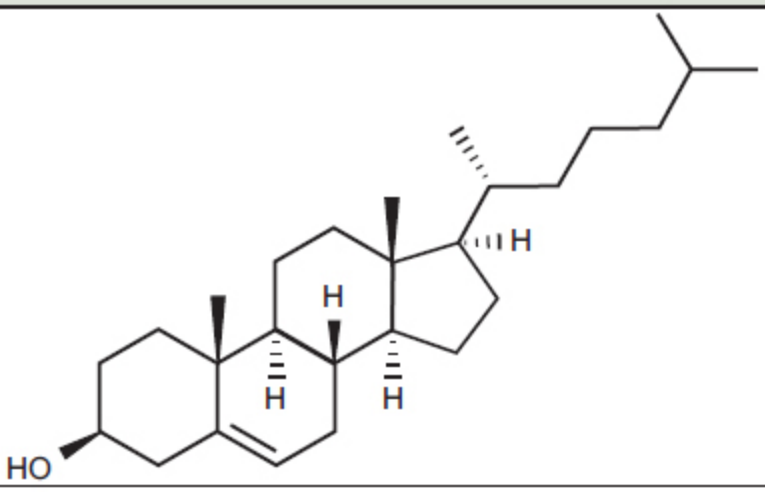
Cholesterol is a sterol synthesized by all animal cells (**Figure 2.1**). About 25% of cholesterol is synthesized in the liver. The adrenal glands, reproductive organs, and intestines also have higher rates of cholesterol synthesis. Synthesis begins with one molecule each of acetyl CoA and acetoacetyl-CoA, which are metabolized through multiple steps to cholesterol (**Figure 2.2**). The rate-limiting step in cholesterol synthesis is the reduction to mevalonate by 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, the target of statins. Downstream metabolites of mevalonate include several biologically active molecules. Cholesterol synthesis is regulated by intracellular cholesterol levels primarily via sterol regulator element-binding proteins (SREBP) 1 and 2.

Cholesterol is largely transported and stored as cholesteryl ester. Cholesteryl esters are taken up by macrophage foam cells, the initiating step in the development of atherosclerosis, with continued accumulation contributing to atherosclerotic plaque growth.

Cholesterol is the backbone for the biosynthesis of steroid hormones. Cholesterol is also required to maintain cell membrane structural integrity and fluidity (**Figure 2.3**). Human cell membranes are composed of a bilayer of phospholipids (which contain 2-fatty acid chains) interspersed with proteins and other structures. The hydroxyl group of the cholesterol molecule interacts with the polar head groups of membrane phospholipids

and sphingolipids. The bulky steroid group and hydrocarbon chain are embedded in the membrane with the nonpolar fatty acids of other lipids. Cholesterol also plays a critical role in intracellular transport via endocytosis and cell signaling via lipid rafts that bring receptor proteins into close proximity with messenger molecules (**Figure 2.3**). Cholesterol is a chief component of the myelin sheath, providing insulation for more efficient nerve conduction. It is possible that some of the "pleiotropic" effects of statins are a downstream result of alterations in cholesterol levels affecting these other functions.

**FIGURE 2.1** — Cholesterol Structure

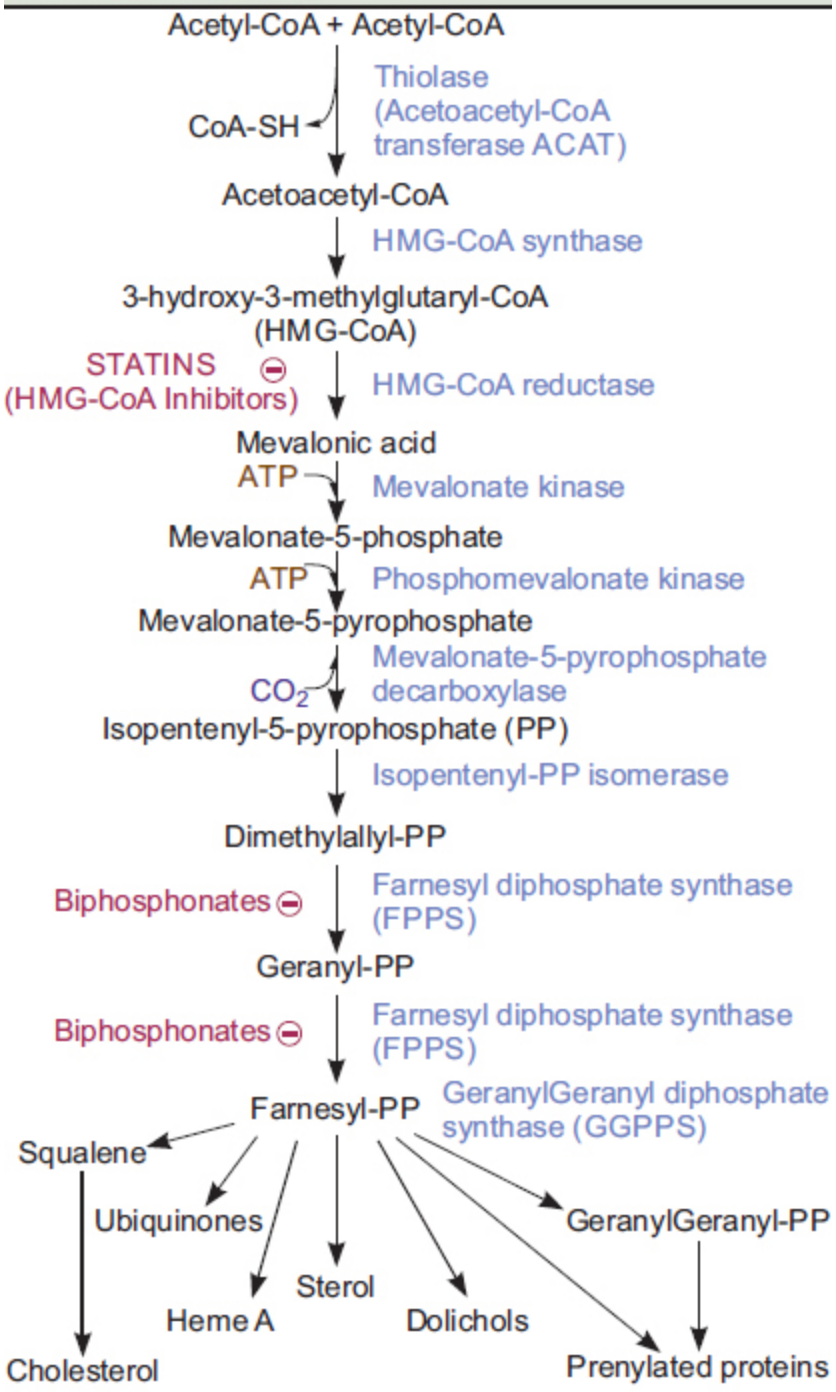



Cholesterol. Wikipedia Web site. http://en.wikipedia.org/wiki/cholesterol. Accessed January 25, 2023.

