

35 - 419 Disorders of Lipoprotein Metabolism

419 Disorders of Lipoprotein Metabolism

Acknowledgment The author acknowledges contributions of the late Phil E. Cryer to this chapter in prior editions of Harrison's. ■ ■ **FURTHER READING** Black JE et al: Real-world effects of second-generation versus earlier intermediate/basal insulin analogues on rates of hypoglycemia in adults with type 1 and 2 diabetes (iNPHORM, US). *Diabetes Ther* 14:1299, 2023. Cryer PE: Hypoglycemia in *Diabetes*, 3rd ed. Alexandria, VA, American Diabetes Association, 2016. Cryer PE: Hypoglycemia, in *Williams Textbook of Endocrinology*, 13th ed, S Melmed et al (eds). Philadelphia, Saunders, 2016,

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Disorders of Lipoprotein Metabolism Lipoproteins are complexes of lipids and proteins that are essential for transport of cholesterol, triglycerides (TGs), and fat-soluble vitamins in the blood. Lipoproteins play essential roles in the transport of dietary cholesterol, long-chain fatty acids, and fat-soluble vitamins from the intestine to peripheral tissues and the liver; the transport of TGs, cholesterol, and fat-soluble vitamins from the liver to peripheral tissues; and the transport of cholesterol from peripheral tissues back to the liver and intestine for excretion. Disorders of lipoprotein metabolism can be primary (caused by genetic conditions) or secondary (to other medical conditions or environmental exposures) and involve either a substantial increase or decrease in specific circulating lipids or lipoproteins. Lipoprotein disorders can have a number of clinical consequences, most notably atherosclerotic cardiovascular disease (ASCVD), and are therefore important to appropriately diagnose and treat. This chapter reviews the etiology and pathophysiology of

TABLE 419-1 Major Apolipoproteins	
APOLIPOPROTEIN	PRIMARY SOURCE
LIPOPROTEIN	ASSOCIATION
FUNCTION	ApoA-I Intestine, liver HDL, chylomicrons Core structural protein for HDL, promotes cellular lipid efflux via ABCA1, activates LCAT
ApoA-II Liver HDL, chylomicrons	Structural protein for HDL
ApoA-V Liver VLDL, chylomicrons	Promotes LPL-mediated triglyceride lipolysis
Apo(a) Liver Lp(a)	Structural protein for Lp(a)
ApoB-48 Intestine Chylomicrons, chylomicron remnants	Core structural protein for chylomicrons
ApoB-100 Liver VLDL, IDL, LDL, Lp(a)	Core structural protein for VLDL, LDL, IDL, Lp(a); ligand for binding to LDL receptor (except for Lp(a))
ApoC-II Liver Chylomicrons, VLDL, HDL	Cofactor for LPL
ApoC-III Liver, intestine	

Chylomicrons, VLDL, HDL Inhibitor of LPL activity and remnant lipoprotein binding to receptors
ApoE Liver Chylomicron remnants, IDL, HDL Ligand for binding to LDL receptor and other receptors
Abbreviations: HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LCAT, lecithin-cholesterol acyltransferase; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); LPL, lipoprotein lipase; VLDL, very-low-density lipoprotein.

0.95 VLDL 1.006 IDL Density, g/mL Chylomicron remnants 1.02 LDL Chylomicron CHAPTER 419
Disorders of Lipoprotein Metabolism 1.06 HDL 1.10 1.20

Diameter, nm FIGURE 419-1 The density and size distribution of the major classes of lipoprotein particles. Lipoproteins are classified by density and size, which are inversely related. HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein. disorders of lipoprotein metabolism and clinical approaches to their diagnosis and management. LIPOPROTEIN STRUCTURE AND METABOLISM Lipoproteins contain an “oil droplet” core of hydrophobic lipids (TGs and cholesteryl esters) surrounded by a shell of hydrophilic lipids (phospholipids, unesterified cholesterol) and proteins (called apolipoproteins) that interact with body fluids (Fig. 419-1). The plasma lipoproteins are divided into major classes based on their relative density: chylomicrons, very-low-density lipoproteins (VLDLs), intermediate-density lipoproteins (IDLs), low-density lipoproteins (LDLs), and high-density lipoproteins (HDLs). Each lipoprotein class comprises a family of particles that vary in density, size, and protein composition. Because lipid is less dense than water, the density of a lipoprotein particle is primarily determined by the amount of lipid per particle. Chylomicrons are the most lipid-rich and therefore least dense lipoprotein particles, whereas HDL have the least lipid and are therefore the most dense. Lipoprotein particles vary widely in size, with the largest particles (chylomicrons) being the most lipid-rich and the smallest particles (HDL) being the most dense. The proteins associated with lipoproteins, called apolipoproteins (Table 419-1), are required for the assembly, structure, function, metabolism, and catabolism of lipoproteins. Apolipoproteins provide a structural basis for lipoproteins, activate enzymes important in lipoprotein metabolism, and act as ligands for cell surface receptors. ApoB is the major structural protein of chylomicrons, VLDLs, IDLs, and LDLs (collectively known as apoB-containing lipoproteins). One

molecule of apoB, either apoB-48 (chylomicrons) or apoB-100 (VLDL, IDL, or LDL), is present on each lipoprotein particle. The human liver synthesizes the full-length apoB-100 (one of the largest proteins in humans), whereas the intestine makes the shorter apoB-48, which is derived from transcription of the same APOB gene after posttranscriptional mRNA editing. HDLs lack apoB and have different apolipoproteins that define this lipoprotein class, most importantly apoA-I, which is synthesized in both the liver and intestine and is found on virtually all HDL particles. ApoA-II is the second most abundant HDL apolipoprotein and is on approximately two-thirds of the HDL particles. ApoC-II, apoC-III, and apoA-V regulate the metabolism of TG-rich lipoproteins. ApoE plays a critical role in the metabolism and clearance of TG-rich particles. Most apolipoproteins, other than apoB, exchange actively among lipoprotein particles in the blood. Apolipoprotein(a) [apo(a)] is a distinctive apolipoprotein that results in the formation of a lipoprotein known as lipoprotein(a) [Lp(a)], which is discussed more below.

