Chapter 32: Dyslipidemia

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UPDATE SUMMARY

Update Summary

July, 2023

The following sections, tables, and figures were updated:

- The chapter has been revised in several sections to reflect the results of the CLEAR-OUTCOMES study, which provides evidence regarding the potential role of bempedoic acid in the prevention of cardiovascular events. Revisions include updates to the following sections:
  - General Approach to Treatment
  - Table 32-3 Select Landmark Clinical Trials
  - Adenosine Triphosphate-Citrate Lyase Inhibitors
- A new paragraph was added to the "Dietary Supplements" section reflecting the results of the SPORT trial which compared rosuvastatin to six commonly used dietary supplements.
- Updates were made throughout the chapter to change PCSK9 inhibitors to the preferred terminology PCSK9 monoclonal antibody (PCSK9 mAb), including Figure 32-7.
- Revisions are done to Figure 32-8 clarifying the approach to treatment of hypertriglyceridemia.
- Information is added about the nocebo effect and how to mitigate it in the "HMG-CoA Reductase Inhibitors" (Statins) section.
- The REPRIEVE study provides new evidence regarding the benefits of statin therapy in patients with human immunodeficiency virus (HIV) infection; updates were made to the "Patients with Chronic Inflammatory Disorders and HIV" section.

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 8, Dyslipidemia.

KEY CONCEPTS

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1. Lipid abnormalities increase the risk of atherosclerotic cardiovascular disease (ASCVD), which includes ischemic coronary heart disease, ischemic stroke, and peripheral arterial disease.
2. Low-density-lipoprotein cholesterol (LDL-C) is the primary target to reduce the risk of ASCVD events.
3. Genetic abnormalities and environmental factors are involved in the development of dyslipidemia.
4. Therapeutic lifestyle change is the first-line therapy for any lipoprotein disorder.
5. If therapeutic lifestyle changes are insufficient, lipid-lowering agents should be chosen based on which lipid is at an undesirable level and the degree to which it is expected to increase the risk of ASCVD.
6. Statins are the drug of choice for dyslipidemia because they significantly lower LDL-C and the risk of ASCVD events and are generally well tolerated.
7. If statin monotherapy is insufficient, patients may be treated with evidence-based combination therapy but should be monitored closely for drug-drug interactions.
8. Reducing total cholesterol and LDL-C reduces CHD and total mortality.
9. Lipid-lowering therapies that reduce ASCVD event rates are cost-effective.
10. Several novel medications, including antisense oligonucleotide inhibitors of apoB, microsomal triglyceride transport protein inhibitors, adenosine triphosphate-citrate lyase (ACL) inhibitors, and proprotein convertase subtilisin/kexin type 9 (PCSK9) modulating therapies, can be used as add-on therapy or in lieu of statin therapy in select high-risk patients.

BEYOND THE BOOK

BEYOND THE BOOK

Watch these YouTube videos to learn about cholesterol basics as well as the physiology of lipoprotein cholesterol and metabolism:

- Cholesterol Good and Bad (https://tinyurl.com/yx6a5ufj) by the US National Library of Medicine
- Physiology of Lipoprotein Cholesterol (https://tinyurl.com/hcy239y) by Armando Hasudungan
- Physiology of Lipoprotein Metabolism (https://tinyurl.com/pwo856o) by National Heart, Lung, and Blood Institute

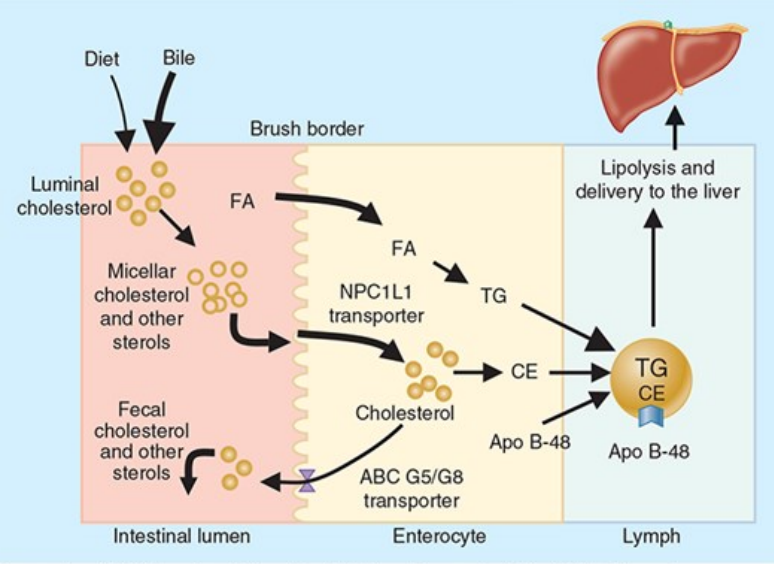
INTRODUCTION

Cholesterol, triglycerides, and phospholipids are the major lipids that combine with proteins to be transported as complexes of lipid and proteins known as lipoproteins. Lipids, such as cholesterol and triglycerides, are insoluble in plasma, which is why the lipoproteins are required for transportation (FIGURE 32-1).[1,2]

FIGURE 32-1

Intestinal cholesterol absorption and transportation. Cholesterol from food and bile enters the gut lumen and is emulsified by bile acids into micelles.

Micelles bind to intestinal enterocytes and cholesterol, and other sterols are transported from the micelles to the enterocytes by sterol transporters. Triglycerides (TG) synthesized by absorbed fatty acids (FA) are incorporated into chylomicrons. Chylomicrons are released into lymphatic circulation and converted to chylomicron remnants (by losing triglyceride), and are then taken up by hepatic LDL-receptor–related protein. (Apo, apolipoprotein; ABC, ATP-binding cassette; CE, cholesterol ester; FA, fatty acid; NPC1L1, Niemann-Pick C1-Like1 protein; TG, triglyceride.) *(Reproduced, with permission, from Chisholm-Burns MA, Schwinghammer TL, Malone PM, Kolesar JM, Bookstaver PB, Lee KC, eds. Pharmacotherapy Principles & Practice. 5th ed. New York: McGraw Hill; 2019.)*

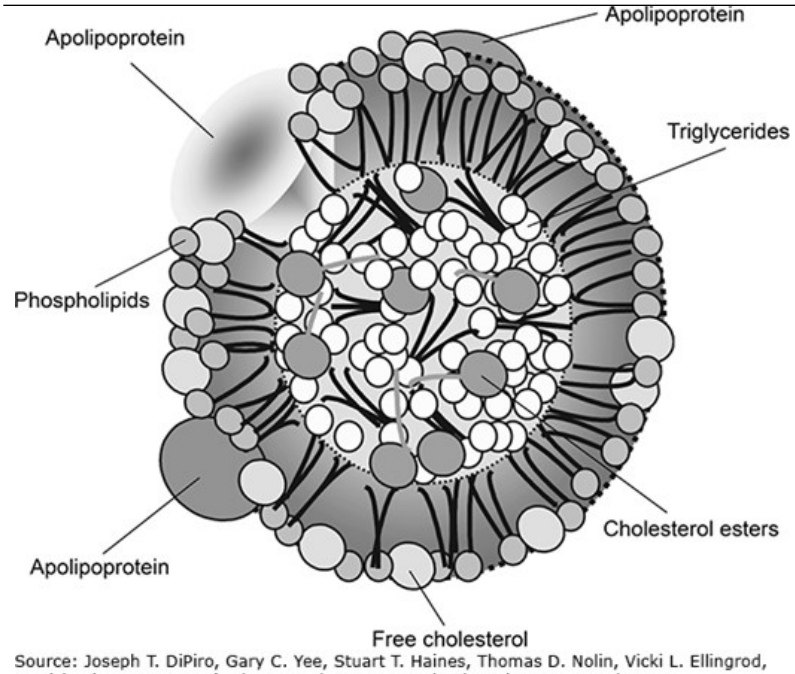


Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

There are three major classes of lipoproteins in the serum. These include low-density lipoproteins (LDL), high-density lipoproteins (HDL), and very-low-density lipoproteins (VLDL). VLDL is the primary carrier of triglycerides (TG) in the circulation. Intermediate-density lipoprotein (IDL) is between VLDL and LDL and is included in LDL-C measurement (FIGURE 32-2).[3]

FIGURE 32-2

Lipoprotein structure, which contains variable amounts of core cholesterol esters and triglycerides and have varying numbers and types of surface apolipoproteins.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

[1] [2] Lipid abnormalities increase the risk of coronary, cerebrovascular, and peripheral vascular arterial disease collectively known as atherosclerotic cardiovascular disease (ASCVD). The ASCVD-risk assessment evaluates a 10-year ASCVD incident. Developing a first ASCVD event is defined as nonfatal myocardial infarction or coronary heart disease (CHD) death, or fatal or nonfatal stroke, over a 10-year period. Premature coronary atherosclerosis is the most common and significant consequence of dyslipidemia. The 2013 guidelines from the American Heart Association (AHA) and American College of Cardiology (ACC) state that there is not sufficient evidence to recommend treating to specific lipid targets but suggests four statin benefit patient populations.[4] Low-density lipoprotein cholesterol (LDL-C) is the primary target of lipid-lowering therapy. Methods for risk assessment were also updated, which increases the number of patients who would qualify for therapy. Primary and secondary CHD prevention measures are provided as well.[4–7]

There are several subtypes of dyslipidemias, including hypertriglyceridemia, low HDL cholesterol (HDL-C), and diabetic dyslipidemia. Hypertriglyceridemia can lead to pancreatitis when very high TG levels (>500 mg/dL [5.65 mmol/L]) are seen. High serum triglycerides should primarily be treated by achieving desirable body weight, consumption of low saturated fat and cholesterol diet, regular exercise, smoking cessation, and restriction of alcohol.[3,5] In patients with borderline-high TG but with accompanying risk factors of established congenital heart disease, family history of premature CHD, concomitant LDL-C elevation or low HDL-C, and genetic forms of hypertriglyceridemia associated with CHD, lipid-lowering therapy should be considered.[8–10]

Low HDL-C is another dyslipidemia subtype that can occur due to insulin resistance, physical inactivity, diabetes, cigarette smoking, high carbohydrate intake, and some medications. In patients with low HDL-C, the primary target remains LDL-C, but an emphasis on weight loss, increased physical activity, and smoking cessation are recommended. No randomized controlled trials (RCT) have shown a reduction in ASCVD risk by raising HDL-C levels.[3,11] Hypertriglyceridemia, low HDL-C, and minimally elevated LDL-C characterize diabetic dyslipidemia. Because the primary target is LDL-C in diabetic dyslipidemia, statins are considered the drugs of choice.[3,5,12,13]

EPIDEMIOLOGY

Total cholesterol and LDL-C increase throughout life in both men and women. According to AHA estimates, approximately 49% of American adults aged 20 years or older have total cholesterol levels exceeding 200 mg/dL (5.17 mmol/L).[14] The prevalence of elevated LDL cholesterol as a risk factor for death in adults has increased from 15th in 1990 to 8th in 2019.[15] Westernized societal diets high in cholesterol are a strong contributor to the increase in total and LDL-C cholesterol. In 2011, CHD caused one in every seven deaths in the United States. About one-third of treated patients are achieving their LDL-C goal; fewer than 20% of CHD patients are at their LDL-C goal. Estimates from the National Cholesterol Education Program (NCEP)

state that only 26% of patients have an optimal LDL-C (<100 mg/dL [2.59 mmol/L]), and that large numbers of patients are either untreated or undertreated. Patients at the highest risk are less likely to be treated to desirable LDL-C values.[15–17] When patients who are at risk but who have not yet experienced initial cardiovascular (eg, myocardial infarction [MI]) or cerebrovascular (eg, ischemic stroke) events are treated, it is termed primary prevention. Treatment for those with manifest ASCVD is termed secondary prevention.[17] Studies, such as the Framingham Heart Study, show that risk for developing cardiovascular disease is related to the degree of LDL-C elevation in a continuous fashion.[3] Hypercholesterolemia, cigarette smoking, hypertension, diabetes, and low HDL-C levels are all additive risk factors for CHD. The risk of MI increases five to seven times with any preexisting CHD or previous MI compared to patients with no history of these. Patients with a history of CHD or MI should be screened, identified, and treated for dyslipidemias. Fifty percent of all MIs and 70% of all deaths due to CHD occur in patients with known CHD.

ETIOLOGY

3 Genetic abnormalities and environmental factors are involved in the development of dyslipidemia. The underlying causes of dyslipidemias can be categorized into two types: primary or secondary. Genetic factors that increase lipid levels can be inherited and cause primary or familial dyslipidemia. By contrast, lifestyles, diseases, medications, and diet can all lead to abnormal lipid levels and cause secondary or “acquired” dyslipidemia.

Primary or Familial Dyslipidemias

Primary or familial dyslipidemias account for a large number of cases of increased total cholesterol, LDL-C, TGs, or decreased HDL-C. There are certain familial or genetic defects that can contribute. Genetic disorders can cause an increase or decrease in different lipoproteins. Primary dyslipidemias result in an increased risk of premature ASCVD due to significant elevations in cholesterol levels. There are different types of familial dyslipidemias, including hypercholesterolemia, hypertriglyceridemia, combined hyperlipidemia, and disorders of HDL-C metabolism, and an excess of lipoproteins. Two other primary disorders include homozygous familial hypercholesterolemia (HoFH) and heterozygous familial hypercholesterolemia (HeFH). HeFH is more common with one case per 250 people versus HoFH with one case per one million people. Heterozygous gene dysfunction usually causes elevations in LDL-C between 250 and 450 mg/dL (6.47-11.64 mmol/L), and homozygous patients may present with LDL-C concentrations above 500 mg/dL (12.93 mmol/L). Tendon xanthomas are thick cholesterol deposits. Xanthelasmas and arcus cornea can also occur, and these are cholesterol deposits in the eyelids and around the corneal rim.[18–20] In familial hypertriglyceridemia, TGs are elevated in the range of 200 to 500 mg/dL (2.26-5.65 mmol/L), but at times can be greater than 1,000 mg/dL (11.3 mmol/L). Patients presenting with TG concentrations greater than or equal to 500 mg/dL (5.65 mmol/L) can have eruptive xanthomas and/or acute pancreatitis.

Secondary or Acquired Dyslipidemias

Secondary or acquired dyslipidemias can accompany genetic disorders or cause lipid imbalances. “The 4D classification” of secondary causes of dyslipidemia include diet, drugs, disorders, and diseases.[19] Regarding diet, an increase in cholesterol can be caused by excessive alcohol use, anorexia, weight gain, excessive carbohydrate intake, and high saturated fat intake. Certain medications can also contribute. For example, some medications that can increase both LDL-C and TGs include atypical antipsychotics, diuretics, beta-blockers, glucocorticoids, oral estrogen and progestin, tacrolimus, and cyclosporine.

Certain metabolism disorders can contribute to cholesterol imbalances. Nephrotic syndrome, renal failure, biliary obstruction, hypothyroidism, and pregnancy can all potentially contribute. Comorbid conditions or diseases such as hypothyroidism, pregnancy, obesity, polycystic ovarian syndrome (PCOS), uncontrolled diabetes, liver disease, and chronic kidney disease can also play a role.