Adults synthesize about 100 mg of cholesterol per day. The average daily dietary intake of cholesterol is about 300 mg. Cholesterol is recycled in the body. Most cholesterol inside of cells is esterified. Non-esterified cholesterol is secreted in the bile and about 50% is reabsorbed back into the bloodstream in the small intestine.

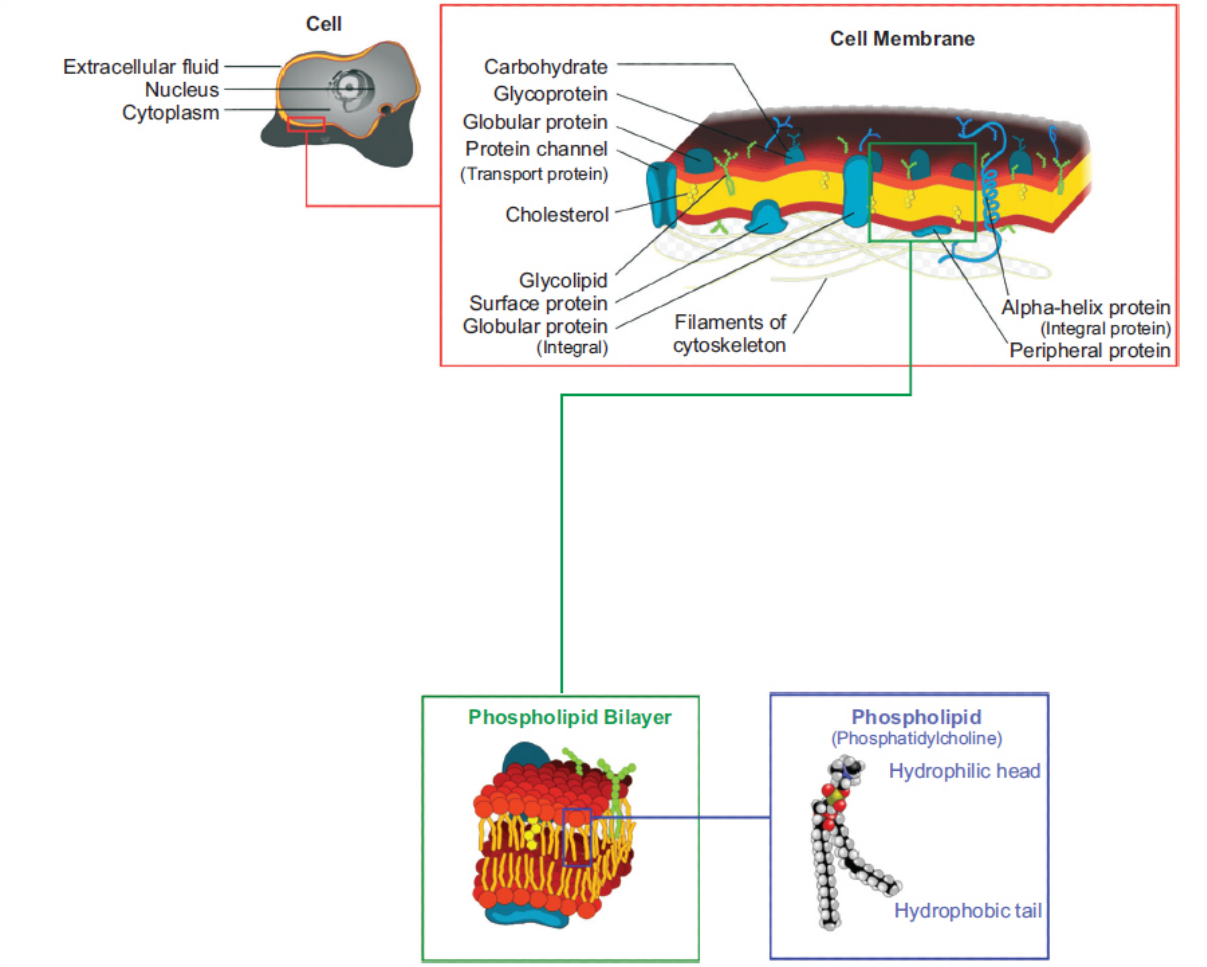
Cholesterol is largely hydrophobic and therefore must be transported in the blood by lipoproteins. Lipoproteins are complex particles, with the water soluble proteins and polar lipid head facing outward, and the water insoluble cholesteryl esters and fatty acid tails of the triglyceride molecules facing inward. The primary circulating lipoprotein transporting cholesterol to the body is low-density lipoprotein (LDL). High-density lipoproteins (HDL) transport cholesterol from the periphery to the liver.

**FIGURE 2.2** — Mevalonate Pathway for Cholesterol Synthesis




Mevalonate pathway. Wikipedia Web site. http://en.wikipedia.org/wiki/Mevalonate_pathway. Accessed January 25, 2023.

**FIGURE 2.3** — Cell Membrane Comprised of Phospholipid Bilayer, Cholesterol, Protein Channels, and Lipid Rafts and Structural Proteins




Cell membrane. Wikipedia Web site. http://en.wikipedia.org/wiki/Cell_membrane. Accessed January 25, 2023.

## Triglycerides

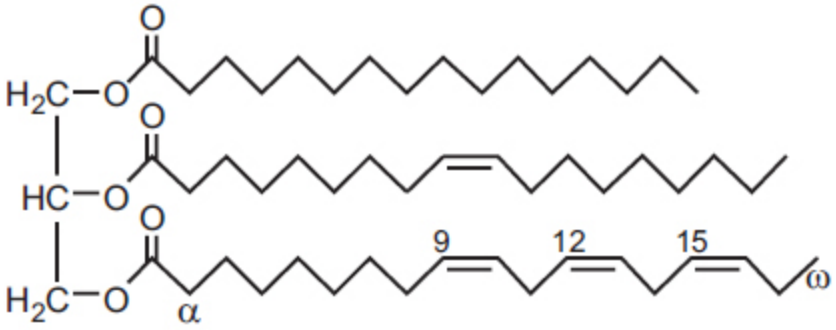
Triglycerides are comprised of three fatty acids bound to glycerol (**Figure 2.4**). Triglycerides are synthesized by the liver or come from dietary fat intake. Triglycerides are the primary method of transporting fatty acids to and from the liver and adipose tissue.

There are three major classes of fatty acids of interest: saturated, monounsaturated, and polyunsaturated (see **Figure 2.4** for examples of each attached to glycerol backbone). Polyunsaturated fatty acids have two or more double bonds between the carbons in the chain. They are liquid at room temperature because the molecules do not stack together as easily due to the nonlinear conformation of the fatty acid carbon chains.

Monounsaturated fatty acids have one double bond, and saturated fatty acids have no double bonds. Hydrogenation is a method of transforming poly- or monounsaturated oils into saturated fatty acids, which are more likely to be solid at room temperature because they can stack together. The fatty composition of the diet contributes to the risk of ASCVD (see *Chapters 4* and *9*).