PART 12 Endocrinology and Metabolism ■ ■ TRANSPORT OF INTESTINALLY DERIVED DIETARY LIPIDS BY CHYLOMICRONS Chylomicrons play a critical role in the efficient transport of absorbed

dietary lipids from the intestine to tissues that require fatty acids for energy or storage and then return of cholesterol, lipids, and fat-soluble vitamins to the liver (Fig. 419-2). Dietary lipids are hydrolyzed by lipases within the intestinal lumen and emulsified with bile acids to form micelles. Dietary cholesterol, fatty acids, and fat-soluble vitamins are absorbed in the proximal small intestine. Cholesterol and retinol are esterified (by the addition of a fatty acid) in the enterocyte to form cholesteryl esters and retinyl esters, respectively. Longer-chain fatty acids (>12 carbons) are incorporated into TGs and packaged with apoB-48, phospholipids, cholesteryl esters, retinyl esters, and α -tocopherol (vitamin E) in a process that requires the action of the microsomal TG transfer protein (MTP) to form chylomicrons. Nascent chylomicrons are secreted into the intestinal lymph and delivered via Exogenous Endogenous Dietary lipids Bile acids + cholesterol LDL LDLR Small intestines Liver HL ApoB-100 ApoE ApoB-48 ApoC's Chylomicron VLDL IDL Chylomicron remnant Capillaries Capillaries LPL FFA LPL FFA Muscle Adipose Muscle Adipose

FIGURE 419-2 The exogenous and endogenous lipoprotein metabolic pathways. The exogenous pathway transports dietary lipids to the periphery and the liver. The endogenous pathway transports hepatic lipids to the periphery. FFA, free fatty acid; HL, hepatic lipase; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; LPL, lipoprotein lipase; VLDL, very-low-density lipoprotein.

the thoracic duct directly to the systemic circulation, where they are extensively processed by peripheral tissues before reaching the liver. The particles encounter lipoprotein lipase (LPL), which is transported from parenchymal cells and anchored to the luminal surface of the endothelium by the protein GPIHBP1 of capillaries in tissues, particularly adipose, heart, and skeletal muscle (Fig. 419-2). ApoC-II and apoA-V are apolipoproteins that are transferred to circulating chylomicrons from HDL in the postprandial state; apoC-II acts as a required cofactor for LPL activation, and apoA-V serves as a facilitator of LPL activity. The TGs in chylomicrons are hydrolyzed by LPL, and free fatty acids are released and taken up by adjacent myocytes or adipocytes and are either oxidized to generate energy or reesterified and stored as TG. Some of the released free fatty acids bind albumin before entering cells and are transported to other tissues, especially the liver. The chylomicron particle progressively shrinks in size as the hydrophobic TG core is hydrolyzed and the excess hydrophilic lipids (cholesterol and phospholipids) and apolipoproteins on the particle surface are transferred to HDL, ultimately creating chylomicron remnants. Chylomicron remnants contain apoB-48, which lacks the region in apoB-100 that binds to the LDL receptor. Nevertheless, they are rapidly removed from the circulation by the liver through a process that critically requires apoE as a ligand for receptors in the liver. Few, if any, chylomicrons or chylomicron remnants are generally present in the blood after a 12-h fast, except in patients with certain disorders of lipoprotein metabolism as described below.

■ ■ TRANSPORT OF HEPATICALLY DERIVED LIPIDS BY VLDL AND LDL Another key role of lipoproteins is the transport of hepatic lipids from the liver to the periphery (Fig. 419-2) to provide an energy source during fasting and to deliver fat-soluble vitamins to key tissues. During the fasting state, lipolysis of adipose TGs generates fatty acids that are transported to the liver, and the liver is also capable of synthesizing fatty acids through de novo lipogenesis. These fatty acids are esterified by the liver into TGs, which are packaged into VLDL particles along with apoB-100, phospholipids, cholesteryl esters, and vitamin E in a process that also requires MTP. VLDL thus resemble chylomicrons in that they are “triglyceride-rich lipoproteins,” but they contain apoB100 rather than apoB-48, are smaller and less buoyant, and have a higher ratio of cholesterol to TG (~1 mg of cholesterol for every 5 mg of TG, whereas in chylomicrons, this ratio is closer to ~1:8). After secretion by the liver into the plasma, the

circulating TGs in VLDL are hydrolyzed by LPL. After the relatively TG-depleted VLDL remnants dissociate from LPL, they are referred to as IDLs, which contain roughly similar amounts of cholesterol and TG by mass. The liver removes ~40–60% of IDL by receptor-mediated endocytosis via binding to apoE, which is acquired through transfer of this protein from HDL. The remainder of IDL is further remodeled by hepatic lipase (HL) to form LDL. During this process, phospholipids and TGs in the particle are hydrolyzed, and most of the remaining apolipoproteins except apoB-100 are transferred to other lipoproteins. LDL is primarily a by-product of fatty acid energy transport by VLDL with little true physiologic role; one exception is that LDL may be partially responsible for delivery of vitamin E to the retina and brain. LDL is ultimately removed from the circulation by receptor-mediated endocytosis (primarily via the LDL receptor) in the liver, with a region of apoB-100 serving as the specific ligand for binding to the LDL receptor. It should be noted that apoB-48 does not contain the LDL receptor-binding ligand region, and therefore, clearance of apoB-48-containing chylomicron remnants is dependent on apoE-mediated clearance as noted above. Some LDL particles are lipolytically processed to small dense LDL particles that are believed to be especially atherogenic. Peripheral tissues

Lp(a) is a lipoprotein similar to LDL in lipid and protein composition, but it contains an additional distinctive protein called apo(a). Apo(a) is synthesized in the liver and attached to apoB-100 by a disulfide linkage. The major site of clearance of Lp(a) is the liver, but the uptake pathway is not known. Lp(a) is now established as causal factor for ASCVD and aortic stenosis, and an elevated level of Lp(a) serves as an independent risk factor and merits more aggressive therapy to reduce LDL cholesterol levels (see below).