Although we classify the lipid disorders into primary and secondary dyslipidemias based on etiologies, most dyslipidemias are a result of a combination of both.[5,19]

PATHOPHYSIOLOGY

Lipoproteins and Cholesterol Synthesis

There are four types of lipoproteins: chylomicrons, VLDL, LDL, and HDL. These lipoproteins vary in the content of lipid and protein. The ratio of protein and lipid in these lipoproteins contributes to the function of each. Chylomicrons contain the most lipid and little protein. HDL contains the most

protein and a small amount of lipids. The small amount of lipid, and in turn cholesterol, in HDL lipoproteins gives HDL the role of picking up extra cholesterol from the tissue. LDL is not necessarily "bad" cholesterol, but in excess, this generates the problem. We need cholesterol for the transportation of fats that are absorbed in our diet and delivered to our tissues. Chylomicrons are not normally in plasma during periods of fasting. In the small intestine, fats are digested and emulsified into micelles. Cholesterol is also absorbed. Fatty acids, cholesterol, and proteins or apoproteins are packaged and form chylomicrons. The chylomicrons circulate around the body and deliver lipids and TGs to tissues in need. The remaining chylomicrons are transported to the liver and bind to LDL receptors. Glucose that has also been absorbed from our diet is delivered to the liver. In the liver, glucose is converted to pyruvate and then to acetyl-CoA. Acetyl-CoA is eventually converted to cholesterol through 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. HMG-CoA reductase is a target for statins, thus stopping cholesterol synthesis. Glycolysis also synthesizes glycerol. Combining glycerol and one fatty acid forms monoacylglycerol, and two more fatty acids form triglycerides. Triglycerides and apoproteins are packed through the Golgi apparatus and form lipoproteins. Lipoproteins contain proteins, apoproteins, TGs, phospholipids, and cholesterol. The liver does not make all lipoproteins. In fact, only empty HDL and VLDL are made in the liver. VLDL has more TGs and lipids than HDL. VLDL transports these lipids and TGs to tissues in need of energy or storage. Adipose tissue stores fat, and many tissues use fatty acids for energy. VLDL is transported across lipase, which changes the VLDL to IDL or intermediate-density lipoproteins. IDL can then be converted to LDL. LDL mainly transports cholesterol to body tissues, which is why LDL contains the most cholesterol. Tissues need cholesterol to make hormones and maintain cell membrane integrity. Once LDL gives these tissues cholesterol, it returns to the liver. LDL binds to LDL receptors and is then either recycled to make more lipoproteins or excreted into the bile. Any excess cholesterol is excreted into the bile, so the body maintains cholesterol balance. HDL or empty HDL plays a role in picking up any or excess cholesterol and returning it to the liver. The full HDL containing the picked up cholesterol binds to scavenger receptors. They are then either recycled or excreted depending on how much cholesterol is needed.[1]

Lipid Metabolism and Transport

Cholesterol is water-insoluble so it cannot circulate through blood without help. Lipoproteins are large carrier proteins to help with transport because they are water-soluble. This allows major lipids to be circulated through the blood. Lipoproteins vary in characteristics depending on the amount of cholesterol, TG, and apolipoproteins. All lipoproteins also have something called apolipoproteins on its surface. Apolipoproteins are necessary for the assembly and secretion of lipoproteins. They are also major structural components of lipoproteins that have ligands for binding to receptors or cell surfaces. These are the cofactors for the activation of enzymes. Apolipoproteins have various functions that transport lipids from sites of absorption to sites where they are used. Apolipoprotein B containing lipoproteins, known as non-HDL, make up the lipid-delivery pathway. Apolipoprotein A-1 or HDL participates in reverse cholesterol transport. ApoB containing lipoproteins arise from two sources, one being intestinal ApoB-48 and the other hepatic ApoB-100 lineage. ApoB containing lipoproteins are secreted from the intestine or liver into the plasma. Apolipoproteins E, C-II, and C-III are secreted with them. These may also be acquired from HDL. Apolipoprotein remodeling begins, and ApoC-II activates lipoprotein lipase (LPL), which hydrolyzes the lipoprotein core TGs into free fatty acids. The fatty acids exit and the lipoproteins become smaller and smaller. Remodeling of the ApoB-100 hepatic lipoprotein, another step by hepatic lipase (HL) is needed to convert IDL to LDL. Most ApoB remnants are recycled to the liver by the LDL-receptor–related protein (LRP). They can have other metabolic requirements, too. Excess ApoB particles can invade arterial walls and become oxidized. Once oxidized, they are taken up by macrophage scavenger receptors creating foam cells that lead to atheroma.

ApoA-1 or HDL pathways are believed to protect our bodies from atherogenesis. HDL has two major protective roles in preventing atherogenesis. Reverse cholesterol transport is the transfer of excess cholesterol from peripheral tissues by HDL. ApoA-1 is secreted from the liver or intestine and is transported to the cells to remove excess cholesterol. HDL has several cholesterol removing mechanisms. Upregulation of the ATP-binding cassette transporter or ABCA-1 transporter is triggered by excess cholesterol in the macrophages. ABCA-1 harvests free cholesterol and delivers it to the cell membrane. The free cholesterol is esterified by lecithin-cholesterol acyltransferase (LCAT). The cholesterol ester moves to the core of the lipoprotein forming the mature HDL3. Further removal of cholesterol by HDL3 occurs through scavenger receptor class B type 1, or SR-B1 receptors and is acted on by LCAT, which expands to HDL2. ABCA-1 and SR-B1 are key for cholesterol efflux. HDL2 cholesterol is transferred to ApoB containing lipoproteins. HDL now has one of three options: HDL triglycerides may be hydrolyzed by HL back into HDL3; HDL2 can return to the liver and through SR-B1 converted back to HDL3; or HDL2 may be catabolized by the liver. All of these systems work together to maintain cholesterol homeostasis (FIGURE 32-3 and FIGURE 32-4).[1]

FIGURE 32-3

Biosynthetic pathway for cholesterol. The rate-limiting enzyme in this pathway is 3-hydroxy- 3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase). (CETP, cholesterol ester transfer protein; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density

lipoprotein; LPL, lipoprotein lipase; VLDL, very-low-density lipoprotein.) (*A*) Exogenous pathway; (*B*) Endogenous pathway; (*C*) Reverse cholesterol transport. *(Adapted from Breslow JL. Genetic basis of lipoprotein disorders. J Clin Invest. 1989;84:373.)*

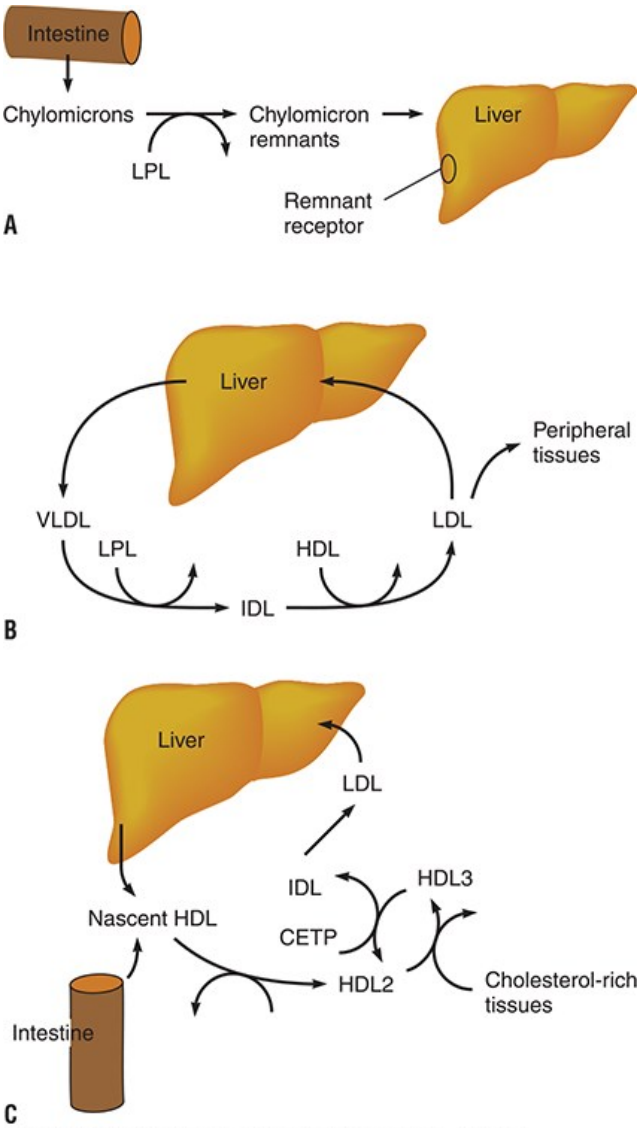
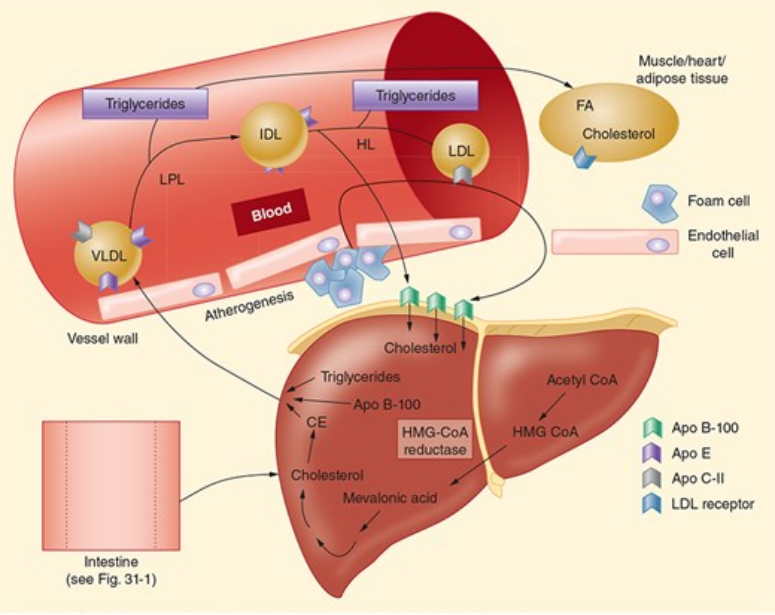


FIGURE 32-4

Endogenous lipoprotein metabolism. In the liver, the cholesterol and triglycerides are packed into VLDL particles and sent into the blood. They are then converted into IDL, which can be cleared by hepatic IDL receptors or metabolized into LDL. LDL can be cleared by LDL receptors or it can enter the arterial walls and contribute to the development of atherosclerotic plaques and cardiovascular disease.



Familial Hypercholesterolemia

Familial hypercholesterolemia is characterized by (a) a selective elevation in the plasma level of LDL; (b) deposition of LDL-derived cholesterol in tendons (xanthomas) and arteries (atheromas); and (c) inheritance as an autosomal dominant trait with homozygotes more severely affected than heterozygotes. The primary defect in familial hypercholesterolemia is the inability to bind LDL to the LDL receptor (LDL-R) or, rarely, a defect of internalizing the LDL-R complex into the cell after normal binding. This leads to a lack of LDL degradation by cells and unregulated biosynthesis of cholesterol, with total cholesterol and LDL-C being inversely proportional to the deficit in LDL receptors. Homozygotes (prevalence 1 in 1,000,000) have severe hypercholesterolemia (650-1,000 mg/dL [16.8-25.9 mmol/L]), with the early appearance of cutaneous xanthomas and fatal CHD generally before the age of 20 and have essentially no functional LDL receptors. Heterozygotes have only about one-half of the normal number of LDL receptors, total cholesterol levels in the range of 300 to 600 mg/dL (7.76-15.52 mmol/L), and cardiovascular events beginning in the third and fourth decades of life.

Secondary causes of dyslipidemia exist and that several drugs and conditions may contribute to abnormal lipid levels (Table 32-1). These secondary forms of dyslipidemia should be managed by addressing the underlying abnormality, including the modification of drug therapy when appropriate.

TABLE 32-1

Secondary Causes of Lipoprotein Abnormalities

Hypercholesterolemia	• Hypothyroidism • Obstructive liver disease • Nephrotic syndrome • Anorexia nervosa • Acute intermittent porphyria • Drugs: progestins, thiazide diuretics, glucocorticoids, beta-blockers, isotretinoin, protease inhibitors, cyclosporine, mirtazapine, sirolimus
Hypertriglyceridemia	• Obesity • Diabetes mellitus • Lipodystrophy • Glycogen storage disease • Ileal bypass surgery • Sepsis • Pregnancy • Acute hepatitis • Systemic lupus erythematosus • Monoclonal gammopathy: multiple myeloma, lymphoma • Drugs: alcohol, estrogens, isotretinoin, beta-blockers, glucocorticoids, bile-acid resins, thiazides, asparaginase, interferons, azole antifungals, mirtazapine, anabolic steroids, sirolimus, bexarotene
Hypocholesterolemia	• Malnutrition • Malabsorption • Myeloproliferative diseases • Chronic infectious diseases: tuberculosis • Monoclonal gammopathy
Low HDL	• Malnutrition • Obesity • Drugs: non-ISA beta-blockers, anabolic steroids, probucol, isotretinoin, progestins

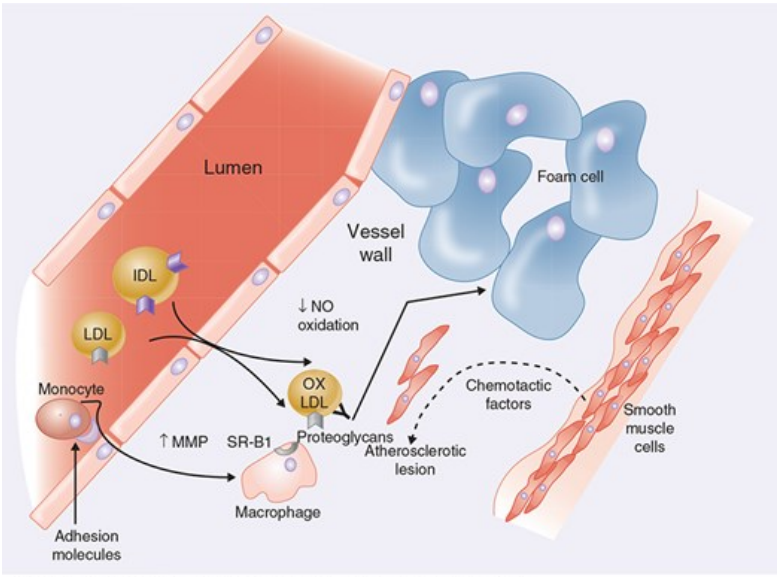
Pathogenesis of Atherosclerotic Cardiovascular Disease

The “response-to-injury” hypothesis states that risk factors such as oxidized LDL, mechanical injury to the endothelium, excessive homocysteine, immunologic attacks, or infection-induced changes in endothelial and intimal function lead to endothelial dysfunction and a series of cellular interactions that culminate in atherosclerosis. C-reactive protein (CRP) is an acute-phase reactant and a marker for inflammation. Measuring one’s CRP levels by means of a high-sensitivity CRP may be useful in identifying patients at risk for developing CAD. Lipid abnormalities increase the risk for CHD and cerebrovascular morbidity and mortality. The eventual outcomes of this atherogenic cascade are clinical events such as angina, MI, arrhythmias, stroke, peripheral arterial disease, abdominal aortic aneurysm, and sudden death. Atherosclerotic lesions are thought to arise from transport and retention of plasma LDL-C through the endothelial cell layer into the extracellular matrix of the subendothelial space. Once in the artery wall, LDL-C is chemically modified through oxidation and nonenzymatic glycation. Mildly oxidized LDL-C then recruits monocytes which transforms into macrophages in the artery wall. Macrophages accelerate LDL-C oxidation and apolipoprotein B accumulation and alter the receptor-mediated uptake

of LDL-C into the artery wall from the usual LDL-R to a “scavenger receptor” not regulated by the cell content of cholesterol. Oxidized LDL-C increases plasminogen inhibitor levels (promotion of coagulation), induces the expression of endothelin (vasoconstrictive substance), inhibits the expression of nitric oxide (a vasodilator and platelet inhibitor), and is toxic to macrophages if highly oxidized. As oxidation of biologically active lipids proceeds, other lipids breakdown products of fatty acids and oxysterol are formed, which continue the reaction within the tissue. These events lead to a massive accumulation of cholesterol. The cholesterol-laden macrophages become foam cells; foam cells are the earliest recognized cells of the arterial fatty streak. Oxidized LDL-C provokes an inflammatory response, which is mediated by a number of chemoattractants and cytokines. The process of aging may lead to lipoproteins that are more susceptible to oxidation and have longer resident time in the vascular compartment. Repeated injury and repair within an atherosclerotic plaque eventually leads to fibrous caps protecting the underlying core of lipids, collagen, calcium, and inflammatory cells such as T-lymphocytes. Maintenance of the fibrous plaque is critical to prevent plaque rupture and subsequent coronary thrombosis.[21] An imbalance between plaque synthesis and degradation may lead to a weakened or vulnerable plaque prone to rupture. The fibrous cap may become weakened through the decreased synthesis of the extracellular matrix or increased degradation of the matrix (FIGURE 32-5).