The structure of circulating plasma lipoproteins are influenced by the bipolar nature of triglycerides (similar to the membrane bilayer assembly of phospholipids). The hydrophilic polar glycerol group of the triglyceride is exposed to the cellular milieu, while the hydrophobic nonpolar fatty acids are sequestered inside the bilayer. Triglycerides are major components of chylomicrons and very low-density lipoproteins (VLDL). Other lipoproteins, such as LDL and HDL, contain varying amounts of triglycerides.

**FIGURE 2.4** — Triglyceride Structure




Triglyceride. Wikipedia Web site. http://en.wikipedia.org/wiki/Triglyceride. Accessed January 25, 2023.

Triglycerides are stored in adipose tissue and their breakdown into fatty acids provides a major fuel source for cellular metabolism. Triglycerides are not taken up directly by cells but require lipolysis to liberate free fatty acids, which can be taken up directly by the cell. Glucagon signals hormone sensitive lipase to break down stored triglycerides into free fatty acids. The brain does not metabolize free fatty acids but does utilize the glycerol component by converting it into glucose via gluconeogenesis.

## Other Lipids

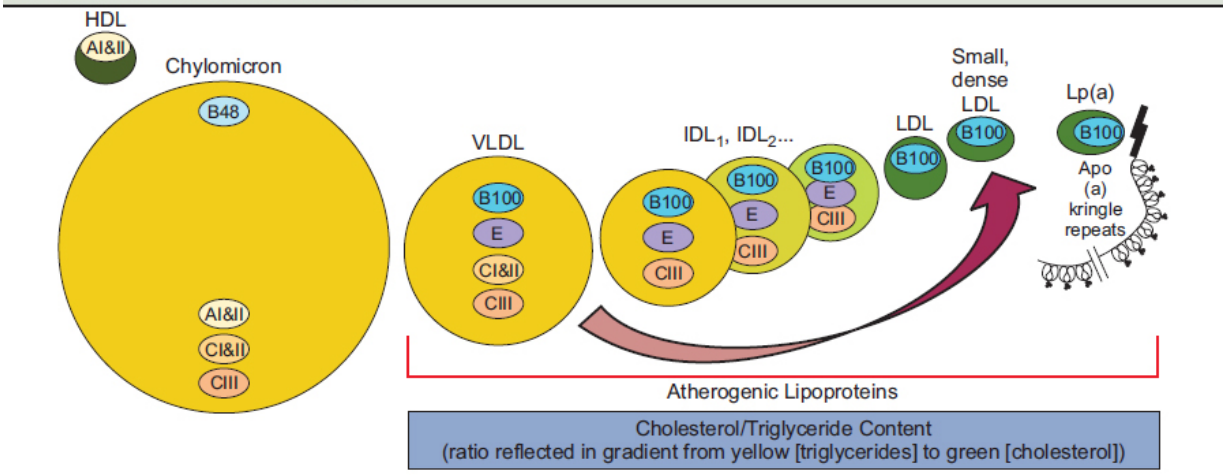
Other lipids, such as sphingosine, sphingomyelin, and ceramides, also play important structural and signaling roles in the body. Sphingolipids are included in circulating lipoproteins and atherosclerotic plaque. However, the role of these lipids in the development of ASCVD is not well understood, and they are not affected by current drug therapies.

## Lipoprotein Metabolism

Cholesterol and triglycerides are either synthesized by the liver or come from the diet. Lipoproteins transport cholesterol and triglycerides in the blood for use throughout the body. Chylomicrons transport dietary fatty acids as triglycerides for uptake by cells throughout the body, including the liver. In the liver, triglycerides are stored, used for energy, or used to construct VLDL. The liver assembles VLDL from triglycerides (either from the diet or synthesized in the liver), apolipoprotein B, and cholesteryl esters. VLDL is then secreted into the blood.

Constituent triglycerides and cholesterol are removed by peripheral cells as VLDL circulates through the body, with short-lived intermediate-density lipoproteins (IDLs) as intermediaries, finally resulting in the longer-lasting LDL particle. LDL comprises the largest fraction of circulating lipoproteins, constituting about 60% to 70% of total cholesterol. The relative size, composition, and atherogenicity of the circulating lipoproteins are shown in **Figure 2.5**.

**FIGURE 2.5** — Lipoprotein Relative Size, Triglyceride, and Cholesterol Composition, Major Apolipoproteins, and Atherogenicity



## HDL

HDL is the smallest and densest of the circulating lipoproteins, with the highest proportion of protein to lipid content. HDL carries apo AI and AII rather than apoB100, which characterizes the atherogenic lipoproteins.

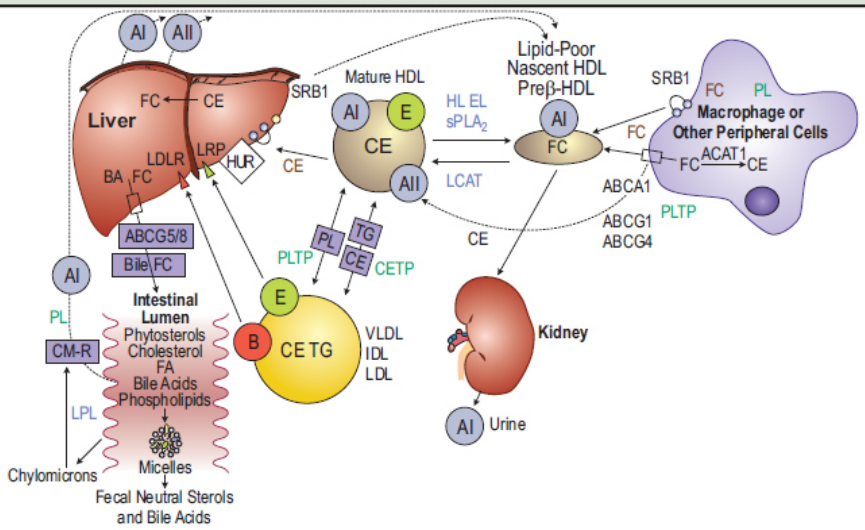
HDL is synthesized in the liver as a complex of apolipoproteins AI and AII and phospholipids in a discoid particle called nascent HDL or pre-ß HDL (**Figure 2.6**). As this particle circulates thought the body and interacts with peripheral cells, it acquires cholesterol and additional phospholipid by binding to adenosine triphosphate-binding cassette protein 1 (ABC1), ultimately resulting in mature HDL. This process is called reverse cholesterol transport. HDL carries about 30% of blood cholesterol.

Inside the HDL particle, unesterified cholesterol is esterified by lecithin-cholesterol acyl transferase (LCAT). Esterified cholesterol can then be taken up by the liver via scavenger receptor B1 (SR-B1) or in the plasma can be exchanged for triglycerides from apoB-containing lipoproteins via cholesteryl ester transfer protein (CETP). CETP inhibitors are under development that markedly raise HDL-C levels, with variable effects on LDL-C.