■ ■ HDL METABOLISM AND REVERSE CHOLESTEROL TRANSPORT All nucleated cells synthesize cholesterol, but only hepatocytes and enterocytes can effectively excrete cholesterol from the body, into either the bile or the gut lumen, respectively. In the liver, cholesterol is secreted into the bile, either directly or after conversion to bile acids. Cholesterol in peripheral cells is transported from the plasma membranes of peripheral cells to the liver and intestine by a process termed reverse cholesterol transport that is facilitated by HDL (Fig. 419-3). Nascent HDL particles are synthesized by the intestine and the liver. Newly secreted apoA-I rapidly acquires phospholipids and unesterified cholesterol from its site of synthesis (intestine or liver) via cellular efflux promoted by the membrane protein ATP-binding cassette protein A1 (ABCA1). This process results in the formation of discoidal HDL particles, which then recruit additional unesterified cholesterol from cells or circulating lipoproteins. Within the HDL particle, the cholesterol is esterified to cholesteryl ester (CE) through the addition of a fatty acid by lecithin-cholesterol acyltransferase (LCAT), a plasma enzyme associated with HDL; the hydrophobic CE forms the core of the mature HDL particle. As HDL acquires more CE, it becomes spherical, and additional apolipoproteins and lipids are transferred to the particles from the surfaces of chylomicrons and VLDLs during lipolysis. HDL cholesterol in the blood is transported to hepatocytes by two major pathways. HDL CE can be “selectively” taken up by hepatocytes via the scavenger receptor class B1 (SR-B1), a cell surface HDL receptor that mediates the selective transfer of CE from HDL with subsequent dissociation and “recycling” of the HDL particle. In addition, HDL CE can be transferred to apoB-containing lipoproteins in exchange for TG by the cholesteryl ester transfer protein (CETP). The CE esters are then removed from the circulation by LDL receptor-mediated endocytosis. HDL-derived CE taken up by the hepatocyte through these pathways is hydrolyzed, and much of the cholesterol is ultimately excreted directly into the bile or converted to bile acids with excretion to bile, providing

Macrophage Free cholesterol IDL LDL VLDL CETP ApoA-I Liver
ApoA-I LCAT CETP Nascent HDL Small intestines Mature HDL Chylomicrons Peripheral cells

FIGURE

419-3 High-density lipoprotein (HDL) metabolism and reverse cholesterol transport. The HDL pathway transports excess cholesterol from the periphery back to the liver for excretion in the bile. The liver and the intestine produce nascent HDLs. Free cholesterol is acquired from macrophages and other peripheral cells and esterified by lecithin-cholesterol acyltransferase (LCAT), forming mature HDLs. HDL cholesterol can be selectively taken up by the liver via SR-BI (scavenger receptor class BI). Alternatively, HDL cholesteryl ester can be transferred by cholesteryl ester transfer protein (CETP) from HDLs to very-low-density lipoproteins (VLDLs) and chylomicrons, which can then be taken up by the liver. IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor.

a biliary route into the intestinal lumen. There is also evidence that, under certain conditions, HDL cholesterol can be transported directly into the intestinal lumen without requiring a transhepatobiliary route, a process known as transintestinal cholesterol excretion.

HDL particles undergo extensive remodeling within the plasma compartment by a variety of lipid transfer proteins and lipases. The phospholipid transfer protein (PLTP) transfers phospholipids from other lipoproteins to HDL or among different classes of HDL particles and is a regulator of HDL metabolism. After CETP- and PLTP-mediated lipid exchange, the TG-enriched HDL becomes a much better substrate for HL, which hydrolyzes the TGs and phospholipids to generate smaller HDL particles. A related enzyme called endothelial lipase (EL) hydrolyzes HDL phospholipids, generating smaller HDL particles that are catabolized faster. Remodeling of HDL influences the metabolism, function, and plasma concentrations of HDL. Disorders of Lipoprotein Metabolism

CHAPTER 419

SCREENING Dyslipidemia is an important causal factor in ASCVD, and treatment has been proven to substantially reduce cardiovascular risk. Therefore, all adults (and many children) should be actively screened for plasma lipids. A lipid panel should be measured, preferably after an overnight fast. In most clinical laboratories, the total cholesterol and TGs in the plasma are measured enzymatically, and then after precipitation of apoB-containing lipoproteins, the cholesterol in the supernatant is measured to determine the HDL cholesterol (HDL-C). The LDL cholesterol (LDL-C) is then estimated using the following equation (the Friedewald formula): $LDL-C = \text{total cholesterol} - (TG/5) - HDL-C$ (The VLDL cholesterol content is estimated by dividing the plasma TG by 5, reflecting the ratio of TG to cholesterol in VLDL particles.) This formula is reasonably accurate if test results are obtained on fasting plasma and if the TG level does not exceed ~200 mg/dL; by convention, it cannot be used if the TG level is >400 mg/dL. LDL-C can be directly measured by a number of methods. The non-HDL-C can be easily calculated by subtracting the HDL-C from the total cholesterol. It has the advantage of incorporating the cholesterol contained within VLDL and IDL, which in most cases is also atherogenic and associated with increased ASCVD risk. There is increasing evidence that measurement of plasma apoB levels may provide a better assessment of cardiovascular risk than the LDL-C level, and even the non-HDL-C level, and is recommended by some experts. While this has not yet become standard clinical practice, the data supporting the use of apoB as a risk marker and guide to therapeutic intervention are quite strong. There is also increasing interest in Lp(a), an independent ASCVD risk factor that is highly heritable and may be helpful in risk stratification. In patients with evidence of dyslipidemia, further evaluation and treatment are based on evidence of preexisting ASCVD and clinical assessment of cardiovascular risk using risk calculators such as the American Heart Association (AHA)/American College of Cardiology (ACC) risk calculator as well as, in some cases, based on additional approaches to risk assessment such as apoB and Lp(a) (see "Approach to the Patient" for more detailed discussion).

LDLR SR-BI DISORDERS ASSOCIATED WITH ELEVATED APOB-CONTAINING LIPOPROTEINS Disorders of lipoprotein metabolism that cause elevated levels of apoB-containing lipoproteins are among the most common and clinically important of the dyslipoproteinemias. They are generally characterized by increased plasma levels of total cholesterol, accompanied by increased TGs, LDL-C, or both. Many patients with hyperlipidemia have some combination of genetic predisposition (often polygenic) and medical

or environmental contribution (medical condition, diet, lifestyle, or drug). Many, but not all, patients with hyperlipidemia are at increased risk for ASCVD, which is the primary reason for making the diagnosis, as intervention can substantially reduce this risk. In addition, patients with severe hypertriglyceridemia may be at risk for acute pancreatitis and require intervention to reduce this risk.