FIGURE 32-5

Atherogenesis is initiated by the migration of LDL and remnant lipoprotein particles into the vessel walls. These particles undergo oxidation and are taken up by macrophages in an unregulated fashion, which induces endothelial cell dysfunction. This, in turn, reduces the ability of the endothelium to dilate the artery and cause a prothrombotic state. Unregulated uptake of cholesterol by macrophages leads to foam cell formation, and thus the development of atherosclerotic plaques. Macrophages eventually produce and secrete matric metalloproteinases, which degrade the collagen matrix of the plaques and cause them to be unstable. This can potentially lead to a myocardial infarction. This is a progressive process. (IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; MMP, matrix metalloproteinase; NO, nitric oxide; SR-B1, scavenger receptor class B type 1.)
(Reproduced, with permission, from Chisholm-Burns MA, Schwinghammer TL, Malone PM, Kolesar JM, Bookstaver PB, Lee KC, eds. Pharmacotherapy Principles & Practice. 5th ed. New York: McGraw Hill; 2019.)



Lipoprotein(a) (Lp[a]), a low-density lipoprotein (LDL) variant, containing both apolipoprotein(a) (apo[a]) and apolipoprotein(b) (apo[b]) covalently bound via a disulfide bridge. Lp(a) is an independent risk factor for ASCVD.[22,23] Thought to be elevated in about 20% of the population, the significance of Lp(a) has been utilized to improve ASCVD risk assessment strategies.[22,23] Most recent evidence supports a relationship between elevated Lp(a) levels and both ASCVD and valvular aortic stenosis (VAS) risks, yet the precise pathophysiological mechanism(s) is not completely understood.[22,23]

Theoretically, the pathophysiological mechanisms of Lp(a)-induced ASCVD events include the interaction between oxidized phospholipids and the apo(a) component of Lp(a), resulting in endothelial disruption, lipid deposition, inflammation, and calcification of the vasculature.[22] Apo(a) has structural similarity with plasminogen which may account for its atherogenic properties because it competitively inhibits fibrinolysis and release of plasminogen activator inhibitor-1.[23] This process could further lead to thrombus formation within arterial plaques or turbulent blood flow within

stenosis, therefore, causing blockage(s) or embolism in VAS.[22]

While recommendations are still being considered and developed regarding how Lp(a) alters therapy in patients with dyslipidemia, the National Lipid Association (NLA) released a scientific statement in May 2019 detailing recommendations for testing and identifying those at high risk of ASCVD due to Lp(a) elevations.[23] These recommendations describe screening considerations, potential Lp(a) cut-points when to initiate treatment as well as primary and secondary prevention strategies.[23]

CLINICAL PRESENTATION

CLINICAL PRESENTATION: Dyslipidemias

General

- Most patients are asymptomatic for years before they develop ASCVD; the initial presentation may be sudden death due to a CHD event.
- Many patients with dyslipidemia also present with one or more of the following abnormalities:
  - Abdominal obesity
  - Atherogenic dyslipidemia
  - Increased blood pressure
  - Insulin resistance and/or glucose intolerance
  - Prothrombotic or proinflammatory state
- Patients with three or more of these abnormalities are considered to have the metabolic syndrome

Symptoms of ASCVD

- Chest pain
- Palpitations
- Sweating
- Anxiety
- Shortness of breath
- Loss of consciousness
- Difficulty with speech or movement
- Abdominal pain

Signs

- Abdominal pain
- Pancreatitis
- Eruptive xanthomas
- Peripheral polyneuropathy

Laboratory Tests

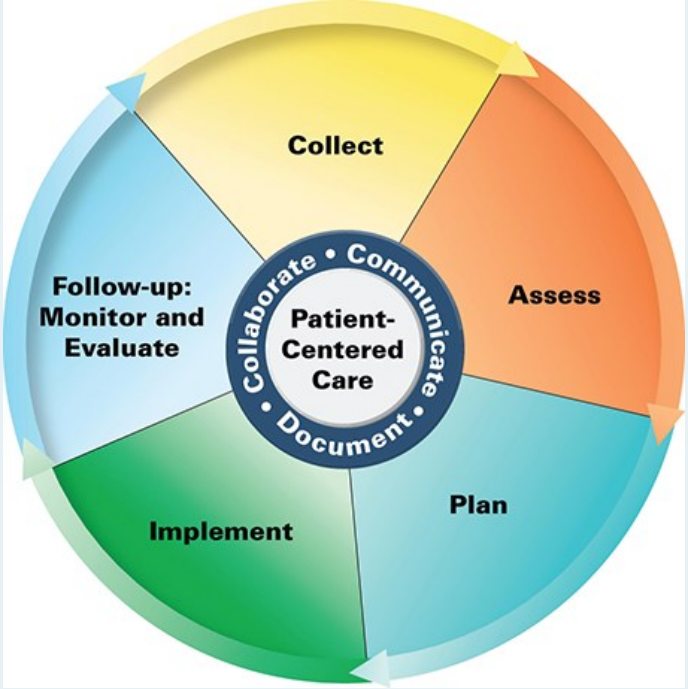
- Elevated total cholesterol, LDL-C, TGs, apolipoprotein B, hsCRP
- Decreased HDL-C

Other Diagnostic Tests

- Screenings for manifestations of vascular disease, including carotid ultrasound, coronary calcium score, ankle-brachial index, and heart catheterization

PATIENT CARE PROCESS

Patient Care Process for the Management of Dyslipidemias



Collect

- Patient characteristics (eg, age, race, gender, pregnant)
- Patients history: Past medical (eg, HTN), family (eg, early-onset coronary heart disease), social
- Current medications (including over-the-counter [OTC]) and prior lipid-lowering medication use
- Socioeconomic factors that may affect access to treatment or other aspects of care
- Lifestyle assessment: smoking status, exercise, diet, and alcohol intake
- Symptoms indicative of ischemic injury (eg, chest pain)
- Objective data
    - Height, weight, BMI, and blood pressure

- Lipoprotein concentrations (eg, total cholesterol/LDL-C/HDL-C/triglycerides)
- Laboratory findings (eg, AST/ALT, urinalysis, TSH, glucose, serum creatinine, and BUN at baseline)

Assess

- Potential secondary causes (eg, diabetes mellitus, alcohol abuse, kidney dysfunction, liver disease, drug-induced, thyroid disorder)
- Special needs of specific patient populations such as children/adolescents, pregnant or menopausal women, older adults, ethnic/racial groups, or high-risk conditions/residual risks (eg, patients with rheumatoid arthritis or residual risk despite statin and lifestyle therapy)
- Presence of high-risk comorbid conditions: diabetes mellitus, peripheral arterial disease, coronary artery disease, chronic kidney disease, carotid artery stenosis, and abdominal aortic aneurysm
- Dyslipidemia-related complications (eg, heart disease, stroke)
- Ten-year ASCVD-risk assessment (only if primary prevention)
- Current medications that may contribute to dyslipidemia
- LDL-C reduction based on statin benefit group (see Table 32-5, FIGURE 32-6, and FIGURE 32-7)
- Appropriateness and effectiveness of current lipid-lowering therapy (if any)*

Plan

- Tailored therapeutic lifestyle changes (eg, diet and nutrition)
- Drug therapy regimen including specific lipid-lowering medication, dose, route, frequency, and duration; specify the continuation and discontinuation of existing therapies (see Table 32-5, FIGURE 32-6, and FIGURE 32-7). Monitoring parameters including efficacy (eg, lipid panel, cardiovascular events), safety (medication-specific adverse effects), and time frame (3-month initial follow-up intervals, followed by 6 to 12 month intervals once at goal)
- Patient education (eg, purpose of treatment, dietary and lifestyle modification, drug therapy). Self-monitoring of weight, exercise, diet, drug adherence/adverse effects
- Referrals to other providers when appropriate for coordination of care (eg, physician, dietician)*

Implement

- Provide patient education regarding all elements of the treatment plan, including self-management training
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up; consider the time frame to achieve goals of therapy

Follow-up: Monitor and Evaluate

- The occurrence of cardiovascular (CV) events
- Determine patient adherence to treatment plan using multiple sources of information
- Determine response to lipid-lowering therapy and weight-loss goals
- Presence of medication-induced adverse effects (eg, elevated transaminases or myalgia on statins)

Collaborate with patient, caregivers, and other healthcare professionals.

TREATMENT

Desired Outcomes

Desired levels of TC, LDL-C, HDL-C, and TG for adults are provided in Table 32-2. While abnormalities in these surrogate markers may impart an increased risk for ASCVD events, the goal of treatment is to not merely correct lab abnormalities but prevent the development and progression of ASCVD. Thus, the desired outcome is to prevent ASCVD-related morbidity and mortality, including revascularization procedures, MI, and ischemic stroke. Initiation of lipid-lowering therapies primarily involves the use of those agents shown in RCT to reduce ASCVD risk.[17,24]

TABLE 32-2

Classification of Total-, LDL-, HDL-Cholesterol, and Triglycerides in Adults

Total Cholesterol	
<200 mg/dL (5.17 mmol/L)	Desirable
200-239 mg/dL (5.17-6.20 mmol/L)	Borderline high
≥240 mg/dL (6.21 mmol/L)	High
Low-Density Lipoprotein Cholesterol	
<100 mg/dL (2.59 mmol/L)	Optimal
100-129 mg/dL (2.59-3.35 mmol/L)	Near or above optimal
130-159 mg/dL (3.36-4.13 mmol/L)	Borderline high
160-189 mg/dL (4.14-4.90 mmol/L)	High
≥190 mg/dL (4.91 mmol/L)	Very high
High-Density Lipoprotein Cholesterol	
<40 mg/dL (1.03 mmol/L)	Low (Men)
<50 mg/dL (1.29 mmol/L)	Low (Women)
Triglycerides	
<150 mg/dL (1.70 mmol/L)	Normal
150-199 mg/dL (1.70-2.25 mmol/L)	Borderline high
200-499 mg/dL (2.26-5.64 mmol/L)	High
≥500 mg/dL (5.65 mmol/L)	Very high

General Approach

6 A comprehensive approach to treating dyslipidemia and all modifiable ASCVD risk factors is required to significantly reduce the risk of first and recurrent CV events. Therapeutic lifestyle change is the first-line therapy for any lipoprotein disorder. A healthy lifestyle should be implemented in all patients with the general components including a reduction in the percent of calories from saturated and *trans* fats, increased intake of soluble fiber,

weight reduction if overweight or obese, increased physical activity, and avoiding or quitting tobacco use.[24] Additionally, patients with a diagnosis of hypertension should achieve optimal blood pressure control based on the 2017 ACC/AHA Guidelines for control of hypertension (see Chapter 30, "Hypertension").[25] Persons with diabetes mellitus, especially those with established ASCVD, should receive glucose-lowering therapies that reduce ASCVD risk (see Chapter 94, "Diabetes Mellitus").[26]

5 If therapeutic lifestyle changes are insufficient, lipid-lowering agents should be chosen based on which lipid is at an undesirable level and the degree to which it is expected to increase the risk of ASCVD. The decision to initiate lipid-lowering therapy in the management of dyslipidemia should be based on an individual's ASCVD risk and not merely plasma levels of atherogenic lipoproteins (such as LDL-C) alone.[27] Patients with established ASCVD are at the highest risk and most likely to benefit from select lipid-lowering therapies (such as statins). Risk assessment in patients without established ASCVD is more of an art that requires careful consideration of traditional (eg, age, hypertension) and nontraditional (eg, autoimmune diseases, socioeconomic status) risk factors, the risks of lipid-lowering therapy, and patient preference. For patients between 40 and 79 years of age and no history of ASCVD, the ASCVD Risk Estimator Plus (available at: www.tools.acc.org/ascvd-risk-estimator-plus) should be used to facilitate a clinician-patient discussion regarding the benefit and risks of lipid-lowering therapy, especially in patients whose 10-year risk is 7.5% or greater (see FIGURE 32-6). The Risk Estimator is comprised of the patient's age, gender, race, TC, HDL-C, blood pressure, diabetes status, smoking status, and use of antihypertensives, statins, and aspirin. Importantly, the Risk Estimator is based on data from large population studies of mostly African American and non-Hispanic white men and women. The Risk Estimator can be used for other ethnic groups if they are designated as non-Hispanic white; however, the Risk Estimator will underestimate the risk of American Indians and Asian Americans of South Asian ancestry, while overestimating the risk of Asian Americans of East Asian ancestry and some Hispanics (eg, Mexican Americans).[27] An estimated lifetime risk for ASCVD can also be performed for patients between age 20 and 39, but results should only be used to justify the need for lifestyle changes and not the initiation of lipid-lowering therapy. Additional tools for ASCVD-risk assessment include high-sensitivity C-reactive protein (hsCRP), apolipoprotein B, and Lp(a) levels that may be obtained to inform decision making in low-intermediate risk patients or those with recurrent ASCVD events despite appropriate lipid-lowering therapy.[27]

6 7 The HMG-CoA reductase inhibitors or "statins" are the drugs of choice for most patients with dyslipidemia.[17] A large body of evidence from randomized, double-blind, placebo-controlled trials has demonstrated the effectiveness of statins on reducing first and recurrent cardiovascular events, cardiovascular mortality, and all-cause mortality.[28] The 2018 ACC/AHA Blood Cholesterol Guideline identified four statin benefit groups where the data from RCT demonstrate clear evidence that the benefit of statin therapy outweighs the potential risks (FIGURE 32-6 and FIGURE 32-7).[17] Nonstatin lipid-lowering therapies (ie, ezetimibe, bempedoic acid, and PCSK9 monoclonal antibodies [mAbs]) play a supportive role in the management of dyslipidemia and are primarily used in combination with statins when adequate LDL-C lowering cannot be achieved with statins alone, or in patients unable to tolerate the recommended dose of a statin (Table 32-5).[17]

FIGURE 32-6

The assessment and treatment decision regarding the use of statin therapy for primary prevention is complex and must consider multiple factors. Patient groups with an untreated LDL-C ≥190 mg/dL (4.91 mmol/L) or type 1 or 2 diabetes (age 40-75 years) are eligible for statin therapy without estimating ASCVD risk using the Pooled Cohorts Equation. Given the limited data in adults over age 75, a patient-clinician discussion regarding the benefits and risks of statin therapy for primary prevention is warranted. For all other individuals, age is a primary consideration to determine the appropriate method of risk assessment and treatment recommendations. For conversion of LDL-C levels from units of mg/dL to SI units of mmol/L multiply by 0.02586.