Phospholipids can be transferred from apoB-containing lipoproteins to HDL via phospholipid transfer protein (PLTP). HDL may also receive triglycerides hydrolyzed from VLDL and chylomicrons by lipoprotein lipase. Hepatic lipase hydrolyzes the triglycerides in HDL, forming smaller HDL particles.

HDL, HDL-C, and Apo AI are all inversely associated with ASCVD risk in epidemiologic studies. An HDL-C <40 mg/dL in men and <50 mg/dL in women is associated with increased ASCVD risk. However, raising HDL-C with drug therapy has yet to be shown to reduce ASCVD risk (see *Chapters 20* and *24*). An uncommon apo AI mutation, Apo AI-milano, causes low HDL-C levels but is not associated with increased ASCVD risk. This is thought to be due to more efficient reverse cholesterol transport. Infusions of Apo AI-milano have been shown to reduce atherosclerosis in animals and humans, but development has not moved forward to date.

**FIGURE 2.6** — HDL Metabolism




*Key*: ABC, ATP-binding cassette; AI or AII, apolipoprotein AI or AII; BA, bile acids; CE, cholesterol ester; CETP, cholesterol ester transport protein; CM-R, chylomicron remnant; E, apolipoprotein E; EL, endothelial lipase; FC, free cholesterol; HL, hepatic lipase; HUR, holouptake receptor; IDL; intermediate-density lipoproteins; LCAT, lecithin-cholesterol acyltransferase; LDL, low-density lipoprotein cholesterol; LDL-R, LDL receptor; LPL, lipoprotein lipase; LRP, LDL receptor-related protein; PL, phospholipids; PLTP, phospholipid transport protein; SRB1, scanvenger receptor B type 1; TG, triglyceride.

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Apo AII has been associated with increased ASCVD risk, although the mechanisms are unclear.

## Chylomicrons

Chylomicrons are the key transporter of fatty acids from the intestine, and also transport a small amount of cholesterol. Dietary triglycerides are broken down by pancreatic lipase in the duodenum. The intestine absorbs free fatty acids, monoglycerides (one glycerol and one fatty acid), and some diglycerides. The enterocyte then reassembles the free fatty acids, monoglycerides and diglycerides into triglycerides which are then packaged with dietary cholesterol, apoB48, and apo A I and II, apo CI, CII, and CIII into chylomicrons. Chylomicrons are secreted by the enterocyte into the lymph system, which drains into the inferior vena cava, and ultimately into the blood.

Chylomicrons can be captured directly by cells, with the triglycerides used as a source of energy, or are stored in some cells. Lipoprotein lipase

releases the fatty acids from triglycerides. Once most of the triglycerides are removed from the chylomicron, the remnant is cleared by the liver B/E receptor. Chylomicron clearance is variable, with slower clearance resulting in postprandial hypertriglyceridemia. Obesity, hypertriglyceridemia in the fasting state, and diabetes slow chylomicron clearance.

Chylomicrons are not atherogenic but the chylomicron remnants may have some atherogenicity.

## VLDL and IDLs

The majority of cholesterol in the body is synthesized in the liver. VLDL transports cholesterol synthesized in the liver to the peripheral tissues. In the liver, microsomal transport protein (MTP) forms VLDL from triglycerides and cholesteryl esters complexed with apoB, apo E, apo CII, apo CIII, and phospholipids. An MTP inhibitor, lomitapide, is approved for lowering blood cholesterol only in patients with homozygous familial hypercholesterolemia because of increased hepatotoxicity, due at least in part to hepatic triglyceride accumulation (see *Chapter 29*).

Once VLDL is secreted into the circulation, triglycerides are removed via lipoprotein lipase to release fatty acids for storage or energy production. VLDL can also exchange triglycerides and phospholipids with HDL via CETP. As triglycerides continue to be removed by lipoprotein lipase and CETP, VLDL transitions to IDLs. When the cholesterol content exceeds the triglyceride content, IDLs become LDL. VLDL and IDLs can also bind hepatic VLDL receptors to apo E.

Insulin resistance, diabetes, and obesity can result in increased production and decreased clearance of VLDL, manifested as moderate to severe hypertriglyceridemia.

VLDL and IDLs are considered atherogenic.

## LDL

LDL is the final step in the pathway from VLDL, and the primary transporter of cholesterol in the body. LDL receptors on the liver bind the apoB-100 in the LDL particles. This complex is endocytosed into the cell,

where the LDL is broken down while preserving the LDL receptor. The LDL receptor then returns to the cell surface, a recycling process that can occur up to 150 times. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a key regulator of the LDL receptor. PCSK9 irreversibly binds to the LDL receptor-LDL complex, which results in the degradation of the LDL receptor along with LDL (**Figure 23.1**). PCSK9 inhibitors have been approved and result in dramatic LDL-C reductions (see *Chapter 23*). Intracellular cholesterol levels regulate the expression of both the LDL-receptor and PCSK9 via SREBP-1.

LDL plays a fundamental role in atherogenesis. Several drugs that lower LDL-C through an LDL receptor–mediated mechanism (statins and ezetimibe) have been shown to reduce ASCVD events.

LDL, enriched in triglycerides by CETP or other pathways, is a substrate for hepatic lipase, which hydrolyzes the triglycerides to produce smaller, denser LDL (small dense LDL). Small, dense LDL was thought to be more atherogenic than larger LDL particles. However, carefully done analyses have found small dense LDL to be a better marker of metabolic abnormalities that increase triglycerides, such as insulin resistance and diabetes.

## Lp(a)

Lipoprotein (a) (Lp(a)) consists of an LDL-like particle that is connected by apoB to apo (a) (**Figure 2.5**). Lp(a) is largely genetically determined at the apo (a) gene. The synthesis and regulation of lipoprotein (a) is not well understood. Lp(a) is assembled in the liver. Apo(a) varies in size due to a variable number of kringle IV protein repeats in the apo(a) gene, known as apo(a) isoforms. Apo(a) size is inversely related to Lp(a) concentration. This is thought to be a result of the longer time it takes to assemble an apo(a) isoform with a large number of kringle repeats.

The metabolism and function of Lp(a) is not well understood. There is homology between apo(a) and plasminogen activator, a thrombotic factor. Lp(a) also transports proinflammatory oxidized phospholipids that recruit inflammatory cells, which has direct inflammatory effects.

The distribution of Lp(a) levels in the population is highly skewed. Epidemiologic data have found an association between Lp(a) levels and

ASCVD risk. Lp(a) levels of >50 mg/dL or >30 mg/dL have been identified as cut-points for increased risk. Data suggest Lp(a) level does add incremental information to traditional risk factors, and so might be considered as part of the clinician-patient discussion when deciding whether to initiate drug therapy based on risk (see *Chapter 14*).

Lifestyle modifications and most drugs do not influence Lp(a) levels. Niacin and PCSK9 inhibitors reduce Lp(a) levels by about 25% to 35%, but it is not clear whether reducing Lp(a) levels prevents ASCVD events (see *Chapter 25*).