Although hundreds of proteins influence lipoprotein metabolism, and genetic variants in most of the genes that encode them interact with each other and the environment to produce dyslipidemia, there are a limited number of discrete “nodes” or pathways that regulate lipoprotein metabolism and are dysfunctional in specific dyslipidemias. These include (1) lipolysis of TG-rich lipoproteins by LPL; (2) receptor-mediated uptake of apoB-containing lipoproteins by the liver; (3) cellular cholesterol metabolism in the hepatocyte and the enterocyte; (4) assembly and secretion of VLDLs by the liver; and (5) neutral lipid transfer and phospholipid hydrolysis in the plasma. Primary genetic disorders of lipoprotein metabolism caused by single-gene mutations (Table 419-2) have taught us a great deal about the physiologic roles of specific proteins in these pathways in humans and are clinically important to diagnose and treat. **PART 12 Endocrinology and Metabolism ■**

■ SEVERE HYPERTRIGLYCERIDEMIA Severe hypertriglyceridemia (HTG) is defined by fasting TG levels

“ 500 mg/dL and is usually accompanied by moderately elevated total cholesterol levels and reduced levels of HDL-C, usually without important elevation in LDL-C or apoB. It is medically important because it is associated with risk of acute pancreatitis and, in some cases, is also associated with increased risk of ASCVD. Severe HTG is usually caused by impaired lipolysis of TGs in TG-rich lipoproteins (TRLs) by the enzyme LPL. LPL is synthesized by adipocytes, skeletal myocytes, and cardiomyocytes, and its posttranslational maturation and folding require the action of lipase maturation factor 1 (LMF1). After secretion, it is transported from the subendothelial to the vascular endothelial surfaces by GPIHBP1, which docks it to the endothelial surface. ApoC-II is a required cofactor for LPL, and apoA-V promotes LPL activity, and both are transported to the bound LPL on the TRLs. Single-gene Mendelian disorders that reduce LPL have been described (Table 419-3) as reviewed below; the majority of patients with severe HTG have a polygenic predisposition to secondary factors like obesity or insulin resistance. **Primary (Genetic) Causes of Severe Hypertriglyceridemia •**

FAMILIAL CHYLOMICRONEMIA SYNDROME (FCS) LPL is required for the hydrolysis of TGs in chylomicrons and VLDLs. Genetic deficiency or inactivity of LPL results in impaired lipolysis and

profound elevations in plasma TGs, mostly in chylomicrons. While chylomicronemia predominates, in fact, these patients often have elevated plasma levels of VLDL as well. The fasting plasma is turbid, and if left undisturbed for several hours, the chylomicrons float to the top and form a creamy supernatant layer. Fasting TG levels are >500 mg/dL and usually >1000 mg/dL. Because chylomicrons contain cholesterol, fasting total cholesterol levels are also elevated. There are five genes in which mutations can result in FCS (Table 419-2). FCS has an estimated frequency of ~ 1 in 200,000–300,000, although its true prevalence is unknown. The most common molecular cause of FCS involves mutations in the LPL gene. LPL deficiency has autosomal recessive inheritance (loss-of-function mutations in both alleles). Heterozygotes with LPL mutations often have moderate elevations in plasma TG levels and increased risk for coronary heart disease (CHD). FCS can also be caused by mutations in genes that affect LPL processing or activity. For example, apoC-II is a required cofactor for LPL. APOC2 deficiency due to loss-of-function mutations in both APOC2 alleles results in functional lack of LPL activity and severe hyperchylomicronemia that is indistinguishable from LPL deficiency. It is also recessive in inheritance pattern and much rarer than LPL deficiency. Another apolipoprotein, apoA-V, facilitates the association of TRLs with LPL and promotes hydrolysis of the TGs. Individuals harboring loss-of-function mutations in both APOA5 alleles causing APOA5 deficiency develop a form of FCS. GPIHBP1 is required for transport and tethering of LPL to the endothelial luminal

surface. Homozygosity for mutations in GPIHBP1 that interfere with its synthesis or folding causes FCS. Autoantibodies to GPIHBP1 have also been reported to cause severe hyperchylomicronemia. Finally, LMF1 is required for appropriate processing and folding of LPL, and biallelic loss-of-function mutations can cause FCS. FCS can present in childhood or adulthood with severe abdominal pain due to acute pancreatitis. In this setting, the diagnosis should be suspected if a fasting TG level is >500 mg/dL. Eruptive xanthomas, which are small, yellowish-white papules, may appear in clusters on the back, buttocks, and extensor surfaces of the arms and legs. On funduscopic examination, the retinal blood vessels may be opalescent (lipemia retinalis). Hepatosplenomegaly is sometimes noted as a result of uptake of circulating chylomicrons by reticuloendothelial cells in the liver and spleen. Premature ASCVD is not generally a feature of FCS. The diagnosis of FCS is a clinical diagnosis based on persistence and severity of HTG, with a history of acute pancreatitis or eruptive xanthomas increasing the suspicion. While LPL activity can be measured in “postheparin plasma” obtained after an IV heparin injection to release the endothelial-bound LPL, this assay is not widely available. Genetic testing of a panel of candidate FCS genes can be used to confirm the diagnosis but is not required for making the clinical diagnosis. Because of the risk of pancreatitis, it is important to consider the diagnosis and institute therapeutic interventions in FCS. The goal is to prevent pancreatitis by reducing fasting TG levels to <500 mg/dL. Consultation with a registered dietician familiar with this disorder is essential. Dietary fat intake should be markedly restricted (to as little as 15 g/d), often with fat-soluble vitamin supplementation. Strict adherence to dietary fat restriction can be successful at controlling the chylomicronemia; fish oils or fibrates (such as fenofibrate) may be tried but are unlikely to be effective. Promising therapeutic approaches include the silencing of APOC3 or ANGPTL3 in the liver. In patients with APOC2 deficiency, apoC-II can be provided exogenously by infusing fresh-frozen plasma to resolve the chylomicronemia in the setting of severe acute pancreatitis. Management of patients with FCS is particularly challenging during pregnancy when VLDL production is increased. FAMILIAL PARTIAL LIPODYSTROPHY (FPLD) FPLD is a genetic condition in which the generation of adipose tissue in certain fat depots is impaired and in others is excessive. FPLD is an underrecognized monogenic cause of severe HTG,