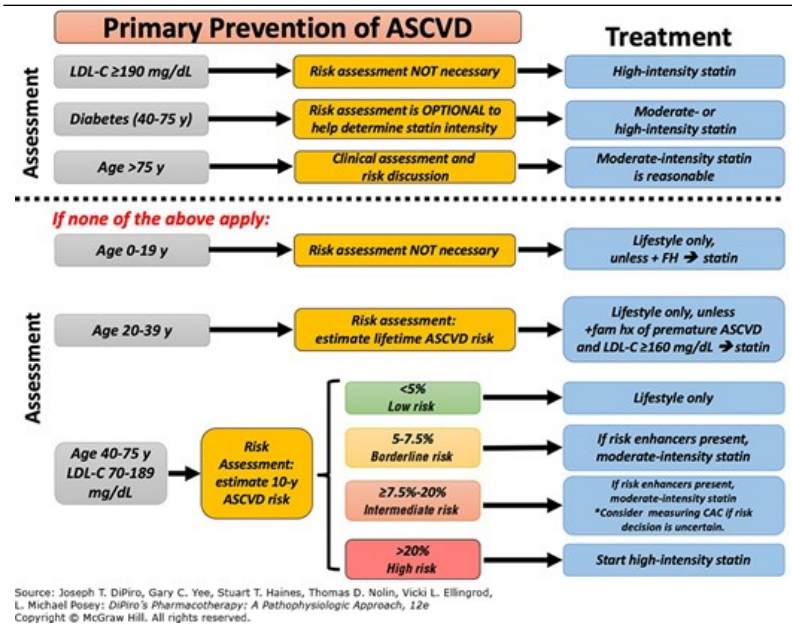
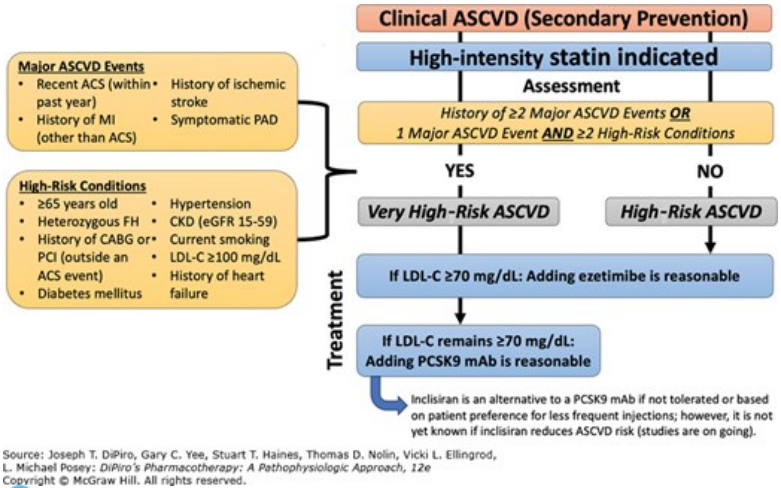


FIGURE 32-7

Patients with established clinical ASCVD are considered secondary prevention and high-intensity statin therapy is automatically indicated. Moderate-intensity statin should only be considered in adults >75 years of age and those unable to tolerate high-intensity statin therapy. After high-intensity statin therapy is initiated, ezetimibe may be added if the LDL-C remains ≥70 mg/dL (1.81 mmol/L). In select, very high-risk patients, adding a PCSK9 mAb is reasonable if the LDL-C remains ≥70 mg/dL (1.81 mmol/L) after adding ezetimibe. Inclisiran may be considered as an alternative to a PCSK9 mAb if not tolerated or less frequent injections are preferred by the patient; however, it is not yet known whether inclisiran reduces ASCVD risk. For conversion of LDL-C levels from units of mg/dL to SI units of mmol/L multiply by 0.02586.



Numerous clinical outcome trials have been performed to determine whether lipid-lowering therapies reduce ASCVD risk in primary and secondary prevention populations. It is beyond the scope of this chapter, however, to discuss each of these trials in detail. Table 32-3 summarizes select trials supporting the use of statins and select nonstatins (ezetimibe and PCSK9 mAb) to reduce ASCVD risk. Most of the primary and secondary prevention studies were double-blinded, randomized, and placebo-controlled, lasting 2 to 7 years, and had sufficient patient numbers to be meaningful. The body of evidence supporting the role of statin therapy to reduce ASCVD is substantial and meta-analysis confirms the first-line role this class of drugs should play in dyslipidemia management.[29] As mentioned previously in this chapter, not all lipid-lowering therapies have translated to reducing ASCVD risk, despite having favorable effects on the lipid profile.

TABLE 32-3

Select Landmark Clinical Trials with Lipid-Lowering Drugs Targeting LDL Cholesterol

Trial	Patient Population (*n*)	Intervention	Primary Endpoint	Event Rates, Intervention vs Control (%)	RRR (%)	ARR (%)	NNT
Statin Landmark Trials—*Primary prevention*							
AFCAPS/TexCAPS	LDL-C 130-190 mg/dL (3.36-4.91 mmol/L) and HDL-C <47 mg/dL (1.22 mmol/L) (*n* = 6,605)	Lovastatin 20-40 mg vs placebo	Acute major coronary events	3.5 vs 5.5	36.4	2.0	50
CARDS	Age 40-75 years with T2DM and LDL-C <160 mg/dL (4.14 mmol/L) plus additional risk factor (*n* = 2,383)	Atorvastatin 10 mg vs placebo	Coronary heart disease events, coronary revascularization, or stroke	5.8 vs 9.0	37	3.2	32
JUPITER	LDL-C <130 mg/dL (3.36 mmol/L) and hsCRP ≥2.0 mg/L (*n* = 17,802)	Rosuvastatin 20 mg vs placebo	5-point MACE	1.6 vs 2.8	44	1.2	82
HOPE-3	Men and women (age 55 years and older) with at least one cardiovascular risk factor (*n* = 12,705)	Rosuvastatin 10 mg vs placebo	3-point MACE	3.7 vs 4.8	24	1.1	91
Statin Landmark Trials—*Secondary prevention*							
HPS	Previous ASCVD or high risk (*n* = 20,536)	Simvastatin 40 mg vs placebo	All-cause mortality	12.9 vs 14.7	13	1.8	56
PROSPER	Elderly (age 70-82 years) with previous vascular disease or elevated risk (*n* = 5,804)	Pravastatin 40 mg vs placebo	3-point MACE	14.1 vs 16.2	15	2.1	48
TNT	Clinical coronary heart disease (*n* = 10,001)	Atorvastatin 80 mg vs 10 mg	4-point MACE	8.7 vs 10.9	22	2.2	45
Non-statin Landmark Trials							
IMPROVE-IT	Recent ACS (*n* = 18,144)	Ezetimibe + simvastatin vs simvastatin	5-point MACE	32.7 vs 34.7	6	2	50
FOURIER	Previous ASCVD (*n* = 27,564)	Evolocumab + statin vs statin	5-point MACE	9.8 vs 11.3	15	1.5	67
ODYSSEY-OUTCOMES	Recent ACS (*n* = 18,924)	Alirocumab + statin vs statin	4-point MACE	9.5 vs 11.1	15	1.6	63

CLEAR-OUTCOMES	Statin-intolerant patients - 70% Secondary Prevention; 30% Primary Prevention (n=13,970)	Bempedoic acid vs placebo	4-point MACE	11.7 vs 13.3	13	1.6	63

ACS, acute coronary syndrome; ARR, absolute risk reduction; AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study[30]; ASCVD, atherosclerotic cardiovascular disease; CARDS, Collaborative Atorvastatin Diabetes Study[12]; CLEAR OUTCOMES, Cholesterol Lowering via Bempedoic Acid [ECT1002], an ACL-Inhibiting Regimen[121] FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Patients with Elevated Risk[31]; HOPE-3, Heart Outcomes Prevention Evaluation 3[32]; HPS, Heart Protection Study[33]; hsCRP, high-sensitivity C-reactive protein; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trail[34]; JUPITER, Justification for the Use of Statins in Prevention[35]; LDL-C, Low-Density Lipoprotein Cholesterol; MACE, Major Adverse Cardiovascular Events; MI, myocardial infarction; NNT, Number Needed to Treat; ODYSSEY-OUTCOMES, Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab[36]; PROSPER, Pravastatin in elderly individuals at risk of vascular disease[37]; RRR, relative risk reduction; T2DM = Type 2 Diabetes Mellitus; TNT, Treat to New Targets Trial[38]; 3-point MACE = cardiovascular death, nonfatal myocardial infarctions, nonfatal stroke. 4-point MACE = death from coronary heart disease, nonfatal MI, fatal or nonfatal stroke, hospitalization for unstable angina. 5-point MACE = cardiovascular death, nonfatal myocardial infarctions, nonfatal stroke, arterial revascularization, hospitalization for unstable angina.

Nonpharmacologic Therapy

Lifestyle modification is the cornerstone of ASCVD-risk reduction and is recommended in all patients, including those receiving lipid-lowering therapy. Weight and body mass index (BMI) should be determined at each visit and lifestyle patterns to induce a weight loss of 5% to 10% should be discussed in persons who are overweight or obese (Table 32-4). Moderate-to-vigorous intensity physical activity is recommended three to four times per week with each session lasting 40 minutes on average. All patients should also be counseled to stop smoking and avoid tobacco products altogether.[24]

TABLE 32-4

Nonpharmacologic Therapy to Improve Lipid Levels and ASCVD Risk

Recommendations to Modify Select Lipid Parameters	
Lower LDL cholesterol	• Increase soluble fiber intake • Phytosterol (2 g/day) supplementation
Increase HDL cholesterol	• Increase physical activity • Smoking cessation
Lower triglycerides	• Lose weight (5%-10% body weight loss) • Increase physical activity • Abstain from alcohol • Reduce intake of refined carbohydrates and sugars
Recommendations to Reduce ASCVD Risk	
Nutrition and diet	• Avoid eating trans fats • Increase intake of vegetables, fruits, legumes, nuts, whole grains, and fish • Replace foods containing saturated fats with unsaturated (monounsaturated and polyunsaturated) fats • Minimize intake of processed meat products, refined carbohydrate foods, and sweetened beverages • Reduce intake of cholesterol and sodium-containing foods • For patients who are overweight or obese, reduce daily calories to achieve and maintain weight loss of 5%-10%
Physical activity	• Obtain at least 150 min/week of moderate-intensity or 75 minutes of vigorous-intensity physical activity • Decrease sedentary behaviors
Other lifestyle factors	• Smoking cessation and avoiding tobacco products • Avoid secondhand smoke exposure

ASCVD, atherosclerotic cardiovascular disease.

It is important to recognize that there is no single diet suitable for every patient. Instead, advise patients to reduce the percent of calories from saturated and *trans* fats by following a dietary pattern that emphasizes vegetables, fruits, whole grains, low-fat dairy, poultry, fish, legumes, and nuts, while limiting the intake of sweets, sugary beverages, and red meat. Plans that closely mirror this dietary pattern and effectively lower LDL-C include DASH, the USDA Food Pattern, and AHA Diet. Although the Mediterranean-style diet has no consistent effect on LDL-C levels, it reduces major cardiovascular events among persons at high cardiovascular risk when compared to a control diet. Any recommended dietary pattern should be adapted to a patient's caloric requirements, cultural food preferences, and other medical conditions (eg, diabetes mellitus). Individualized diet counseling that provides acceptable substitutions for unhealthy foods and ongoing reinforcement by a registered dietitian are necessary for maximal effect. It is also important to involve all family members, especially if the patient is not the primary person preparing food.[24]

Less than one-third of Americans meet the 2015-2020 Dietary Guidelines for Americans limit of less than 10% of calories from saturated fats.[39] In patients with lipid disorders, the 2013 AHA/ACC Lifestyle Management Guideline recommended only 5% to 6% of total calories from saturated fat.[24] This can be achieved by recommending patients limit or avoid fast food, high-fat dairy products, and sweets. Previous dietary guideline

recommendations to limit dietary cholesterol to 300 mg/day was omitted in 2015. However, it is still recommended that individuals limit their daily dietary cholesterol intake. A dietary pattern low in saturated and *trans* fats will typically result in a reduction in dietary cholesterol since foods high in saturated and *trans* fats are often high in cholesterol. A 12-week trial of lifestyle modification is generally recommended before considering lipid-lowering therapy in patients without evidence of ASCVD, diabetes, or other high-risk features. Importantly, lifestyle modification alone is inappropriate for patients with established ASCVD or diabetes given the benefit of statins in these high-risk patients.

Few clinical trials have compared dietary supplements to statin therapy. In 2023, the Supplements, Placebo, or Rosuvastatin Study (SPORT) trial compared the LDL-C lowering efficacy of rosuvastatin 5 mg daily to six commonly used dietary supplements: fish oil, cinnamon, garlic, turmeric, plant sterols, and red yeast rice.[122] This single-center, prospective, randomized trial enrolled adults who were not taking any prescription lipid-lowering therapies and had no history of ASCVD, an LDL-C between 70 and 189 mg/dL, and an increased 10-year risk ASCVD risk between 5% and 20%. When compared to placebo, the low-dose rosuvastatin produced a significant reduction in LDL-C from baseline (-35.2%), while none of the dietary supplements produced a significant reduction in LDL-C. Importantly, the incidence of adverse events was similar between groups. While some participants did have a significant reduction in LDL-C when taking a dietary supplement, a similar number of individuals had little to no response or experienced an increase in LDL-C. This did not occur in the participants randomized to rosuvastatin. The SPORT study confirms the LDL-C lowering efficacy and safety of statin therapy, even at low doses, and suggests that dietary supplements should play a limited role.

Dietary Supplements

Select dietary supplements may be useful to augment diet and lipid-lowering therapy. Increased intake of soluble fiber in the form of oat bran, pectins, certain gums, and psyllium products can reduce total and LDL-C, but have little or no effect on HDL-C or TG levels. Soluble fiber binds cholesterol and bile acids in the small intestine, which decreases absorption and reabsorption. Total daily fiber intake should be about 25 g/day, yet most Americans average only half of the recommended amount.[40] Dietary supplements containing fiber may be used to supplement the diet and achieve the recommended daily intake. An intake of 3 to 12 g/day show reductions in total and LDL-C of 10 mg/dL (0.26 mmol/L) and 12 mg/dL (0.31 mmol/L), respectively, compared to control.[27] It remains unknown if soluble fiber supplements have any impact on cardiovascular morbidity and mortality. Although seemingly safe, patients should be advised to stay well hydrated to avoid gastrointestinal distress. These products may also be useful in managing constipation associated with the bile acid sequestrants (BASs).

In epidemiologic studies, ingestion of large amounts of oily, cold-water fish (such as salmon) is associated with a reduction in ASCVD risk. Modest consumption (1-2 servings per week) reduces the risk of cardiovascular death and total mortality.[41] The American Heart Association recommends eating oily fish at least twice a week; however, there are concerns with some types of fish (such as tuna) that often have high levels of environmental contaminants. There are also concerns about environmental sustainability. Fish oil supplementation is an alternative option that provides a consistent daily intake of omega-3 PUFA such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Fish oil supplementation significantly reduces TG levels and VLDL-C but may increase total cholesterol and LDL-C. Other potentially favorable cardiovascular effects of fish oil supplementation include antiarrhythmic, antiplatelet, and anti-inflammatory properties. Despite this, a meta-analysis of 10 RCTs found low doses (less than 2 g/day) of omega-3 PUFA supplementation did not reduce the risk of ASCVD events.[42] Low-dose omega-3 PUFA supplementation is not recommended in primary prevention patients, especially those with diabetes who do not have established ASCVD.[43,44] Additional details regarding prescription omega-3 PUFA products are further discussed under drug therapy.

Phytosterols, including plant sterols and stanols isolated from vegetable oils, also reduce LDL-C levels. Ingestion of 2 g/day will reduce LDL-C by 5% to 15%, while doses above 3 g/day confer no additional LDL-C lowering.[27] The efficacy of plant sterols and plant stanols is comparable. The mechanism by which phytosterols reduce LDL-C remains unclear but may decrease the transport of cholesterol in the intestinal brush border membrane and affect cholesterol uptake via Niemann-Pick C1-Like 1 (NPC1L1) and other transporters. Because lipids are needed to solubilize stanol/sterol esters, they are usually available in commercial butter-like spreads (such as Benecol®). The presence of plant stanols/sterols is listed on the food label. Phytosterols should be administered 2 to 4 hours before or after BASs to avoid the binding of phytosterols in the gut. Although phytosterols are generally recognized as safe (GRAS) in the United States, they can cause gastrointestinal distress and should be avoided in patients with sitosterolemia, a rare genetic disorder characterized by a 50- to 100-fold increase in plant sterol levels and rapid onset of atherosclerosis.[45] The effects of long-term phytosterol supplementation on ASCVD risk remains unknown.

Red yeast rice is a commonly used dietary supplement in the United States that originates from Chinese medicine. The active ingredient of red yeast

rice is monacolin K, which is chemically identical to lovastatin. This leads some patients to believe red yeast rice is a "natural" statin and, therefore, safer than statins available only by prescription; however, the active ingredient in over-the-counter (OTC) red yeast rice products vary by over 120-fold. Many products contain little to no monacolin.[46] Conversely, case reports of rhabdomyolysis, liver toxicity, and renal failure have raised concerns about some red yeast rice formulations containing significantly higher levels of monacolin K than described on the label.[47] Red yeast rice is not recommended as a suitable alternative to statins. However, if patients choose to take red yeast rice, it is recommended that they purchase it from a reputable supplier and avoid concurrent use with prescription statins.