## RECOMMENDED READINGS


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# Cholesterol and Atherogenesis

Over a century of epidemiologic studies and randomized trials have definitively established the causal role of cholesterol in the development of atherosclerosis.[1-5] Total cholesterol, and later LDL-C, were shown to be necessary for atherogenesis, a process that is accelerated in the presence of other cardiovascular risk factors. Conversely, atherosclerotic plaque stabilization and regression can occur when LDL-C levels are lowered, resulting in the reduction of clinical ASCVD events.

The lipid hypothesis was first proposed over 150 years ago by Virchow and colleagues, who described cholesterol accumulation as the hallmark of atherosclerotic plaque.[6] Ignatoski, Anitschkow, and colleagues described atherosclerosis in rabbits fed a diet high in animal products 50 years later.[7]

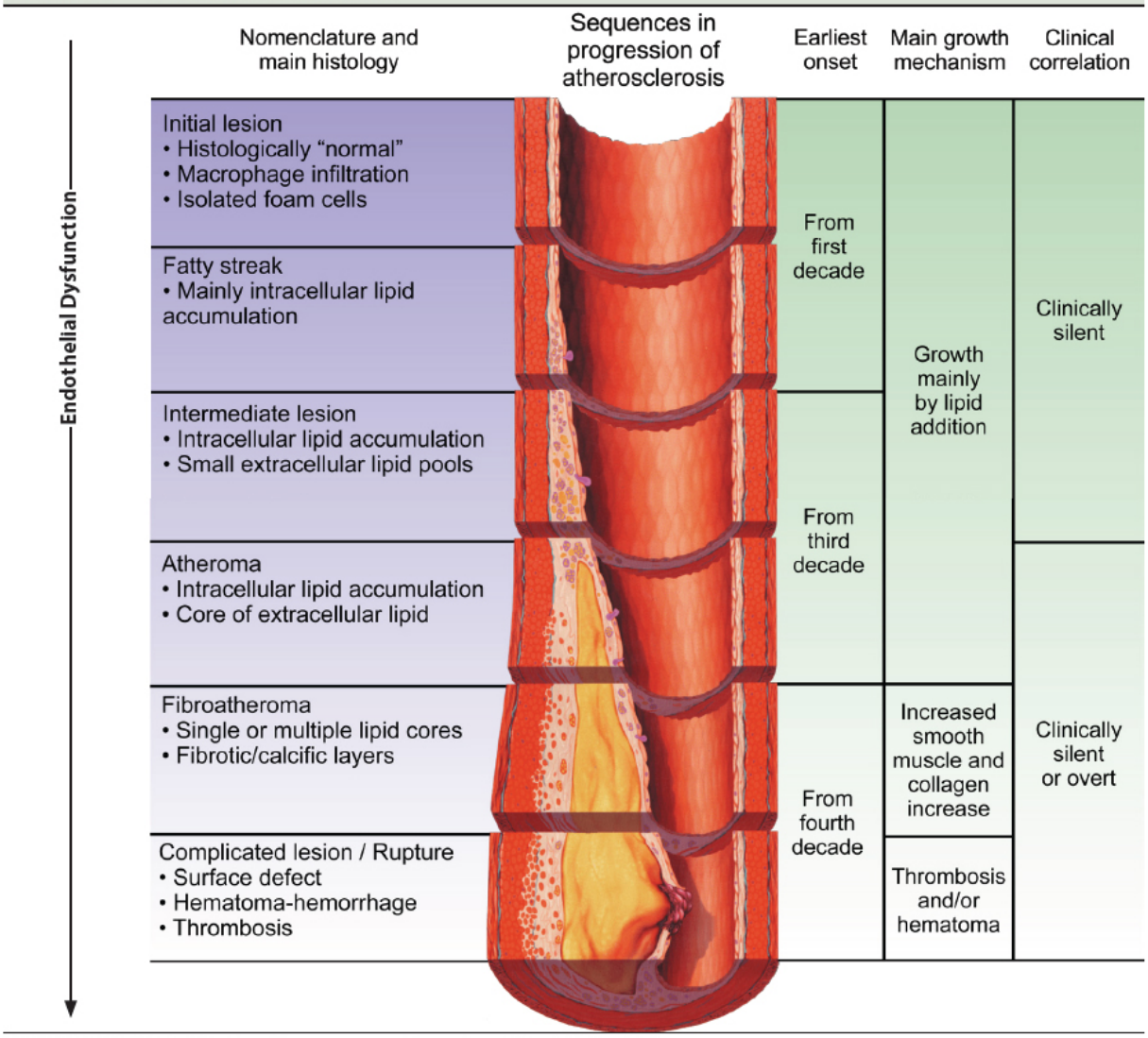
## Pathophysiology[8-12]

LDL is a critical factor in all stages of atherogenesis, although VLDL and IDL play a role as well. Cardiovascular risk factors, such as smoking, hypertension, and insulin resistance/hyperglycemia, influence endothelial function. A dysfunctional endothelium facilitates the entry of atherogenic lipoproteins into the intima, either via the LDL-receptor or through direct infiltration through the endothelium.

LDL can be oxidized in the blood or as it passes through the proteoglycan matrix of the endothelium. Oxidation promotes atherogenesis through a number of mechanisms. Increased retention of oxidized LDL in the intima stimulates uptake by macrophages. Accumulating cholesterol transforms the macrophage into a lipid-laden foam cell.

**Figure 3.1** provides an overview of plaque initiation and progression.

**FIGURE 3.1** — Atherosclerotic Progression






Oxidized LDL also triggers secretion of chemoattractant factors that recruit inflammatory leukocytes and lymphocytes, in addition to promoting transcription of proatherogenic genes, production of matrix metalloproteinases and tissue factors, smooth muscle cell apoptosis, and suppression of nitric oxide production. Endothelial dysfunction due to decreased nitric oxide synthesis is one of the earliest physiologic manifestations of atherosclerosis.

Macrophage foam cells produce cytokines that stimulate smooth muscle cell infiltration, which in turn promotes extracellular matrix production and fibrosis. This contributes to plaque progression and arterial remodeling.

Continued exposure to the pro-atherogenic milieu accelerates the recruitment of inflammatory cells and macrophages, continued lipid accumulation, neovascularization, necrosis of the lipid core, and fibrous cap formation.

Proteolytic enzymes released by the inflammatory cells can degrade the extracellular matrix, leading to destabilization of overlying thin fibrous cap and plaque rupture.

Complex advanced atherosclerotic lesions are characterized by compensatory vascular remodeling to preserve lumen diameter. Enlargement of the lesion beyond the effective diffusion distance for oxygen from the lumen leads to neovascularization, which in turn facilitates lipid core expansion, intraplaque hemorrhage, and calcification.