which is likely due to both increased lipid synthesis and VLDL production, as well as reduced LPL-mediated clearance of TRLs. FPLD is typically a dominantly inherited disorder caused by mutations in several different genes, including lamin A/C (LMNA), PPAR γ (PPARG), perilipin (PLIN1), AKT2, and ADRA2A (Table 419-2). FPLD is characterized by loss of subcutaneous fat in the extremities and buttocks, often accompanied by increased visceral fat. Because of the reduced or absent subcutaneous fat in the arms and legs, patients are often described as having a “muscular” appearance. In addition to severe HTG, FPLD patients usually have insulin resistance, often quite severe, accompanied by type 2 diabetes and hepatosteatosis. Pancreatitis secondary to HTG can be a complication; in addition, ASCVD risk is substantially increased in FPLD patients. The diagnosis of FPLD is a clinical diagnosis based on the constellation of metabolic findings accompanied by the distinctive distribution of adipose tissue. Genetic testing of a panel of candidate FPLD genes can be used to confirm the diagnosis but is not required for making the clinical diagnosis, and a negative result does not rule out the diagnosis. Because FPLD is a dominant disorder, the finding of a causal mutation should lead to family-based screening. The dyslipidemia of FPLD can be difficult to manage clinically. Patients should be treated aggressively not only to reduce TG levels but also with statins and, if necessary, additional LDL-lowering therapies to reduce atherogenic lipoproteins. The insulin-resistant diabetes often requires aggressive management as well. Some patients have progression of fatty liver disease to metabolic-associated steatohepatitis, fibrosis, and cirrhosis. A different group of very rare patients have congenital generalized lipodystrophy, a recessive disorder caused by mutations in the AGPAT2 and BSCL2 genes. These patients have nearly complete absence of subcutaneous fat, accompanied by profound

TABLE 419-2 Primary Dyslipoproteinemias Caused by Known Single-Gene Mutations

GENETIC DISORDER	GENES MUTATED	LIPOPROTEINS AFFECTED	CLINICAL FINDINGS	GENETIC TRANSMISSION	ESTIMATED PREVALENCE
Severe Hypertriglyceridemia	Familial chylomicronemia syndrome (FCS)				
Biallelic LoF mutations in:	LPL, APOC2, APOA5, GPIHBP1, LMF1	Elevated: Chylomicrons, VLDL	Reduced: HDL	Familial partial lipodystrophy (FPLD)	Heterozygous LoF mutations in: LMNA, PPARG, PLIN1, AKT2, ADRA2A
Elevated: Chylomicrons, VLDL		Reduced: HDL	Hypercholesterolemia	Familial hypercholesterolemia (FH)	Heterozygous LoF mutations in LDLR
Elevated: LDL		Tendon xanthomas, premature atherosclerotic cardiovascular disease (ASCVD)	Familial defective apoB100 (FDB)	Heterozygous LoF receptor binding region mutations in APOB	Elevated: LDL
Tendon xanthomas, premature ASCVD	Autosomal dominant hypercholesterolemia (ADH), type 3	Heterozygous GoF mutations in PCSK9	Elevated: LDL	Tendon xanthomas, premature ASCVD	Autosomal recessive hypercholesterolemia (ARH)
Biallelic LoF mutations in LDLRAP1	Elevated: LDL	Tendon xanthomas, premature ASCVD	Sitosterolemia	Biallelic LoF mutations in ABCG5, ABCG8	Elevated: LDL
Tendon xanthomas, premature ASCVD	Lysosomal acid lipase deficiency	Biallelic LoF mutations in LIPA	Elevated: LDL	Reduced: HDL	Mixed Dyslipidemia
Familial dysbetalipoproteinemia (FDBL)	Biallelic carriers of the APOE2 variant	Elevated: Chylomicron remnants, IDL	Hepatic lipase deficiency	Biallelic LoF mutations in LIPC	Elevated: Chylomicron remnants, IDL, HDL
Familial Hypolipidemia Syndromes	Abetalipoproteinemia	Biallelic LoF mutations in MTP	Absent: LDL	Reduced: TG, HDL	Familial hypobetalipoproteinemia
Heterozygous truncating mutations in APOB	Reduced: LDL	Fatty liver, reduced risk of ASCVD	Familial PCSK9 deficiency	Heterozygous LoF mutations in PCSK9	Reduced: LDL
Reduced risk of ASCVD	AD ~1/1,000	Familial combined hypolipidemia	Heterozygous LoF mutations in ANGPTL3	Reduced: TG, LDL, HDL	Reduced risk of ASCVD
AD <1/1,000,000	Primary Low HDL Cholesterol Syndromes	ApoA-I deletions/ mutations	Heterozygous structural mutations in APOA1	Reduced: HDL	Variable depending on

mutation: premature ASCVD, systemic amyloidosis Tangier disease Biallelic LoF mutations in ABCA1 Nearly absent: HDL Reduced: LDL Elevated: TG Familial LCAT deficiency (FLD); fish eye disease (FED) Biallelic LoF mutations in LCAT Markedly reduced: HDL Corneal opacities (both FLD and FED), progressive chronic kidney disease (FLD only) Abbreviations: AD, autosomal dominant; apo, apolipoprotein; AR, autosomal recessive; ARH, autosomal recessive hypercholesterolemia; CHD, coronary heart disease; GoF, gain of function; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LCAT, lecithin-cholesterol acyltransferase; LDL, low-density lipoprotein; LoF, loss of function; LPL, lipoprotein lipase; PVD, peripheral vascular disease; TG, triglyceride; VLDL, very-low density lipoprotein. leptin deficiency, insulin resistance, severe HTG, and accumulation of TGs in multiple tissues including the liver. Patients with generalized lipodystrophy can be effectively treated with recombinant leptin administration, which often manages the multiple metabolic issues in these patients.