Pharmacologic Therapy

9 There are numerous randomized, double-blinded clinical trials demonstrating that reduction of LDL-C reduces ASCVD-event rates in the setting of primary and secondary prevention.[29] Epidemiological studies suggest that every 38 mg/dL (0.98 mmol/L) reduction in LDL-C produces a 21% reduction in ASCVD event rates over 5 years.[48] Additional findings from large prospective cohort studies and Mendelian randomization studies have also demonstrated a dose-dependent log-linear association between LDL-C and ASCVD risk[49] and that lower levels of LDL-C achieve significant reductions in ASCVD risk. These studies provide a strong rationale for attempting to lower plasma cholesterol and LDL-C in patients at risk for ASCVD.[49] It should be noted, however, that not all lipid-lowering agents that reduce LDL-C have resulted in a reduction in ASCVD events (eg, CETP inhibitors). Thus, LDL-C lowering alone should not be the sole basis for selecting an appropriate agent.[17,27] Lipid-lowering drugs can be broadly divided into agents that primarily decrease atherogenic cholesterol-containing lipoprotein particles (such as statins) and those that primarily decrease TG levels (such as fibrates).

Treatment of Specific Dyslipidemia Subtypes

Familial Hypercholesterolemia

Individuals with familial hypercholesterolemia (FH) have a high lifetime risk of developing ASCVD. Compared to the general population, FH is associated with a 24-fold higher risk of developing acute MI before the age of 40 years.[50] FH should be suspected in adults with untreated LDL-C levels of 190 mg/dL (4.91 mmol/L) or greater or non-HDL cholesterol levels of 220 mg/dL (5.69 mmol/L) or greater who have a family history of high cholesterol or ASCVD in first-degree relatives. Physical findings (such as xanthomas or corneal arcus) may be present in some patients with FH, but their absence does not rule out a diagnosis of FH. In clinical practice, one of several validated tools, including the Dutch Lipid Clinic Network, US Make Early Diagnosis Prevent Early Death (MEDPED), and Simon-Broome Registry, are used to make a formal diagnosis of FH. Genetic testing is available, however, approximately 20% of patients with clinically definite FH will not have an identifiable mutation; therefore, a negative genetic test does not exclude FH.[51] Importantly, cascade screening of all first-degree relatives of diagnosed FH patients is highly recommended as an effective strategy to identify previously undiagnosed FH patients.

Intensive lifestyle and pharmacological therapy are often necessary for adults with FH. In patients with FH who have not had an ASCVD event, a high-intensity statin is warranted and those with an LDL-C ≥100 mg/dL (2.59 mmol/L) despite max-tolerated statin should receive ezetimibe, bempedoic acid, and/or a PCSK9 mAb. The LDL-C threshold to consider nonstatin therapies in patients with FH and a history of ASCVD, however, is ≥70 mg/dL (1.81 mmol/L).

10 Lomitapide is an orphan drug indicated for use in patients with HoFH and reduces LDL-C levels by ~40%.[52] Orally administered, lomitapide is a microsomal triglyceride transfer protein, or microsomal TG transfer protein inhibitor, which reduces the level of cholesterol that the liver and intestines assemble and secrete into the circulation. Lomitapide has a black box warning for severe hepatotoxicity and is only available through restricted Risk Evaluation and Mitigation Strategy (REMS) programs.[52] Other treatment options for HoFH patients include evinacumab, LDL apheresis (a process similar to dialysis that removes LDL from the blood) and liver transplant.[50]

Evinacumab was approved to lower LDL-C in patients with HoFH at the age of 12 years and older. Evanicumab is a humanized monoclonal antibody that inhibits angiopoietin-like 3 (ANGPTL3) protein and is administered as an IV infusion every 4 weeks. The ANGPTL3 protein regulates lipid metabolism by inhibiting LPL and endothelial lipase enzymes. Inhibition of ANGPTL3 with Evinacumab reduces LDL-C by ~50% and also reduces TG by ~55% in patients with HoFH.[53] Adverse effects of Evinacumab include infusion-site reactions, influenza-like illness, and rhinorrhea. It is unknown whether evinacumab reduces ASCVD events.

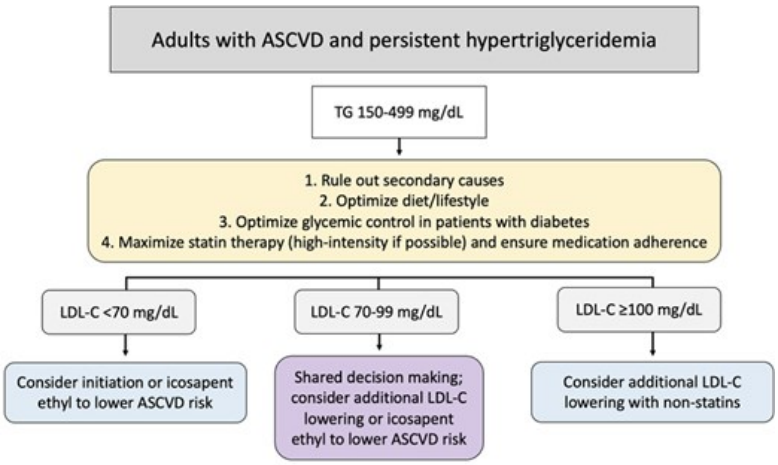
Hypertriglyceridemia

10 Elevated TG levels are strongly associated with an increased risk of ASCVD; however, the direct role of TG in the development of ASCVD is debated.[54] All patients with elevated TG levels (see Table 32-2) should be advised to implement lifestyle interventions that reduce TG levels, including a 5% to 10% reduction in body weight, reducing consumption of sugar and refined carbohydrates, increasing physical activity, smoking cessation, and restricting alcohol. Secondary causes of hypertriglyceridemia should also be identified and addressed. Uncontrolled diabetes and chronic kidney disease are common causes of elevated TG levels, along with certain medications (such as protease inhibitors and atypical antipsychotics). The best approach to managing patients whose TG levels remain elevated after optimizing lifestyle interventions and addressing secondary causes remains unclear, but statins are generally considered first-line given they can reduce TG levels by up to 30% at higher doses and help achieve desired levels of LDL-C.[55] Fibrates effectively lower TG levels but are not routinely used for borderline-high TG levels as there is no evidence supporting their use to reduce ASCVD risk. Omega-3 PUFA also significantly lower TG levels at higher doses (2-4 g/d) but only icosapent ethyl (EPA-only) prescription product is indicated for borderline-high TG levels and to reduce ASCVD risk.[56]

Fasting TG levels exceeding 500 mg/dL (5.65 mmol/L) are more commonly associated with pancreatitis and other consequences of hyperchylomicronemia (such as eruptive xanthomas). At this level of elevated TG, a genetic form of hypertriglyceridemia often coexists with other causes of elevated triglycerides such as diabetes. Dietary fat restriction is a basic element of treatment as this reduces the synthesis and entry of additional chylomicrons into the circulation. Lipid-lowering therapies that primarily lower TG levels (ie, fibrates and omega-3 PUFA) are recommended as first-line agents.[56] However, statins are a reasonable first-line options as hypertriglyceridemia is considered a risk-enhancing factor. If TG levels are persistently over 500 mg/dL (5.65 mmol/L), it is reasonable to consider adding omega-3 PUFA or fibrate therapy (Figure 32-8). The goal is to reduce triglycerides below 500 mg/dL (5.65 mmol/L) and prevent pancreatitis.

FIGURE 32-8

Hypertriglyceridemia management focuses primarily on ruling out secondary causes and optimizing lifestyle behaviors. In patients with T2DM, optimizing glycemic control can significantly reduce TG levels. Importantly, individuals with elevated TG levels should be evaluated for their risk of ASCVD and statin therapy should be initiated when indicated. In some patients, TG levels will remain significantly elevated (≥500 mg/dL) and require additional therapy, such as fenofibrate or omega-3 fatty acids, to reduce the risk of acute pancreatitis.



Low HDL Cholesterol

Low HDL-C is a strong independent risk predictor of ASCVD5.[7] Low HDL-C is defined as less than 40 mg/dL (1.03 mmol/L) for men and less than 50 mg/dL (1.29 mmol/L) for women, but there is no specified goal for HDL-C raising. Low HDL-C may be a consequence of insulin resistance, physical inactivity, diabetes, cigarette smoking, high carbohydrate intake, and certain drugs. In patients with low HDL-C levels, the primary target remains LDL-

C. Niacin has the potential for the greatest increase in HDL-C compared to other lipid-lowering therapies and the effect is more pronounced with regular or immediate-release forms than with sustained-release forms. However, no RCT has resulted in a reduction in ASCVD risk by increasing HDL-C5.[8,57] Additionally, several CETP inhibitors capable of raising HDL-C levels as much as 135% were evaluated in randomized, placebo-controlled trials but no additional benefit was found when these drugs were added to background statin therapy.[58] Due to the lack of pharmacological agents demonstrating an improvement in clinical outcomes by focusing on raising HDL-C, lifestyle modification (such as smoking cessation and increasing physical activity) remains the preferred approach. Although alcohol consumption increases HDL-C, it is not acceptable to recommend this to patients who do not already consume alcohol.

Medications That Primarily Lower Atherogenic Cholesterol

HMG-CoA Reductase Inhibitors (Statins)

Statins (such as atorvastatin) are considered the first-line lipid-lowering therapies for managing dyslipidemia due to robust evidence from multiple RCTs demonstrating that statins significantly decrease the risk of first (primary prevention) and recurrent (secondary prevention) cardiovascular events.[17,48] Statins significantly reduce LDL-C levels (20%-60%), modestly increase HDL-C (6%-12%), and decrease TG levels (10%-29%).[59] Statins interrupt the conversion of HMG-CoA to mevalonate, the rate-limiting step in de novo cholesterol biosynthesis, by inhibiting HMG-CoA reductase (see FIGURE 32-4). Metabolic studies with statins in normal volunteers and patients with hypercholesterolemia suggest a reduced synthesis of LDL-C, as well as enhanced catabolism of LDL mediated through LDL receptors, as the principal mechanisms for lipid-lowering effects. Statin selection is primarily based on the patient's individual ASCVD risk and indicated intensity (see Table 32-5). Currently available products in order of decreasing LDL-C lowering potency include rosuvastatin, atorvastatin, pitavastatin, simvastatin, lovastatin, pravastatin, and fluvastatin.[59] The plasma half-lives for all the statins are relatively short (1-3 hours) except for atorvastatin, pitavastatin, and rosuvastatin, which may account for their potency.[59] Statins are generally well tolerated but are not without adverse effects. However, discontinuation rates due to adverse effects in randomized, double-blind, placebo-controlled trials have often been similar between statin and placebo.[60]

TABLE 32-5

Intensity of Statin Therapy by Drug and Daily Dose

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Lowers LDL-C on average by ≥50%	Lowers LDL-C on average by 30% to <50%	Lowers LDL-C on average by <30%
Atorvastatin 40-80 mg **Rosuvastatin 20-40 mg**	**Atorvastatin 10-20 mg** **Rosuvastatin 5-10 mg** **Simvastatin 20-40 mg**[a] Pravastatin 40-80 mg **Lovastatin 40 mg** Fluvastatin XL 80 mg **Fluvastatin 40 mg BID** Pitavastatin 2-4 mg	Simvastatin 10 mg **Pravastatin 10-20 mg** **Lovastatin 20 mg** Fluvastatin 20-40 mg Pitavastatin 1 mg

[a]Simvastatin is not recommended by the FDA to be initiated at 80 mg/day due to increased risk of myopathy and rarely rhabdomyolysis.

FDA, Food and Drug Administration; RCT, randomized clinical trials.

Boldface type indicates medications that have cardiovascular outcome data from RCTs when given in the specified dose.

Statin-associated muscle symptoms (SAMS) are reported by 10% to 25% of statin users and are frequently reported by patients as a reason for statin discontinuation.[61] While various definitions of SAMS exist, the clinical diagnosis of SAMS is based on a subjective clinical assessment. Myalgia is the

most reported muscle-related adverse effect with statin therapy and refers to bilateral muscle achiness, weakness, or cramps affecting larger muscle groups (such as thighs and back). Myopathy is often used interchangeably with myalgia, but myopathy is a general term used for any muscle-related symptoms. The most concerning of SAMS is rhabdomyolysis, which is a rapid breakdown of skeletal muscle resulting in creatine kinase (CK) elevations greater than 10 times the upper limit of normal. The release of myoglobin from damaged muscle tissue may also compromise renal function and lead to acute kidney injury. Patients presenting with rhabdomyolysis will often describe their urine as dark or "tea-colored" and present with nausea, vomiting, confusion, coma, cardiac arrhythmias, electrolyte disturbances, and even death. Fortunately, rhabdomyolysis in statin-treated patients is exceedingly rare occurring in only 0.1% of patients in RCT compared to 0.04% of patients receiving placebo. Rhabdomyolysis is not only caused by statins but can also be induced by extreme physical exercise, certain metabolism disorders (eg, diabetic ketoacidosis), other drugs (eg, colchicine), toxins, and infection.

Certain risk factors are known to increase the risk of developing SAMS and recognition of these risk factors at the time of statin initiation may minimize the risk of SAMS. Known risk factors include advanced age, female gender, low body mass index, frequent heavy exercisers, comorbidities (eg, kidney disease, hypothyroidism), and increased serum statin concentrations due to drug-drug interactions.[61] A lower dose might be necessary for patients with multiple risk factors for SAMS, and once the starting dose is tolerated, the dose can be titrated to the desired potency. Avoiding major drug-drug interactions is a significant modifiable risk factor for SAMS that pharmacists can directly impact. Nearly 80% of all medications are metabolized in the liver by the cytochrome P450 system (CYP) with CYP3A4 being the most predominant.[62] Statins are no different as nearly all statins, except pravastatin, are metabolized to some degree by CYP isoenzymes. Lovastatin, simvastatin, and atorvastatin are associated with more significant drug-drug interactions since they are predominantly metabolized by CYP3A4, while fluvastatin, pitavastatin, and rosuvastatin rely on other CYP isoenzymes (eg, CYP2C9, CYP2C8, CYP2C19).[63]

The co-prescribing of medications that compete with or inhibit the same CYP isoenzyme (ie, verapamil) can increase serum statin concentrations and the risk for SAMS. The concurrent use of medications such as gemfibrozil that interfere with statin glucuronidation, which is responsible for statin clearance, increases the risk of SAMS.

The management of SAMS requires a multifaceted approach. Documentation of the patients' reported symptoms and determining the probability of SAMS is an important first step. A Statin Intolerance App (available at: http://www.acc.org/statinintoleranceapp) created by the ACC is a helpful resource that can be used to determine the possibility of SAMS and provide guidance on managing patients with possible SAMS. Statin therapy should be generally discontinued in patients with intolerable symptoms. If symptoms resolve, initiate a different statin at a lower dose.[61,64] Additionally, hydrophilic statins (such as rosuvastatin) may be better tolerated than lipophilic statins (such as simvastatin). In patients where symptoms do not improve, other potential causes of muscle pain should be excluded, including hypothyroidism and vitamin D deficiency, before a statin rechallenge.[64] Alternative dosing strategies (eg, every other day) using statins with long half-lives (atorvastatin, rosuvastatin, and likely pitavastatin) may also be considered. Nonstatin therapies may be considered in patients who fail multiple statins. While routine CK monitoring is not recommended, a CK measurement prompted by patient symptoms can be used to exclude rhabdomyolysis and can assist with identifying those with definite myalgia. Importantly, patients should be reassured that statins are effective and safe, and SAMS is reversible with statin discontinuation.