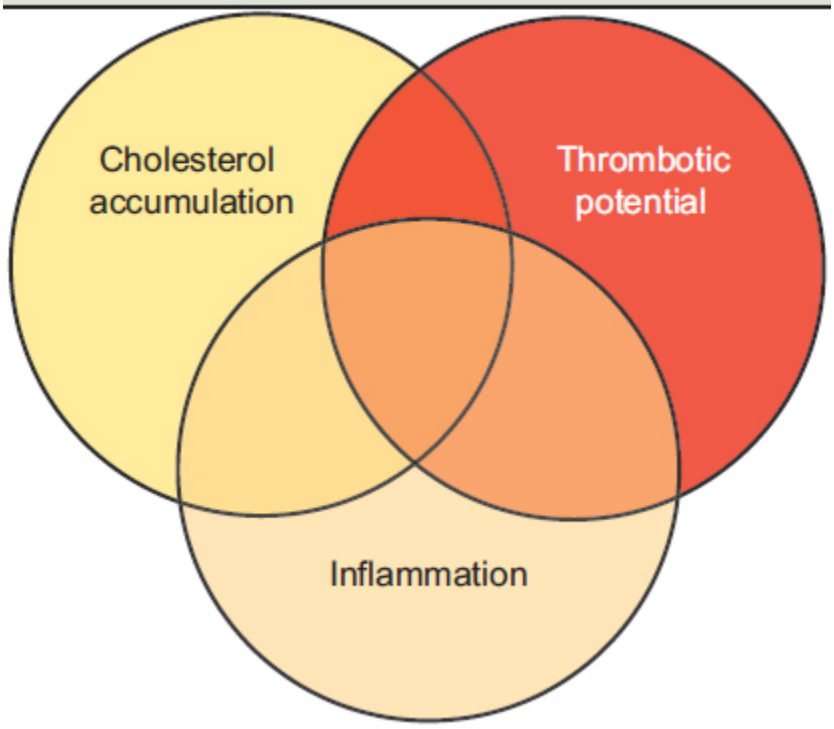
Lipid-rich plaques are extremely thrombogenic. When ruptured, they release intracellular membrane proteins and tissue factor into the lumen. Sufficient accumulation of thrombus occludes the artery, precipitating an acute ASCVD event such as myocardial infarction (MI) or stroke.

Cholesterol, inflammation, and thrombosis are important causal factors of atherosclerosis (**Figure 3.2**). This lethal triad is ultimately expressed clinically as acute ASCVD events sometime during the lifespan the majority of adults in the United States.

## Atherosclerosis Through the Lifespan[9-14]

Atherosclerotic plaque progresses through several pathologically distinct phases (**Figure 3.3**), with the rate of progression depending on the diet and level of other cardiovascular (CV) risk factors.

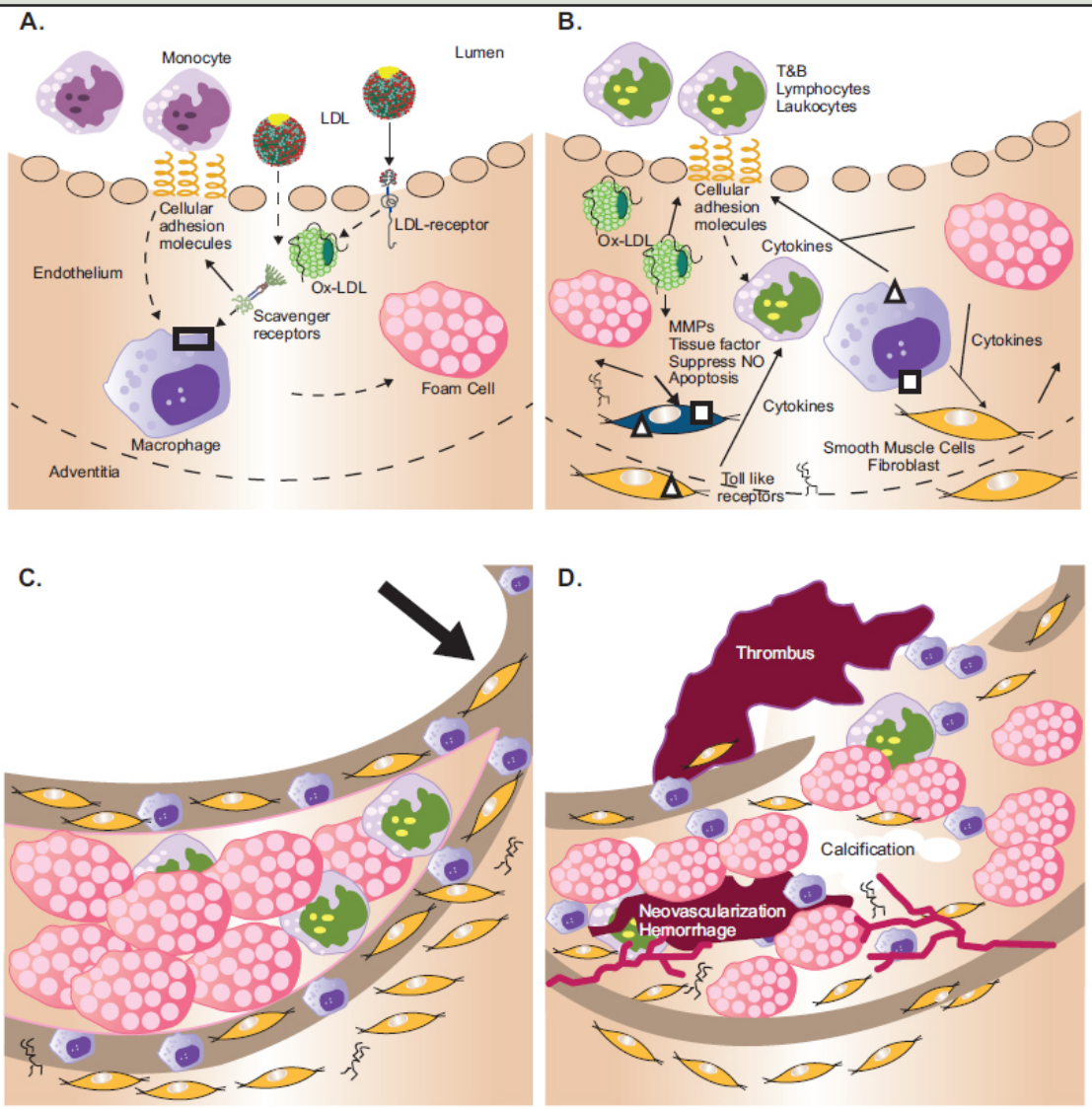
**FIGURE 3.2** — Unholy Triad of Atherogenesis




In countries with habitual atherogenic diets, cholesterol-laden macrophages begin to accumulate as fatty streaks by age 2. Fibrous plaques develop in the teens, and are characterized by a thin fibrous cap overlying a lipid-rich core with smooth muscle cell infiltration and extracellular matrix accumulation. By the mid-30s, fibrous plaques constitute about 50% of coronary lesions in men and 30% in women. As atherosclerosis progresses, advanced plaques with large extracellular lipid accumulation develop and fibrous plaques become confluent. Advanced plaque is prone to rupture due to the high lipid content, increased inflammatory cell infiltration, and the overlying thin fibrous cap. By age 50, advanced plaque occurs in the majority of individuals in Western populations. In low-risk populations, half of individuals will have advanced plaque by age 65.