Pancreatitis, eruptive xanthomas, hepatosplenomegaly AR ~1/200,000–300,000 Insulin resistance, fatty liver disease, pancreatitis, central obesity, lack of subcutaneous adipose in extremities AD <1/1,000,000 Disorders of Lipoprotein Metabolism CHAPTER 419 AD ~1/250 AD ~1/1500 AD <1/1,000,000 AR <1/1,000,000 AR <1/1,000,000 Fatty liver disease, micronodular cirrhosis AR <1/1,000,000 Palmar and tuberoeruptive xanthomas, premature ASCVD AR ~1/10,000 Premature ASCVD AR <1/1,000,000 Spinocerebellar degeneration, retinal degeneration AR <1/1,000,000 AD <1/1,000,000 AD <1/1,000,000 Peripheral neuropathy, hepatosplenomegaly AR <1/1,000,000 AR <1/1,000,000 Multifactorial Severe Hypertriglyceridemia Most patients with severe HTG do not have a single-gene mutation but instead have a multifactorial etiology that includes genetics and environment. The prevalence of this phenotype is ~1 in 1000. HTG often runs in families, and the term familial HTG has been employed; however, except for the

TABLE 419-3 Secondary Causes of Altered Lipid and Lipoprotein Levels LDL-C HDL-C LP(a)
ELEVATED TG ELEVATED ELEVATED REDUCED ELEVATED REDUCED High-carbohydrate diet
Alcohol Obesity Insulin resistance Type 2 diabetes Lipodystrophy Chronic kidney disease Nephrotic
syndrome Viral hepatitis Sepsis Cushing's syndrome Acromegaly Glycogen storage disease
Pregnancy Drugs: estrogen, glucocorticoids, isotretinoin, bexarotene, other retinoids, beta
blockers, bile acid binding resins Hypothyroidism Cholestasis Nephrotic syndrome Cushing's
syndrome Acute intermittent porphyria Drugs: corticosteroids, cyclosporin, sirolimus,
carbamazepine Vegan diet Malabsorption Malnutrition Severe liver disease Gaucher's disease
Chronic infectious disease Hyperthyroidism PART 12 Endocrinology and Metabolism Abbreviations:
HDL-C, high-density lipoprotein cholesterol; LAL, lysosomal acid lipase; LDL-C, low-density
lipoprotein cholesterol; Lp(a), lipoprotein(a); TG, triglyceride. genes in which mutations cause FCS
or FPLD, reviewed above, no other classic Mendelian causes of HTG have been identified to date.
Instead, extensive human genetic studies have clearly established a polygenic basis to this
phenotype that consists of two categories: (1) rare heterozygous variants in the five genes
discussed earlier that cause FCS in the homozygous state, and (2) a high burden of common
variants that have small individual effects at raising TGs. Patients who inherit some combination
of rare and common TG-raising alleles often have environmental factors that exacerbate their HTG.
These "secondary" factors are reviewed in detail below, but the quantitatively most important fac-
tors promoting HTG include obesity, type 2 diabetes, insulin resistance, high-carbohydrate diet,
and alcohol use. Multifactorial HTG is characterized by elevated fasting TGs but average to below
average LDL-C levels and low HDL-C levels; apoB levels are not generally elevated. This condition is

not generally associated with a significantly increased risk of ASCVD. However, if the HTG is exacerbated by environmental factors, medical conditions, or drugs, the TGs can rise to a level at which acute pancreatitis is a risk. Indeed, management of patients with this condition is mostly focused on reduction of TGs to prevent pancreatitis. It is important to consider and rule out secondary causes of the HTG. Patients who are at high risk for ASCVD due to other risk factors should be treated with statin therapy. In patients who are otherwise not at high risk for ASCVD, lipid-lowering drug therapy can frequently be avoided with appropriate dietary and lifestyle changes. Patients with plasma TG levels >500 mg/dL after a trial of diet and exercise should be considered for drug therapy with a fibrate or fish oil to reduce TGs in order to prevent pancreatitis. These patients should also be carefully evaluated for ASCVD risk and may be candidates for statin therapy to further reduce cholesterol and cardiovascular risk. ■ ■HYPERCHOLESTEROLEMIA (ELEVATED LDL-C) Elevated LDL-C is common and is medically important because it is associated with risk of premature ASCVD. Elevated LDL-C is often caused by impaired uptake of LDL by the liver. As discussed above, the LDL receptor is the major receptor responsible for uptake of LDL, and most causes of elevated LDL-C converge on reduced expression or activity of the LDL receptor in the liver. One major environmental factor that reduces LDL receptor activity is a diet high in saturated and trans fats. Other medical conditions that reduce LDL receptor activity include hypothyroidism and estrogen deficiency. The diagnosis of familial hypercholesterolemia involving several genes that influence LDL clearance should be considered in patients with LDL-C levels

“ 190 mg/dL (Table 419-2). However, the majority of patients with

High-fat diet Alcohol Exercise Drugs: estrogen, phenytoin Hypertriglyceridemia Vegan diet Malabsorption Malnutrition Sedentary lifestyle Smoking Obesity Gaucher's disease LAL deficiency Drugs: anabolic steroids, testosterone, beta blockers Chronic kidney disease Nephrotic syndrome Inflammation Menopause Orchiectomy Hypothyroidism Acromegaly Drugs: growth hormone, isotretinoin elevated LDL-C have a polygenic predisposition exacerbated by secondary factors like a diet high in saturated and trans fats. Primary (Genetic) Causes of Elevated LDL-C • FAMILIAL HYPERCHOLESTEROLEMIA (FH) FH is an autosomal dominant disorder characterized by elevated plasma levels of LDL-C usually with relatively normal TG levels. FH is caused by mutations that lead to reduced function of the LDL receptor, with the most common being mutations in the LDLR gene itself. The reduction in LDL receptor activity in the liver results in a reduced rate of clearance of LDL from the circulation. The plasma level of LDL increases to a level such that the rate of LDL production equals the rate of LDL clearance by residual LDL receptor as well as non-LDL receptor mechanisms. Individuals with two mutated LDLR alleles (homozygotes or compound heterozygotes) have much higher LDL-C levels than those with one mutant allele, causing a condition known as homozygous FH. Although mutations in LDLR are the most common cause of FH (and originally the term FH was used specifically for patients with LDLR mutations), mutations in at least two other genes, APOB and PCSK9, can also cause FH. ApoB-100 is the critical structural protein in LDL and contains a domain that serves as the ligand for binding to the LDL receptor. Mutations in the LDL receptor-binding domain of apoB-100 reduce the affinity of apoB/LDL binding to the LDL receptor, such that LDL is removed from the circulation at a reduced rate. This condition has also been termed familial defective apoB (FDB). Of note, truncating mutations in APOB cause low LDL-C levels (see below). The proprotein convertase subtilisin/kexin type 9 (PCSK9) is a secreted protein