Other notable adverse effects of statins include mild elevations in serum transaminase levels (primarily alanine aminotransferase [ALT]). Liver enzymes are not, however, an accurate measure of liver function, and there is no causal relationship between statin use and liver failure. Therefore, routine periodic monitoring of liver enzymes is not required, but liver enzyme tests should be obtained before starting statin therapy to have a baseline value for comparison if liver enzymes are later discovered to be elevated. Other potential causes for elevated liver enzymes, including excessive alcohol intake, infection, and select medications should also be evaluated. Statins may be initiated in patients with chronic liver disease, compensated cirrhosis, and nonalcoholic fatty liver disease; however, statins are contraindicated in patients with decompensated cirrhosis or acute liver failure.[64]

Statin use is also associated with a small increased risk of new-onset diabetes.[61] This was first observed in the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial, where the number of new-onset diabetes cases was 0.6% higher in those receiving rosuvastatin 20 mg/day compared to placebo.[35] Subsequent meta-analyses of statin trials have also found a modest increase in the number of new-onset diabetes cases among statin-treated patients compared to placebo, but the absolute risk increase is <1%.[65,66] Common attributes of statin users who develop new-onset diabetes include receiving higher doses of statins and having other risk factors for diabetes, including obesity, impaired fasting glucose, HbA1c >6% (0.06; 42 mmol/mol), or metabolic syndrome.[67] Mechanisms to explain the association between statin use and

new-onset diabetes remain unclear. However, observational data suggest that higher cholesterol levels are protective against developing diabetes. This may be attributable to changes at the cellular level involving disruption of cholesterol-sensitive cellular functions that affect insulin secretion and insulin sensitivity.[61] Ultimately, the benefit of statin therapy greatly outweighs the risk of new-onset diabetes as statin use in patients at high ASCVD risk will prevent approximately three ASCVD events for every new case of diabetes. Table 32-6 lists common adverse effects of available lipid-lowering therapies.

While statins are generally well tolerated, approximately 5% to 30% of patients will have statin intolerance, which is defined by the National Lipid Association as side effects associated with statin therapy that resolve or improve after a dose decrease or discontinuation of statin therapy after attempting at least two statins, with one at the lowest approved dose.[123] Importantly, statin intolerance can be complete – inability to tolerate any statin dose – or partial – inability to tolerate the dose required to achieve the desired level of LDL-C. Complete statin intolerance, however, is rare and estimated to affect <5% of statin users. Clinicians should also consider the "nocebo" effect, which occurs when a patient expects harm from a medication that is then perceived as a side effect. It's estimated that up to 90% of SAMS may be attributable to the nocebo effect; however, such symptoms reported by a patient must still be acknowledged and addressed by the clinician.

TABLE 32-6

Safety of Lipid-Lowering Therapies

Lipid-Lowering Drug Class	Adverse Effects		Contraindications
	Common/Possible (1%-10%)	Rare/unlikely (<1%)	
Statins	• Statin-associated muscle symptoms (myalgia/myopathy) • New-onset diabetes mellitus • Transient, mild elevation in transaminase levels	• Rhabdomyolysis • Severe hepatotoxicity	• Pregnancy/breastfeeding • Decompensated cirrhosis • Acute liver failure
Cholesterol absorption inhibitors	• GI adverse effects • Myalgias (when used with statin) • Elevated transaminase levels (when used with statin)	• Thrombocytopenia	• Pregnancy/breastfeeding • Acute liver failure
Bile acid sequestrants	• GI adverse effects and/or obstruction • Impaired absorption of fat-soluble vitamins • Reduced bioavailability of select drugs	• Ileus • Cholecystitis • Severe hypertriglyceridemia	• History of bowel obstruction • Fasting TG are 300 mg/dL or higher
ACL inhibitors	• Hyperuricemia • Cholelithiasis	• Increased risk of tendon rupture • Increased risk of benign prostate hyperplasia	
PCSK9 mAbs	• Injection-site reactions • Flu-like symptoms post-injection		• Hypersensitivity reaction to alirocumab or evolocumab
Fibrates	• GI adverse effects • Transient elevation in transaminases	• Increased risk of gallstones	• Pre-existing gallbladder disease • CrCl of 30 mL/min (0.5 mL/s) or lower

	• Myalgias (especially when used with statin) • Mild increase in serum creatinine		
Omega-3 PUFA	• GI adverse effects • Eructation • Increased risk of bleeding when used with antiplatelets or anticoagulants • Increased risk of atrial fibrillation or flutter		• Caution in patients with allergy or sensitivity to fish and/or shellfish
Niacin	• Dermatologic effects (flushing/itching) • Increased transaminases • Hyperuricemia • Hyperglycemia	• Increased risk of atrial fibrillation or flutter • Rhabdomyolysis (with statin) • Hepatotoxicity (with statin)	• Active peptic ulcer • Arterial hemorrhage • Persistently elevated transaminase levels
Inclisiran	• Injection-site reactions		• Pregnancy/breastfeeding
Evinacumab	• Infusion-site pruritus • Influenza-like reactions • Rhinorrhea		• Pregnancy/breastfeeding

ACL, adenosine triphosphate-citrate Lyase; CrCl, creatinine clearance; mAbs, monoclonal antibodies; PUFA, polyunsaturated fatty acids; SAMS, statin-associated muscle symptoms.

Cholesterol Absorption Inhibitors

Ezetimibe is a preferred adjunct therapy given, it modestly reduces the risk of recurrent cardiovascular events in a secondary prevention population when used in combination with statin therapy.[34] The primary lipid-lowering effect of ezetimibe is a modest reduction in LDL-C of 15% to 24%; with higher reductions achievable when used in combination with statin therapy.[34,68] Ezetimibe reduces LDL-C by inhibiting the NPC1L1 protein, an important transporter of cholesterol absorption in the small intestine and hepatocytes.[68] Some polymorphisms of the *NPC1L1* protein are associated with lower LDL-C levels and lower ASCVD risk, which explains why ezetimibe reduces ASCVD risk.[69] Other than mild gastrointestinal complaints (ie, diarrhea) and post-marketing reports of myalgia and mild ALT elevations when used in combination with statins, ezetimibe is generally well tolerated. Previous concerns over a potential increased risk of cancer have been nullified given recent prospective clinical trial data showing there is no increased risk of cancer with ezetimibe use.[34] Ezetimibe has no effects on the CYP450 enzyme system; however, concomitant use with cyclosporine can lead to increased exposure to both ezetimibe and cyclosporine.[68]

The BASs, such as colesevelam, modestly reduce LDL-C (13%-20%) and reduce cardiovascular events when used as monotherapy.[70] There is no data to determine if the benefits observed with BAS monotherapy translates to its use in combination with statin therapy. As such, BAS are generally used as adjunct therapy with statins when desired LDL-C levels are not achieved with statins alone. Importantly, BAS are considered first line during pregnancy since they are not systemically absorbed and pose no risk to the fetus. The primary action of BAS is to bind bile acids in the intestinal lumen, with a concurrent interruption of enterohepatic circulation of bile acids and a markedly increased excretion of acidic steroids in the feces. This decreases the bile acid pool size and stimulates the hepatic synthesis of bile acids from cholesterol. Depletion of the hepatic pool of cholesterol results in an increase in cholesterol biosynthesis and an increase in the number of LDL-R on the hepatocyte membrane. The increased number of receptors stimulates an enhanced rate of catabolism from plasma and lowers LDL-C levels. The increase in hepatic cholesterol biosynthesis may be paralleled by increased

hepatic VLDL production and, consequently, BAS may aggravate hypertriglyceridemia and should be avoided in those with TG levels exceeding 300 mg/dL (3.39 mmol/L).[71]

One of the main barriers to BAS is their poor tolerability profile. Early BAS (such as cholestyramine) were developed as powders that require mixing with water or juice to create a slurry for oral administration. Gastrointestinal complaints of constipation, bloating, epigastric fullness, nausea, and flatulence are commonly reported with these formulations.[71] These adverse effects can be minimized by increasing fluid intake, modifying the diet to increase bulk, and using stool softeners. Tablet forms of BAS (ie, colesevelam) are generally better tolerated than resin powders and associated with lower overall discontinuation rates.[72] Other potential adverse effects include impaired absorption of fat-soluble vitamins A, D, E, and K; gastrointestinal obstruction; and reduced bioavailability of other drugs such as warfarin, levothyroxine, and phenytoin.[71] Drug-drug interactions may be avoided by taking other medications 1 hour before or 4 hours after the BAS.[71] Colesevelam is not only approved as a lipid-lowering agent but also as an antihyperglycemic that modestly lowers glucose levels in patients with type 2 diabetes mellitus.[36] Given the better safety and tolerability profile of ezetimibe, BAS should be reserved only for those patients unable to tolerate ezetimibe who need additional LDL-C lowering despite maximally tolerated statin therapy.[71]

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Modulating Therapies

Inhibition of PCSK9 reduces LDL-C by as much as 60% when added to background statin therapy. Reducing PCSK9 levels promotes LDL-R recycling to the cell surface, which increases LDL-C clearance from the circulation. Both alirocumab and evolocumab are fully human monoclonal antibodies to PCSK9 and were approved by the FDA in 2015.[31] Randomized, double-blind clinical trials have also shown that these agents effectively reduce recurrent cardiovascular events in patients following an acute coronary event and secondary prevention populations when added to background statin therapy.[31,73] Alirocumab and evolocumab are both administered by subcutaneous injection. Although this may be a barrier for some patients, PCSK9 mAbs can be administered bi-weekly or once monthly. The most common adverse effect reported are injection site reactions, which can be minimized by allowing the injection to come to room temperature before use and icing the site before injecting. Some patients may also report “flu-like” symptoms after the injection. There were initial concerns over a potential increased risk for neurocognitive adverse effects; however, a randomized trial found no difference in cognitive function between those randomized to evolocumab *versus* placebo over 19 months of follow-up.[74] Furthermore, those patients who reach low levels of LDL-C (less than 20 mg/dL [0.52 mmol/L]) do not appear to be an increased risk of adverse events.[75] Despite this favorable data, the long-term effects of achieving low levels of LDL-C with PCSK9 mAbs remain unknown. Despite their LDL-C lowering potency and favorable safety profile, PCSK9 mAbs frequently require a prior authorization due to their higher cost compared to other LDL-C lowering therapies. Although PCSK9 mAbs should primarily be used in combination with maximally tolerated statins in high-risk patients unable to achieve desired LDL-C levels with a statin alone, alirocumab and evolocumab are FDA-approved for use as monotherapy in patients with primary hyperlipidemia (ie, heterozygous familial hypercholesterolemia).[31,73]

Inclisiran is a small interfering RNA (siRNA) molecule that reduces the production of PCSK9 by inhibiting messenger RNA.[76] This novel biological agent has a sustained effect on LDL-lowering and is given subcutaneously every 6 months. In Phase 3 clinical trials, inclisiran reduced LDL-C by an average of 50% when given as add-on therapy in patients who were treated with a high-intensity statin but had not achieved their LDL-C goal. Inclisiran is approved as an additional treatment to maximally tolerated statin therapy to further lower LDL-C in adults with HeFH or ASCVD. The most common adverse effects reported are injection-site reactions, which are generally transient and mild. Whether inclisiran lowers cardiovascular event rates is currently being investigated in the ORION-4 trial (NCT03705234).

Adenosine Triphosphate-Citrate Lyase Inhibitors

Adenosine triphosphate-citrate lyase (ACL) is a cytoplasmic enzyme responsible for generating acetyl coenzyme A which is needed during the de novo synthesis of fatty acids and cholesterol. ACL inhibitors prevent cholesterol production upstream from HMG CoA reductase inhibitors (ie, statins) and the two therapeutic strategies can be used in combination. Bempedoic acid is an orally administered ACL inhibitor that provides additional LDL-C lowering. In Phase 3 clinical trials, bempedoic acid produced modest reductions in LDL-C (15%-20%) when combined with statin therapy or used as monotherapy in patients who are unable to tolerate statins.[76] Importantly, randomized controlled trial evidence has demonstrated that bempedoic acid significantly reduces the risk of cardiovascular events in patients intolerant of statin therapy; however, a prespecified analysis of the trial results showed this benefit was only observed in those without ASCVD at baseline (i.e., primary prevention).[121] Bempedoic acid is available in a combination

product that contains ezetimide. Bempedoic acid plus ezetimibe can reduce LDL-C by 36% from baseline.[77] Bempedoic acid is generally well tolerated and associated with fewer muscle symptoms when compared to statins. However, bempedoic acid may cause hyperuricemia and is associated with a higher incidence of new-onset gout, and may increase the risk of acute gout in those with a history of gouty arthritis. Mechanistically, bempedoic acid inhibits the renal tubular organic anion transporter 2 (OAT2), which plays a role in the renal uptake of uric acid from the blood. Cholelithiasis can also occur (2.2%), although this was only observed in the CLEAR OUTCOMES trial.[121] Though rare, bempedoic acid was associated with an increased risk of tendon rupture or injury (0.5%) in early clinical trials, but the incidence was similar to placebo in the CLEAR OUTCOMES trial. This uncommon but potentially debilitating adverse effect was not reported in patients who received a placebo. Risk factors for tendon rupture are age greater than 60 years, concurrent use of corticosteroids or fluoroquinolones, renal failure, and history of tendon disorders. Bempedoic acid has emerged as an effective therapy for the primary prevention of ASCVD events in patients with statin intolerance, unable to tolerate recommended doses, or unwilling to take a statin.

Drug That Primarily Lower Triglycerides

Fibric Acid Derivatives (Fibrates)

Although fibrates, such as gemfibrozil, reduce cardiovascular events when used as monotherapy, the evidence to support their use in combination with statin therapy is weak.[54,55] In the most robust clinical trial conducted to date, combining a fibric acid derivative with a statin is the Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes (PROMINENT) trial.[124] Pemafibrate is a selective PPARα agonist available in Japan but has not been approved for use in the United States or Europe. In patients with T2DM, mild-moderate hypertriglyceridemia (TG 200-499 mg/dL) and low HDL-C (<40 mg/dL), on background statin therapy, pemafibrate did not provide additional cardiovascular benefit when compared to placebo. Additionally, pemafibrate increases the risk of adverse kidney events and venous thromboembolism. This study provides compelling evidence that adding fibrates to statin therapy does not reduce cardiovascular risk.

Fibrates are primarily used in patients with TG levels that exceed 500 mg/dL (5.65 mmol/L) to reduce the risk of acute pancreatitis. The two available fibrates, gemfibrozil and fenofibrate, are potent TG-lowering therapies (20%-50%), but can cause a modest reciprocal rise in LDL-C in patients with severely elevated TG levels.[55] Plasma HDL-C concentrations increase by 10% to 15% or more with fibrates. Gemfibrozil increases the activity of LPL and reduces to a lesser extent the synthesis or secretion of VLDL from the liver into the plasma. Fenofibrate increases LPL activity and reduces apoprotein C-III (an inhibitor of LPL) by activating peroxisome proliferator-activated receptor α (PPARα), which regulates the expression of genes involved in the regulation of lipids and other metabolic processes.

Fibrates are generally well tolerated, but gastrointestinal complaints and transient elevations in transaminase levels have been reported.[78] Both gemfibrozil and fenofibrate require dose adjustments for significant renal impairment and fenofibrate has been reported to worsen renal function, although this is usually transient and self-limiting.[17,79] Muscle-related adverse effects can occur with both gemfibrozil and fenofibrate alone but is more common when used in combination with statins to manage complex dyslipidemia or elevated TG levels. Gemfibrozil, and its glucuronide metabolite, has potent effects on CYP450 enzymes (ie, CYP3A4), intestinal, hepatic, and renal transporters making it highly prone to significantly increasing serum statin concentrations and the risk of SAMS.[63] For this reason, current guidelines do not recommend gemfibrozil to be initiated in patients receiving statin therapy; fenofibrate is favored instead.[17] Fenofibrate and gemfibrozil and may enhance the formation of gallstones, but this occurs rarely.[80] Fibrates may potentiate the effects of warfarin and the international normalized ratio (INR) should be monitored closely with this combination.[81]

Omega-3 Polyunsaturated Fatty Acids (PUFA)

High doses of omega-3 PUFA (2-4 g/day of EPA/DHA) significantly reduce TG and VLDL cholesterol levels (20%-50%) with lesser effects on other lipoproteins.[54] The mechanisms by which omega-3 PUFA reduce TG levels include increasing hepatic oxidation of free fatty acids, increasing LDL hydrolysis by activating PPARα, and inhibiting apolipoprotein C-III. The omega-3 PUFA formulations approved by the FDA for treating TG levels of 500 mg/dL (5.65 mmol/L) or greater include an omega-3-acid ethyl ester of EPA/DHA (Lovaza®), omega-3-carboxylic acid of EPA/DHA (Epanova®), and ethyl ester of EPA only (Vascepa®). DHA and EPA have different effects on LDL-C as EPA prevents LDL oxidation and promotes LDL clearance, whereas DHA does not; however, the clinical significance of this remains unclear.[82] Prescription omega-3 PUFA products contain approximately 1 g of EPA/DHA per

capsule, whereas the EPA/DHA content of OTC "fish oil" supplements is often less than 300 mg/capsule and are not regulated by the FDA. Unless patient affordability is an issue, prescription omega-3 PUFA is preferred to minimize pill burden and ensure product quality.