Complicated lesions arise as advanced plaques erode or rupture with overlying thrombosis. Thrombosis is usually nonocclusive and clinically silent. Occlusive thrombosis most often occurs in a nonstenotic lesion. As the ruptured plaque heals, with further infiltration by smooth muscle and inflammatory cells and accumulation of extracellular matrix, calcification and some degree of stenosis often occur at this stage.

**FIGURE 3.3** — Initiation and Progression of Atherosclerotic Plaque



A.

1. Endothelial activation results in increased LDL uptake, expression of adhesion molecules for circulating monocytes, and monocyte migration.
2. Entry of LDL into the subendothelium directly or via the LDL receptor.
3. LDL becomes oxidized as it passes through the intima (Ox-LDL).
4. Ox-LDL stimulates uptake by macrophages via scavenger receptors.
5. Scavenger receptors further stimulate monocyte adhesion.
6. Continued uptake of Ox-LDL transforms macrophage into a foam cell.

B.

7. Oxidized LDL also initiates production of matrix metalloproteinases (MMPs) and tissue factor, suppression of endothelial nitric oxide (NO) production, and promotion of smooth cell apoptosis, and monocyte, lymphocyte, and leukocyte migration.
8. Oxidized LDL also initiates production of matrix metalloproteinases (MMPs) and tissue factor, suppression of endothelial nitric oxide (NO) production, and promotion of apoptosis, and monocyte, lymphocyte, and leukocyte migration.
9. The CD40 receptor and CD40 ligand are expressed by macrophages, T and B lymphocytes, endothelial cells, vascular smooth muscle cells, and fibroblasts contributing to leukocyte adhesion, matrix degeneration, and cytokine-induced inflammation.
10. Macrophage/foam cells produce cytokines that stimulate neighboring smooth muscle cells to increase extracellular matrix production (ECM) and fibrosis.
11. Toll-like receptors attract additional inflammatory cells.

C.

12. Lipid accumulates and a fibrous cap is formed along with a necrotic core and continued infiltration of inflammatory cells.
13. Plaque rupture frequently occurs where the fibrous cap is thinnest and foam cell accumulation the densest, often at the shoulder or between the plaque and adjacent arterial wall.

D.

14. Proteolytic enzymes released by inflammatory cells leads to destabilization of the overlying thin fibrous cap and plaque rupture.
15. Extravasation of highly thrombotic necrotic lipid core and tissue factor promote formation of overlying thrombosis
16. Complex advanced lesions are characterized by compensatory vascular remodeling to preserve lumen diameter.
17. Enlargement of the lesion beyond the effective diffusion distance of oxygen leads to neovascularization.
18. These changes in turn lead to further lipid core expansion, intraplaque hemorrhage, and calcification.

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## Cholesterol-Lowering and Plaque Stabilization and Regression[11,15]

Lowering LDL-C has been shown to stabilize atherosclerotic plaques by shrinking the lipid core, reducing inflammatory cell infiltration and microvessels, and thickening the overlying fibrous cap. More aggressive LDL-C lowering with high intensity statins has a greater impact on plaque stabilization and can result in plaque regression. Microvessels are thought to serve as a potential pathway for reverse cholesterol transport. Microvessels regress once the cholesterol-rich core has been depleted.

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CHAPTER **4**

# Epidemiology of Cholesterol and Cardiovascular Disease

Humans appear predisposed to atherosclerosis. Evidence of atherosclerosis has been found in mummies from Egypt, Peru, Ancestral Puebloans, and Alaskan hunter-gatherers.[1] Cholesterol was implicated in the pathogenesis of atherosclerosis over 150 years ago (see *Chapter 3*). In 1920, the structure of cholesterol was elucidated and the relationship between blood cholesterol levels and premature atherosclerosis in Dutch families was found.

During both World Wars, with famine and severe shortages of fat, autopsy studies found low levels of serum cholesterol, reduced burdens of atherosclerosis, and lower rates of coronary arter disease (CAD) mortality.[2,3] Following World War II, numerous animal models of high-fat and high-cholesterol diets demonstrated atherosclerosis initiation and progression, and regression of atherosclerosis with low-fat diets.

Circulating cholesterol-containing lipoproteins in plasma were demonstrated to be the source of cholesterol in plaque. Metabolic ward studies by Keys, Hegsted, and others quantitated the response of blood cholesterol levels to changes in dietary fat and cholesterol intake. An association between blood cholesterol and the rate of coronary death was found across countries in the Seven Countries and other studies.[4] The seminal Framingham study was launched in 1948 to prospectively study risk factors for ASCVD.[5]

Autopsies of young soldiers killed in Korea found a high prevalence of coronary atherosclerosis in US soldiers, with virtually no atherosclerosis found in Koreans.[6] Migration studies clearly established that lifestyle, and not genes, was the crucial determinant of serum cholesterol levels and the development of CAD. The Ni-Hon-San study showed that Japanese men in Nippon, Japan, and in the US cities of Honolulu and San Francisco had

progressively more Westernized diets, higher dietary cholesterol, and saturated fat intake from animal fats, and higher serum cholesterol levels accompanied by progressively higher risk of CAD.[7]

Through the 1990s, more than 65 cohorts on four continents have reported a clear and consistent relationship between lifetime blood cholesterol levels, the number of other CV risk factors, and the subsequent development of CAD and other ASCVD.[8,10] Countries with habitual diets high in cholesterol and fat, such as northern European countries with high dairy intake, had high rates of CAD. CAD was uncommon in countries with a diet high in vegetables and low in fat and cholesterol, such as the Mediterranean countries and Japan (**Figure 4.1**). In high-risk populations, the relationship between cholesterol and CAD mortality is curvilinear (**Figures 4.1** and **4.2**). In lower-risk populations, the association appears more linear (**Figure 4.1**).

Earlier epidemiologic studies measured total cholesterol. Later studies have found the same robust relationship between LDL-C levels and ASCVD risk.[11] LDL-C typically makes up 60% to 70% of total serum cholesterol. In most populations studied, an LDL-C ≥100 mg/dL (or total cholesterol ≥150 mg/dL or non–HDL-C ≥130 mg/dL) is atherogenic in both women and men.[12,13] Newborns have LDL levels of approximately 30 mg/dL and LDL levels of 25-60 mg/dL appear sufficient for normal physiologic processes.[13] Total cholesterol is associated with ASCVD risk at every age in men and women (**Figure 4.3**).[14] While the relative risk of ASCVD associated with increasing total cholesterol levels is highest in middle age, the absolute risk is highest in older age groups due to the lifetime exposure to even modestly elevated blood cholesterol levels.[15]

**FIGURE 4.1** — Relationship Between Serum Total Cholesterol Concentration and Coronary Death, Adjusted for Age, Cigarette Smoking, and Systolic Blood Pressure in High-, Moderate-, and Low-Risk Countries