that binds to the LDL receptor and targets it for lysosomal degradation. Normally, after LDL binds to the LDL receptor, it is internalized along with the receptor, and in the low pH of the endosome, the LDL receptor dissociates from the LDL and recycles to the cell surface. When circulating PCSK9 binds the receptor, the complex is internalized and the receptor is directed to the lysosome, rather than to the cell surface, reducing the number of active LDL receptors. Gain-of-function mutations in PCSK9 that enhance the activity of PCSK9 cause a form of FH, also known as ADH type 3. Of note, loss-of-function mutations in PCSK9 reduce LDL-C levels (see below). The population frequency of heterozygous FH was originally estimated to be 1 in 500 individuals, but recent data suggest it may be as high as ~1 in 250 individuals, making it one of the most common single-gene disorders in humans. FH has a much higher prevalence in certain founder populations, such as South African Afrikaners, Christian Lebanese, French Canadians, and Lancaster County Amish.

Heterozygous FH is characterized by elevated plasma levels of LDL-C (usually >190 mg/dL) and relatively normal levels of TGs. Patients with FH have hypercholesterolemia from birth, and FH diagnosis is often based on detection of hypercholesterolemia on routine lipid screening; this serves as the basis for the recommendation to screen children between the ages of 9 and 11. A family history of hypercholesterolemia or premature ASCVD should prompt targeted screening. Inheritance of FH is dominant, meaning that the condition is inherited from one parent, and ~50% of the patient's siblings and children can be expected to have FH. For this reason, family-based "cascade screening" can be very effective in identifying additional persons with FH. Physical findings in some, but not all, patients with FH may include corneal arcus and/or tendon xanthomas, particularly involving the dorsum of the hands and the Achilles tendons. Untreated heterozygous FH is associated with a markedly increased risk of cardiovascular disease; untreated men with heterozygous FH have an ~50% chance of having a myocardial infarction before age 60 years, and women with heterozygous FH are at substantially increased risk as well. The age of onset of cardiovascular disease is highly variable and depends on the specific molecular defect, the level of LDL-C, and coexisting cardiovascular risk factors. The diagnosis of FH is generally a clinical diagnosis based on hypercholesterolemia with LDL-C >190 mg/dL in the absence of a secondary etiology and ideally with a family history of hypercholesterolemia and/or premature ASCVD. Secondary causes of significant hypercholesterolemia such as hypothyroidism, nephrotic syndrome, and obstructive liver disease should be excluded. Sequencing of an FH gene panel (LDLR, APOB, PCSK9) to confirm the diagnosis is widely available and worthy of consideration; persons with molecularly confirmed FH are at higher risk of ASCVD and therefore may benefit from more aggressive treatment, and the finding of a specific causal variant has implications for family-based cascade screening. FH patients should be actively treated to lower plasma levels of LDL-C, preferably starting in childhood. Initiation of a diet low in saturated and trans fats is recommended, but heterozygous FH patients almost always require pharmacologic therapy for effective control of their LDL-C levels. Statins are the initial drug class of choice, and usually "high-intensity" statin therapy is needed. Many FH patients cannot achieve adequate control of their LDL-C levels even with high-intensity statin therapy, and a cholesterol absorption inhibitor (ezetimibe), a PCSK9 inhibitor, an ACL inhibitor (bempedoic acid), and a bile acid sequestrant are other classes of drugs that can be added to statins (Table 419-4). Some patients with severe heterozygous FH cannot be adequately managed using existing therapies and are candidates for LDL apheresis, a physical method of purging the blood of LDL in which the LDL particles are selectively removed from the circulation. Other novel approaches for these patients are under development. Homozygous FH (HoFH) is caused by loss-of-function mutations in both alleles of the LDL receptor or double

heterozygosity for mutations in two FH genes. Patients with HoFH have been classified into those with virtually no detectable LDL receptor activity (receptor negative) and patients with markedly reduced but detectable LDL receptor activity (receptor defective). Untreated LDL-C levels in patients with HoFH range from ~400 to >1000 mg/dL, with receptor-defective patients at the lower end and receptor-negative patients at the higher end of the range. TGs are usually relatively normal. Some patients with HoFH, particularly receptor-negative patients, present in childhood with cutaneous planar xanthomas on the hands, wrists, elbows, knees, heels, or buttocks. The devastating consequence of HoFH is accelerated ASCVD, which often presents in childhood or early adulthood. Atherosclerosis often develops first in the aortic root, where it can cause aortic valvular or supravulvular stenosis, and typically extends into the coronary ostia, which become stenotic. Symptoms can be atypical, and sudden death is not uncommon. Untreated, receptor-negative patients with HoFH rarely survive beyond the second decade; patients with receptor-defective LDL receptor defects have a better prognosis but almost invariably develop clinically apparent atherosclerotic vascular disease by age 30 and often much sooner.

HoFH should be suspected in a child or young adult with LDL

“ 400 mg/dL without secondary cause. Cutaneous xanthomas, evidence of ASCVD, and/or hypercholesterolemia in both parents all are supportive of the diagnosis. While the diagnosis is usually made on clinical grounds, genetic testing should be performed to identify specific causal variants. Patients with HoFH must be treated aggressively to delay the onset and progression of cardiovascular disease (CVD). Although receptor-negative patients have no response to statins and PCSK9 inhibitors, receptor-defective patients can have modest responses to these medicines, and they should be tried in patients with HoFH. Two drugs that reduce the hepatic production of VLDL and thus LDL, a small-molecule inhibitor of MTP and an antisense oligonucleotide to apoB, and an antibody that inhibits ANGPTL3 are approved for the treatment of patients with HoFH and should be considered in HoFH patients. LDL apheresis should be considered in HoFH patients who have persistently elevated LDL-C levels despite drug therapy. Liver transplantation is effective in decreasing plasma LDL-C levels in this disorder and is sometimes used as a last resort. Liver-directed gene therapy is under development for HoFH, as are other new therapeutic approaches intended to address the remaining unmet medical need.