Randomized clinical trials of omega-3 PUFA have shown mixed results due to the lack of generalizability due to the population studied, the background lipid-lowering therapy used, and the dose taken.[82] Table 32-7 lists select TG-lowering and cardiovascular trials of available omega-3 PUFA products. The REDUCE-IT study evaluated the effects of icosapent ethyl (4 g/day), a high-potency EPA derivative, used as add-on therapy to statins compared to mineral oil placebo.[83] At baseline, patients enrolled in the REDUCE-IT study had a median TG level of 216 mg/dL (2.44 mmol/L) and the majority had a history of ASCVD. Icosapent ethyl reduced the rate of ischemic events by 25% and significantly reduced the risk of cardiovascular death when compared to placebo. This benefit is not related to TG reduction, however, and may be due to increases in EPA levels. In contrast, the STRENGTH trial evaluated the omega-3-carboxylic acid of EPA/DHA in a randomized controlled trial using corn oil placebo in a population similar to that of REDUCE-IT; however, there was no observed benefit with the intervention.[84] The debate is ongoing as to why these trials produced completely different results, including differences in the omega-3 PUFA product used (EPA only vs EPA/DHA) and type of placebo used (mineral oil vs corn oil).

TABLE 32-7

Select Clinical Trials of Omega-3 PUFA Effects on TG Lowering and Cardiovascular Events

Product	Omega-3 Acid Ethyl Esters (Lovaza)	Icosapent Ethyl (Vascepa)	Omega-3 Carboxylic Acids (Epanova)
Indicated uses	To reduce TG in adults with severe hypertriglyceridemia (TG ≥500 mg/dL [5.65 mmol/L])		
		Reduce major vascular events in adults with elevated TG (150-499 mg/dL [1.70-5.64 mmol/L]) and elevated cardiovascular risk while taking statin therapy	
Omega-3 fatty acid contents (per 1 g)	465 mg EPA 375 mg DHA	1 g EPA	550 mg EPA 200 mg DHA
TG-lowering efficacy in patients w/TG ≥500 mg/dL	**Harris et al.**[85] Patients with TG 500-2,000 mg/dL (5.65-22.6 mmol/L) Intervention: 4 g/d EPA + DHA ethyl esters vs placebo TG-lowering from baseline: −45% vs +16%	**MARINE** Patients with TG 500-2,000 mg/dL (5.65-22.6 mmol/L) Intervention: 4 g/d EPA vs placebo TG-lowering from baseline: −26.6% vs +9.7%	**EVOLVE** Patients with TG 500-2,000 mg/dL (5.65-22.6 mmol/L) Intervention: 4g/d EPA + DHA carboxylic acids vs 4 g/d olive oil TG-lowering from baseline: −30.9% vs -4.3%
Cardiovascular event reduction in patients at high risk of cardiovascular events	**VITAL** US patients without ASCVD (*n* = 25,871) **Intervention:** 1 g EPA + DHA ethyl esters vs placebo **Event rates:** 3.0% vs 3.2% HR 0.92 (0.80-1.06)	**REDUCE-IT** Patients with increased CV risk and elevated TG while receiving max-tolerated statin (*n* = 8,179) **Intervention:** 4 g/day EPA vs mineral oil **Event rates:** 17.2% vs 22.2% HR 0.75 (0.68-0.83)	**STRENGTH** Patients with increased CV risk and elevated TG and low HDL-C while receiving max-tolerated statin (*n* = 13,078) **Intervention:** 4 g/day EPA + DHA carboxylic acids vs corn oil **Event rates:** 12.0% vs 12.2% HR 0.99 (0.9-1.09)

DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; EVOLVE, epanova for lowering very high triglycerides[86]; MARINE, multi-center, placebo-controlled, randomized, double-blind, 12-week study with an open-label extension[87]; REDUCE-IT, reduction of cardiovascular events with icosapent ethyl–intervention trial[83]; STRENGTH, effect of high-dose omega-3 fatty acids vs corn oil on major adverse cardiovascular events in patients at high cardiovascular risk[84]; TG, triglycerides; VITAL, marine n−3 fatty acids and prevention of cardiovascular disease and cancer.[88]

Gastrointestinal complaints (ie, abdominal pain and “fishy burps”) are common with omega-3 PUFA products but may be minimized by refrigerating the capsules. However, they should not be kept frozen in the freezer. Caution is advised in patients with known sensitivities or allergies to fish or shellfish. Drug-drug interactions are minimal with omega-3 PUFA, although caution is advised when used concomitantly with antiplatelet agents or

anticoagulants since omega-3 PUFA may prolong bleeding time. Both low- and high-dose omega-3 PUFA supplementation has been observed to increase the risk of incident atrial flutter or fibrillation.[89]

Niacin

Niacin (nicotinic acid) increases HDL-C (5%-30%), and lowers TG (20%-50%) and LDL-C (5%-20%). Despite these favorable changes in the lipid profile, niacin has not been shown to improve cardiovascular outcomes in patients on background statin therapy with relatively well-controlled lipids at baseline.[57,90] Niacin primarily lowers TG levels by inhibiting lipolysis with a decrease in free fatty acids in plasma and decreased hepatic esterification of TG. It also significantly raises HDL-C by reducing its catabolism and selectively decreasing hepatic removal of HDL apoA-I but not the removal of cholesterol esters, thereby increasing the capacity of retained apoA-I to augment reverse cholesterol transport in isolated hepatic cells. Niacin also reduces the hepatic synthesis of VLDL, which, in turn, leads to a reduction in the synthesis of LDL. However, the modest decrease in serum LDL-C levels is dose dependent.

Niacin has many adverse drug reactions that frequently limit its use. Cutaneous flushing and itching are prostaglandin mediated and can be reduced by administering aspirin 325 mg given shortly before niacin ingestion.[91] Flushing seems to be related to rising plasma concentrations of niacin and the use of immediate-release formulations; taking the dose with meals and slowly titrating the dose upward may also minimize these effects. Extended- or sustained-release products may minimize these complaints in some patients. The only legend form of niacin, Niaspan® (Abbott), is an extended-release form of niacin with pharmacokinetics intermediate between immediate- and sustained-release products that are sold as food supplements rather than legend products. In controlled trials, Niaspan® is reported to have fewer dermatologic reactions and has a lower risk for hepatoxicity.[91] Potentially important laboratory abnormalities occurring with niacin therapy include elevated liver function tests, hyperuricemia, and hyperglycemia. With less than 3 g/day, the degree of liver function test elevation is generally not marked and often transient, and a temporary reduction in dosage frequently corrects the problem. Pre-existing gout and diabetes may be exacerbated by niacin; these patients should be monitored more closely and their medication titrated appropriately.[92,93] Niacin is contraindicated in patients with active liver disease and active peptic ulcer disease. Concomitant alcohol and hot beverages may magnify flushing and pruritus with niacin and they should be avoided at the time of ingestion. Nicotinamide should not be used in the treatment of hyperlipidemia, as it does not effectively lower cholesterol or TG levels.

Special Populations

Older Adults

Dyslipidemia is an independent risk factor for ASCVD in older adults (older than 65 years), as it is in younger patients.[94] The attributable risk, which is the difference in absolute rates of cardiovascular events between segments of the population with higher or lower serum cholesterol levels, increases with age. The benefits of drug therapy, in principle, differs little from younger patients, and older patients respond to lipid-lowering therapies as well as younger patients. Primary prevention in younger patients requires about 2 years before reduction in ASCVD risk is apparent, and this lag time should be taken into consideration, along with life expectancy, when determining if statin therapy is appropriate in an older adult. The gain in life expectancy may be small depending on the age at the start of treatment and the magnitude of LDL-C reduction. The benefits of moderate-to-high intensity statin therapy in older adults for secondary prevention is quite clear, while the benefit of statins in older adults for primary prevention is more controversial.[94] This is especially true in individuals older than 75 years since this age group is poorly represented in RCTs.[17] One observational cohort study assessed cardiovascular events among a cohort of patients aged 75 years with no previous ASCVD who either continued or discontinued statin therapy prior to their 75th birthday.[95] Compared to patients who continued, patients who discontinued statin therapy had a 33% increased risk of being admitted for a cardiovascular event. A posthoc meta-analysis of the JUPITER and HOPE-3 primary prevention trials assessed major cardiovascular events by age (<65 years, 65-69 years, and 70 years or older).[96] Combined results of both trials reported that statin treatment was associated with a 26% lower risk of major cardiovascular events among patients aged 70 years or older, but was only significant within the JUPITER population. The ongoing Statin Therapy for Reducing Events in the Elderly (STAREE) trial (NCT02099123) is evaluating the efficacy of atorvastatin for the primary prevention of ASCVD events in those 70 years or older without diabetes and will provide additional information regarding the benefits of statins for primary ASCVD prevention in the elderly.

The risks of statin therapy in older adults must also be considered. Changes in body composition, renal function, and other physiologic changes of aging may make older patients more susceptible to the adverse effects of lipid-lowering drug therapy.[94] Older adults are more prone to developing

SAMS and the effects of SAMS on the risk of falls and functional status remains unclear.[82] There is also concern regarding the potential negative effects of statins on cognitive function; however, data from meta-analyses have suggested statins are not associated with adverse cognitive effects.[97,98] Statin use has also been associated with an increased risk of cataracts, which is highly prevalent among older adults, yet a meta-analysis found no clear evidence showing statins increase the risk of cataracts.[99] Older adults are also more likely to develop type 2 diabetes and the impact of statin therapy on new-onset diabetes in older adults is a concern warranting further study. Several factors including worsening physical or cognitive function, multi- or worsening comorbidities, advancing frailty, and/or reduced life expectancy may favor discontinuing statin therapy in adults 75 years and older taking statins for primary prevention.[17] Clinician-patient discussion regarding potential benefits and risks of discontinuing statin therapy is recommended to ensure individualized treatment decisions.

Children

While cardiovascular events rarely occur in those under 18 years of age, the process of atherosclerosis often begins during childhood.[100] Early identification and management of risk factors is critical for primordial prevention of ASCVD. Dyslipidemia in children can develop from secondary causes, similar to adults, or may present as primary dyslipidemia (ie, FH). Universal lipid screening is recommended between age 9 and 11 years as this is a stable time for lipid assessment before the onset of puberty, which decreases cholesterol levels 10% to 20%.[100] Lipid screening before age 9 is only recommended in children with a significant family history of premature ASCVD, known first-degree relatives with dyslipidemia, or other cardiovascular risk factors (ie, diabetes, obesity, or hypertension).[100]

Drug therapy in children is not recommended until the age of 10 years or older, and the guidelines for initiation of therapy and acceptable levels of cholesterol and lipoproteins are quite different than adults.[100] Children younger than 10 years should only receive drug therapy if they have a genetic lipid disorder (ie, FH) or high-risk ASCVD condition (ie, diabetes); these children should be referred to a pediatric lipid specialist.[100] Lifestyle interventions are generally the mainstay of therapy, yet children with FH will often require drug therapy. Rosuvastatin may be used in children with HoFH at age 7. Pravastatin, pitavastatin, and rosuvastatin may be used in children as young as 8 years, while all other statins are indicated for use in children 10 years of age and older.[100] Start with the lowest available statin dose and titrate every 3 months as necessary to achieve treatment goals and consider additional LDL-C lowering agents to achieve individual treatment goals. Appropriate contraception strategies are recommended in females taking statins who are sexually active. Ezetimibe and BAS also have data suggesting that they are safe and effective to use in children aged ten years or older. Now, evolocumab is the only PCSK9 mAb with safety and efficacy data in children aged 13 years or older with HoFH.[101] The safety and efficacy of fibrates and omega-3 PUFA have not been established.

Women

The leading cause of death in women is ASCVD, and as many women as men die of ASCVD annually. This is mostly due to a longer average life expectancy and a higher lifetime risk of ischemic stroke than men.[102] Age is an important factor when estimating cardiovascular risk in women, as most ASCVD events occur in postmenopausal women. The decline in estrogen levels that occurs during menopause is associated with increased cardiovascular risk, yet hormone replacement therapy is not recommended as studies have shown it does not reduce cardiovascular risk.[103,104] Other age-related changes, including increases in blood pressure and LDL-C, play a significant role as well in both women and men. Women have been underrepresented in RCT of lipid-lowering therapies; however, a meta-analysis of 27 RCTs found that statin therapy is equally effective in men and women.[105] Nonstatin therapies also appear to be equally effective except for fenofibrate, which is associated with an increased ASCVD risk in women when combined with simvastatin.[106] This finding was not, however, observed in another RCT comparing fenofibrate to placebo.[107] The clinical significance of this subgroup finding remains unknown.

Pregnancy is associated with a progressive rise in cholesterol and TG levels, yet dietary therapy is the mainstay of treatment, with emphasis on maintaining a nutritionally balanced diet as per the needs of pregnancy.[108] If the patient is at high risk or has FH, a BAS may be considered during pregnancy since there is no systemic drug exposure.[108] In July 2021, the FDA recommended that statins no longer be considered contraindicated in pregnant patients, but may be used in select pregnant patients with a high risk of cardiovascular events. Most pregnant patients should still be advised to discontinue statin treatment; statin use while breast feedings is not recommended. Women of childbearing age who are on statin therapy and are sexually active should use a reliable form of contraception to prevent pregnancy. Women who plan to become pregnant should discontinue the statin 1 to 2 months before pregnancy is attempted. Ezetimibe and niacin are pregnancy category C drugs but no data are available in humans. Increased

intake of omega-3 PUFA, particularly DHA, during pregnancy is important for fetal brain development; however, prescription omega-3 PUFA products are pregnancy category C.[109] There is no information on the safety of PCSK9 mAbs in pregnant women.

Patients with Diabetes

Diabetes is a major risk factor for ASCVD, and persons with type 1 or type 2 diabetes are at greater risk of morbidity and mortality following an ASCVD event.[17] The dyslipidemia commonly found in persons with diabetes is often characterized by hypertriglyceridemia, low HDL-C concentrations, and modestly elevated but dense LDL-C that are highly atherogenic.[110] Despite the modest elevation in LDL-C observed in these patients, statins are the first-line therapy given the significant body of evidence from RCT demonstrating that statins reduce ASCVD events and mortality in persons with diabetes.[17] However, the risk among those with diabetes who have no history of ASCVD is not homogenous, so the 10-year ASCVD-risk score may be used to determine the appropriate statin intensity (see Table 32-5 and FIGURE 32-6).[17] High-intensity statin therapy is preferred in those with diabetes and a history of ASCVD (secondary prevention) given these patients are at high risk of recurrent ASCVD events.

The role of nonstatin therapies in persons with diabetes is complex but has become clearer in recent years. In the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) the benefit of adding ezetimibe to simvastatin was significantly enhanced in those with diabetes compared to patients without diabetes.[111] The addition of evolocumab to background statin therapy in the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial was equally effective in those with and without diabetes.[112] Given the mixed dyslipidemia associated with diabetes, there has been considerable interest in the potential of fibrates to reduce ASCVD risk. However, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD), the combination of fenofibrate and a statin in patients with type 2 diabetes did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke compared to simvastatin alone.[106] Subgroup analyses from two RCTs have suggested a potential benefit with fenofibrate in those with TG levels >204 mg/dL (2.31 mmol/L) and HDL-C <34 mg/dL (0.88 mmol/L), but this has not been evaluated in a prospective RCT.[106,107] Additionally, fenofibrate reduces the progression of diabetic retinopathy, as well as the need for laser treatment.[113] The BAS colesevelam is FDA-approved to improve both glycemic and lipid control, but it can exacerbate hypertriglyceridemia, which is commonly observed in those with diabetes.[55] Niacin modestly increases fasting plasma glucose (~5%) and HbA1c levels (~0.25%).[92] Given the lack of evidence to support its use, niacin should not be routinely used in persons with diabetes.