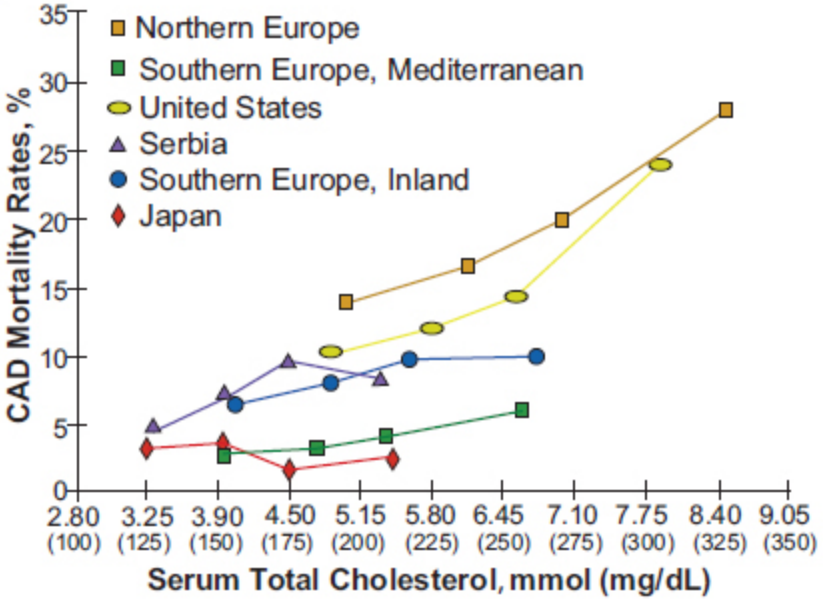


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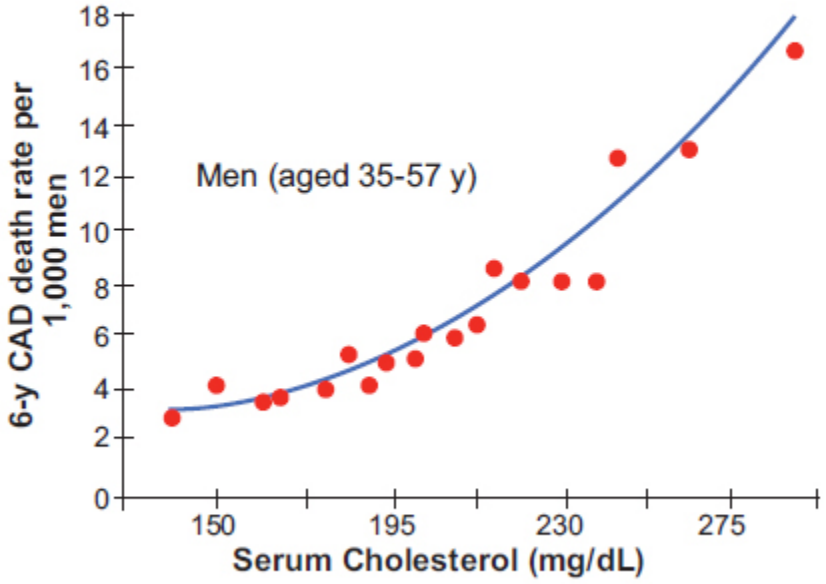
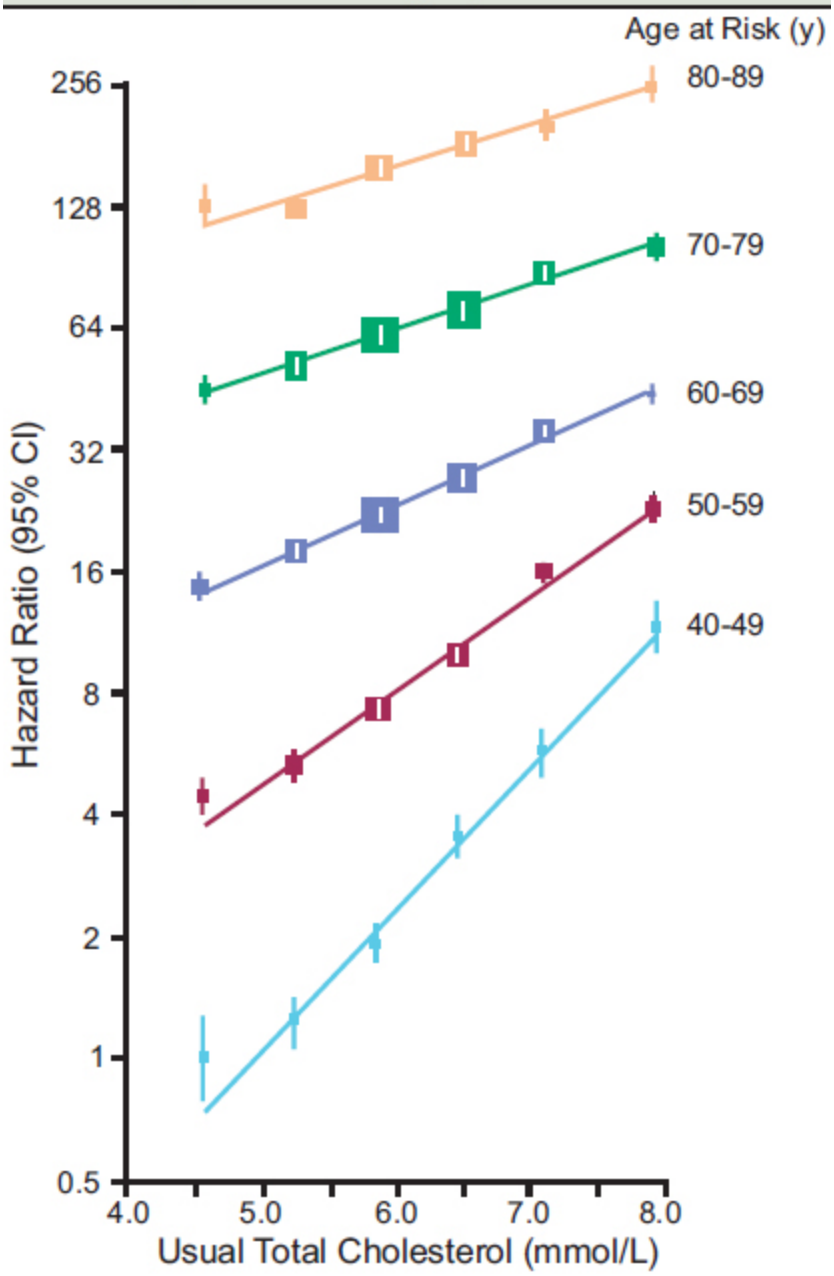
**FIGURE 4.2** — MRFIT: Epidemiologic Association Between Cholesterol and Coronary Heart Disease Death in a High-Risk Population of US Men




Martin MJ, et al. *Lancet*. 1986;2(8513):933-936.

**FIGURE 4.3** — Age-Specific Associations of Atherosclerotic Coronary Heart Disease, Mortality, and Total Cholesterol Level From the Prospective Studies' Meta-Analysis of 892,337 Apparently Healthy Adults in 61 Cohorts (1 mmol = 39 mg/dL)

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