Patients with Kidney Disease

Dyslipidemia is highly prevalent among patients with kidney disease.[114] The dyslipidemia pattern in patients with kidney disease includes hypertriglyceridemia, slightly elevated total cholesterol, and LDL-C and low HDL-C levels.[114] These abnormalities are thought to be caused by a deficiency in apolipoprotein C-II, perhaps as a result of sustained use of heparin during hemodialysis and depletion of LPL, carbohydrate-induced obesity and hypertriglyceridemia, loss of carnitine during hemodialysis, use of acetate buffer (acetate is a precursor to fatty acid synthesis) during hemodialysis, and decreased LCAT activity during hemodialysis.[115] Dialysis does not correct the lipid abnormalities. Renal transplantation may correct lipid abnormalities in some patients; however, in others, the use of transplantation-related medications such as corticosteroids and cyclosporine may aggravate lipid abnormalities.[115]

Statins effectively reduce LDL-C in patients with kidney disease, yet the cardiovascular event reduction is less robust in patients with kidney disease.[114] Notably, rosuvastatin failed to prevent cardiovascular events in an RCT of patients undergoing hemodialysis suggesting statins should not be initiated in this population.[116] Statins are generally continued, however, in patients who are on statins before progressing to end-stage renal disease and requiring dialysis.[114] Moderate-intensity statins are generally preferred in patients with kidney disease to minimize the risk of adverse effects (ie, SAMS).[114] Kidney transplant recipients are at considerably high risk of future cardiovascular events and should receive statin therapy; however, appropriate statin selection is important given the potential for drug-drug interactions with antirejection therapies (ie, cyclosporine).[114] Ezetimibe may also be used in combination with statin therapy based on RCT evidence showing that this combination reduces cardiovascular events compared to placebo in patients at various stages of advanced kidney disease.[117] Current guidelines do not advocate for routine use of other nonstatin therapies, given the paucity of efficacy data and safety concerns.[114]

Patients with Chronic Inflammatory Disorders and HIV

It is well established that chronic inflammation and immune activation occur with chronic inflammatory disorders (eg, rheumatoid arthritis, lupus) and human immunodeficiency virus (HIV) and this accelerates the development and progression of atherosclerosis. These nontraditional risk factors are not included in the ASCVD-risk estimator, but they should be considered when assessing individual ASCVD risk. After a 3- to 6-month trial of lifestyle interventions, these patients should have their 10-year ASCVD risk estimated. In those with a 10-year ASCVD risk of 5% or greater, it is reasonable to initiate moderate-intensity statin therapy. Anti-inflammatory therapies (eg, tociluzimab, methotrexate) used in the management of rheumatoid arthritis have produced mixed results in terms of their effects on lipid levels and ASCVD risk reduction.

The Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) study, the largest clinical trial conducted in persons with HIV, randomized patients to receive pitavastatin or placebo. After a planned interim analysis, the study was discontinued early due to the robust reduction in CV events observed in those taking pitavastatin.[125] While the full results have not yet been published, the study appears to provide strong evidence supporting HIV as an ASCVD risk factor and that statin therapy is an effective strategy to reduce ASCVD risk in patients 40 to 70 years of age living with HIV. In addition to statin therapy, the long-term use of antiretroviral therapy mediates the development and progression of atherosclerosis in patients with HIV. Many antiretrovirals (eg, protease inhibitors) can significantly increase TG levels.

EVALUATION OF THERAPEUTIC OUTCOMES

Short-term evaluation of therapy for dyslipidemia is based on a complete lipid panel obtained 4 to 12 weeks after initiation or following a dose adjustment of lipid-lowering therapy to evaluate therapeutic response.[17] This is especially important with statin therapy given there are numerous pharmacokinetic and pharmacodynamic differences among statins that give rise to variable response to therapy.[118] Long-term evaluation is based on a repeat lipid panel obtained every 3 to 12 months to ensure adherence to lipid-lowering therapy and maintenance of desired levels of LDL-C.[17] It should be noted that although total cholesterol (TC) HDL-C, and TG levels are directly measured, LDL-C is typically estimated using the Friedewald equation, LDL-C = TC – HDL-C – (TG/5) (or LDL-C = TC – HDL-C – [TG/2.2] when lipid levels are all expressed in mmol/L), which does not provide an accurate estimate of VLDL-C.[119] As such, the Friedewald equation can underestimate LDL-C in patients with high TG levels as well as those with very low LDL-C levels. Given VLDL-C concentrations are typically small in comparison to LDL-C, the inaccuracy of VLDL-C has previously been accepted. However, given the increased prevalence of obesity, metabolic syndrome, and diabetes, more patients have elevated levels of VLDL-C. Useful alternatives in these patients include apoB, non-HDL-C (TC minus HDL-C), and direct LDL-C measurements, which are more accurate than estimated LDL-C using the Friedewald equation.[119] A nonfasting lipid panel is generally acceptable, except in patients with hypertriglyceridemia, where a fasting lipid panel is preferred to minimize interference from chylomicrons.[120] Routine safety monitoring of hepatic function and CK levels is not recommended in statin-treated patients, but these may be obtained if the patient has signs or symptoms suggestive of liver or muscle injury.[17] Patients taking niacin, on the other hand, should have hepatic function tests performed at baseline, after each dosage increase, and every 6 months thereafter while taking a stable dose.[17] Periodic monitoring of A1c is warranted in persons with diabetes receiving niacin and patients treated with statins who are at high risk for developing diabetes.[17]

Dietary therapy is an important part of treating dyslipidemia and a dietitian should be consulted to perform an initial evaluation with periodic follow-up thereafter if the goals of therapy are not achieved.[24] Use of food diaries and recall surveys enable the collection of information about diet in a systematic manner and may improve patient adherence to dietary recommendations. In patients treated with lipid-lowering therapy for secondary prevention, symptoms such as angina or intermittent claudication may improve over months to years. If patients have xanthomas or other external manifestations of dyslipidemia, these lesions should regress with therapy.[50] Modifiable risk factors such as hypertension, smoking, exercise and weight control, and glycemic control in persons with diabetes should also be monitored and evaluated.[17,27]

ABBREVIATIONS

ACL	adenosine triphosphate-citrate lyase
Apo	apolipoprotein

ASCVD	atherosclerotic cardiovascular disease
ALT	alanine transaminase
ANGPTL3	angiopoietin-like 3
AST	aspartate transaminase
ATP	adenosine triphosphate
BASs	bile acid sequestrants
BMI	body mass index
BUN	blood urea nitrogen
CE	cholesterol ester
CETP	cholesterol ester transfer protein
CHD	coronary heart disease
CKD	chronic kidney disease
CVD	cardiovascular disease
DHA	docosahexaenoic acid
EPA	eicosapentaenoic acid
HbA1c	glycosylated hemoglobin A1c
HDL-C	high-density lipoprotein-cholesterol
HIV	human immunodeficiency virus
HMG-CoA	β-hydroxy β-methylglutaryl coenzyme A
HTN	hypertension
IDL-C	intermediate-density lipoprotein-cholesterol
LCAT	lecithin-cholesterol acyltransferase
LDL-C	low-density lipoprotein-cholesterol
LPL	lipoprotein lipase
LRP	LDL-receptor-related protein
mAb	monoclonal antibodies

NPC1L1	Niemann-Pick C1-like1
OTC	over-the-counter
PCOS	polycystic ovarian syndrome
PSCK9	proprotein convertase subtilisin/kexin type 9
PUFA	polyunsaturated fatty acid
RCT	randomized controlled trial
SAMS	statin-associated muscle symptoms
T2DM	type 2 diabetes mellitus
TC	total cholesterol
TG	triglyceride
TSH	thyroid-stimulating hormone
UA	urinalysis
VLDL-C	very-low-density lipoprotein-cholesterol

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SELF ASSESSMENT QUESTIONS

1. Which of the following nonpharmacologic interventions would be most effective to lower LDL-C?

   A. Smoking cessation

   B. Increase daily intake of soluble fiber

C. Complete 150 minutes per week of physical activity

D. Reduce intake of sugar-sweetened beverages

2. Which of the following is the most appropriate therapy for a 64-year-old patient without a history of diabetes or ASCVD and a 10-year ASCVD risk score of 15.6%?

A. Pravastatin 20 mg daily

B. Rosuvastatin 10 mg daily

C. Atorvastatin 40 mg daily

D. Pitavastatin 1 mg daily

3. Which of the following is included in the ASCVD risk estimator?

A. Family history

B. Duration of diabetes mellitus

C. Smoking status

D. History of ASCVD

4. Which of the following factors is associated with a higher risk of developing statin-associated muscle symptoms (SAMS)?

A. High body mass index

B. Physical inactivity

C. Male gender

D. Kidney disease

5. Which of the following is the most appropriate initial approach to managing a patient experiencing statin-associated muscle symptoms (SAMS)?

A. Switch to a non-statin lipid lowering medication

B. Stop the statin for at least 2 weeks

C. Add coenzyme-Q10

D. Measure creatine kinase (CK) levels

6. Which of the following is the primary target for lipid-lowering therapy?

A. Triglycerides

B. Lipoprotein (a)

C. High-Density lipoprotein cholesterol

D. Low-Density lipoprotein cholesterol

7. Which of the following is the *LEAST* common familial dyslipidemia?

A. Hypertriglyceridemia

B. Homozygous familial hypercholesterolemia

C. Heterozygous familial hypocholesteremia

D. Combined hyperlipidemia

8. What is the rate-limiting step in the biosynthetic pathway for cholesterol?

A. HMG-CoA reductase

B. ABCA-1 inhibition

C. Lipoprotein lipase

D. Reverse cholesterol transport

9. Which of the following would most likely lower triglyceride levels?

A. Increase soluble fiber intake

B. Phytosterol 2 grams/day supplementation

C. Alcohol abstinence

D. Smoking cessation

10. Which medication reduces triglyceride levels by activating peroxisome proliferator-activated receptor α?

A. Ezetimibe

B. Niacin

C. Omega-3 fatty acids

D. Fenofibrate

11. What is the LDL-C threshold to consider adding ezetimibe and/or PCSK9 mAb to maximally tolerated statin therapy in a patient who is at very high risk ASCVD?

A. ≥50 mg/dL

B. ≥70 mg/dL

C. ≥100 mg/dL

D. ≥130 mg/dL

12. Which of the following patients is at the highest risk for ASCVD?

A. 35-year-old with high blood pressure

B. 47-year-old with type 2 diabetes mellitus

C. 59-year-old with heart failure

D. 68-year-old with a history of MI and hypertension

13. Which non-statin has the greatest LDL-C lowering effect?

A. Ezetimibe

B. Bempedoic acid

C. PCSK9 mAbs

D. Bile acid sequestrants

14. What is the primary effect of omega-3 fatty acids on the lipid profile?

A. Lower LDL-C

B. Increase HDL-C

C. Lower triglycerides

D. Lower Lp(a)

15. Which omega-3 fatty acid product has been shown to reduce the risk of ASCVD events in patients with a history of ASCVD or high-risk patients with diabetes?

A. Omega-3 carboxylic acid (Epanova®)

B. Icosapent ethyl (Vascepa®)

C. Omega-3 acid ethyl esters (Lovaza®)

D. Over-the-counter (OTC) fish oil

SELF-ASSESSMENT QUESTION-ANSWERS

1. **B.** Increasing soluble fiber has been associated with lower LDL-C values. See Table 32-4 for more information on nonpharmacologic therapies and their effects on lipid parameters and ASCVD risk.

2. **B.** Moderate-intensity statin is recommended for primary prevention in patients with a 10-year ASCVD risk score. Rosuvastatin 10 mg daily is the only moderate-intensity statin listed. See FIGURE 32-6 for assessment and treatment decision pathways for primary ASCVD prevention.

3. **C.** Age, gender, race, blood pressure, diabetes status, and smoking status are among the main patient-factors included in the ASCVD Risk Estimator. See ASCVD Risk Estimator is discussion in paragraph beginning with learning objective #5.

4. **D.** Kidney disease is a known risk factor for developing SAMS. See text discussing SAMS in the "HMG-CoA Reductase Inhibitors (Statins)" section and the section on treating dyslipidemia in patients with kidney disease.

5. **B.** Stopping the statin for at least 2 weeks is the initial step as this allows time for the symptoms to resolve, which increases the probability of SAMS. If symptoms do not resolve, then additional workup for other potential causes may be warranted. See text discussing SAMS in the "HMG-CoA Reductase Inhibitors (Statins)."

6. **D.** The primary target for lipid-lowering therapy is LDL-C due to its relationship to atherosclerotic cardiovascular disease (ASCVD). Even in cases of sub-types of dyslipidemia (eg, low HDL-C), LDL-C remains the primary target of therapy. See the section "Introduction" for more information on this.

7. **B.** Homozygous familial hypercholesterolemia is extremely rare with an estimated prevalence of one case per one million people, while heterozygous familial hypercholesterolemia is one of the most common genetic disorders affecting one in every 250 people. See the section "Primary or Familial Dyslipidemias" for more information on familial dyslipidemias and their specific descriptions.

8. **A.** HMG-CoA reductase is responsible for the development of cholesterol. HMG-CoA reductase is also the target for statin medications that are

highly effective at reducing blood cholesterol, furthering the evidence for the rate-limiting nature of the enzyme. See the section "Lipoproteins and Cholesterol Synthesis" and FIGURE 32-3 for more information on the biosynthetic pathway for cholesterol.

9. **A.** Alcohol is both a secondary cause of hypertriglyceridemia and a contributing factor to pancreatitis, which is a life-threatening risk of uncontrolled hypertriglyceridemia. See the section "Nonpharmacologic Therapy" and Table 32-4 for more information nonpharmacologic therapy to improve lipids.

10. **D.** Fenofibrate is a PPAR α agonist that regulates the expression of genes involved in several metabolic processes. See the section "Drugs that Primarily Lower Triglycerides" for more information on these therapeutic options.

11. **B.** An LDL-C threshold of ≥70 mg/dL warrants consideration of either adding ezetimibe and/or a PCSK9 mAb to maximally tolerated statin therapy. This is based on randomized controlled trial evidence and ensures that additional LDL-C lowering therapies are used in patients at very high risk ASCVD who are most likely to benefit. See FIGURE 32-7 and the section "General Approach" for more information.

12. **D.** Very-high risk ASCVD is classified as either having ≥2 major ASCVD events OR 1 major ASCVD event AND ≥2 high-risk conditions. The scenario in option D meets this definition as it includes 1 major ASCVD event (history of MI) and two high-risk conditions (≥65 years old and hypertension). See FIGURE 32-7 for more information.

13. **C.** The PCSK9 mAbs, alirocumab and evolocumab, reduce LDL-C levels by approximately 60% and are the most potent non-statin LDL-C lowering agents. Ezetimibe, bempedoic acid, and bile acid sequestrants modestly reduce LDL-C levels by approximately 15% to 25%. See section, "Medications that Primarily Lower Atherogenic Cholesterol" for more information.

14. **C.** Omega-3 fatty acids primarily reduce triglycerides through multiple mechanisms. When used as monotherapy, omega-3 fatty acids can increase LDL-C levels or have a neutral effect. The increase in HDL-C observed with omega-3 fatty acids is quite modest and omega-3 fatty acids do not appear to lower Lp(a). See section, "Omega-3 Polyunsaturated Fatty Acids (PUFA)" for more information.

15. **B.** In the REDUCE-IT trial, the addition of 4g/d of icosapent ethyl to background statin therapy reduced ASCVD events. No other omega-3 fatty acid product has been shown to reduce the risk of ASCVD events. See section, "Omega-3 Polyunsaturated Fatty Acids (PUFA)" and Table 32-7 for more information.