Disorders of Lipoprotein Metabolism CHAPTER 419 FH is an autosomal dominant disorder. There are a few rare conditions that cause an FH-like phenotype in an autosomal recessive manner and should be considered in patients with severe hypercholesterolemia who do not report a family history of hypercholesterolemia or premature CHD. AUTOSOMAL RECESSIVE

HYPERCHOLESTEROLEMIA (ARH) ARH is a very rare autosomal recessive disorder that was originally reported in individuals of Sardinian descent. The disease is caused by mutations in the gene LDLRAP1 encoding the protein LDLR adaptor protein (also called the ARH protein), which is required for LDL receptor-mediated endocytosis in the liver. LDLRAP1 binds to the cytoplasmic domain of the LDL receptor and links the receptor to the endocytic machinery. In the absence of

LDLRAP1, LDL binds to the extracellular domain of the LDL receptor, but the lipoprotein-receptor complex fails to be internalized. ARH, like HoFH, is characterized by hypercholesterolemia, tendon xanthomas, and premature coronary artery disease (CAD). The levels of plasma LDL-C tend to be intermediate between the levels present in FH homozygotes and FH heterozygotes, and CAD is not usually symptomatic until the third decade. LDL receptor function in cultured fibroblasts is normal or only modestly reduced in ARH, whereas LDL receptor function in the liver is negligible. Unlike FH homozygotes, the hyperlipidemia responds to treatment with statins, but these patients often require additional therapy to lower plasma LDL-C to acceptable levels.

SITOSTEROLEMIA

Sitosterolemia is a rare autosomal recessive disease that is caused by biallelic loss-of-function mutations in either of two members of the ATP-binding cassette (ABC) half transporter family, ABCG5 and ABCG8. These genes are expressed in both enterocytes and hepatocytes. The proteins heterodimerize to form a functional complex that transports plant sterols such as sitosterol and campesterol, and animal sterols, predominantly cholesterol, across the apical biliary membrane of hepatocytes into the bile and across the apical luminal membrane of enterocytes into the gut lumen, thus reducing their (re)absorption and promoting their excretion. In normal individuals, <5% of dietary plant sterols are absorbed by the proximal small intestine. The small amounts of plant sterols that enter the circulation are preferentially excreted into the bile, and thus, levels of plant sterols are kept very low in tissues. In sitosterolemia, the intestinal absorption of sterols is increased and biliary and fecal excretion of the sterols is reduced, resulting in increased plasma and tissue levels of both plant sterols and cholesterol. The increase in hepatic sterol levels results in transcriptional suppression of the expression of the LDL receptor, resulting in reduced uptake of LDL and substantially increased LDL-C levels. In addition to the clinical picture of severe hypercholesterolemia, often accompanied by tendon xanthomas and premature ASCVD, these patients also have anisocytosis and poikilocytosis of erythrocytes and megathrombocytes due to the incorporation of plant sterols into cell membranes. Episodes of hemolysis and splenomegaly are a distinctive clinical feature of this disease compared

TABLE 419-4 Drugs Used to Treat Dyslipidemia			
MAJOR INDICATIONS	STARTING DOSE	MAXIMAL DOSE	MECHANISM
LDL-Lowering Drugs			
HMG-CoA reductase inhibitors (statins)	Elevated LDL-C; increased CV risk	↓ Inhibition of cholesterol synthesis → ↑ Hepatic LDL receptors	
Lovastatin	20–40 mg daily	80 mg daily	
Pravastatin	40–80 mg daily	80 mg daily	
Simvastatin	20–40 mg daily	80 mg daily	
Fluvastatin	20–40 mg daily	80 mg daily	
PART 12 Endocrinology and Metabolism			
Atorvastatin	20–40 mg daily	80 mg daily	
Rosuvastatin	5–20 mg daily	40 mg daily	
Pitavastatin	1–2 mg daily	4 mg daily	
Cholesterol absorption inhibitor			
Elevated LDL-C	↓ Cholesterol absorption → ↑ LDL receptors		
Ezetimibe	10 mg daily	10 mg daily	
Bile acid sequestrants			
Elevated LDL-C	↑ Bile acid excretion → ↑ LDL receptors		
Cholestyramine	4 g daily	32 g daily	
Colestipol	5 g daily	40 g daily	
Colesevelam	3750 mg daily	4375 mg daily	
PCSK9 inhibitors			
Evolocumab (Ab)	140 mg SC every 2 weeks	75 mg SC every 2 weeks	
Alirocumab (Ab)	150 mg SC every 2 weeks	150 mg SC every 2 weeks	
Inclisiran (siRNA)	300 mg SC every 6 months	300 mg SC every 6 months	
↓ PCSK9 synthesis due to siRNA silencing → ↑ LDL receptors			
ATP citrate lyase inhibitor			
Bempedoic acid	Elevated LDL-C	180 mg daily	180 mg daily
↓ Inhibition of cholesterol synthesis → ↑ LDL receptors			
MTP inhibitor			
Lomitapide	HoFH	5 mg daily	60 mg daily
MTP inhibition → ↓ VLDL assembly and secretion			
ApoB inhibitor (ASO)			
Mipomersen	HoFH	200 mg SC weekly	200 mg SC weekly
↓ ApoB synthesis due to ASO silencing → ↓ ApoB/VLDL secretion			
ANGPTL3 inhibitor (Ab)			
Evinacumab	HoFH	15 mg/kg IV q 4 weeks	15 mg/kg IV q 4 weeks
↓ ANGPTL3 activity due to Ab inhibition → ↑ LPL and EL activity, ↑ LDL catabolism			
TG-Lowering Drugs			
Fibric acid derivatives			

(fibrates) Gemfibrozil Fenofibrate Elevated TG 600 mg bid 40–160 mg daily

depending on product Omega-3 fatty acids Acid ethyl esters Elevated TG 4 g daily 4 g daily ↑ TG catabolism Dyspepsia Icosapent ethyl 4 g daily 4 g daily Abbreviations: Ab, antibody; GI, gastrointestinal; HDL-C, high-density lipoprotein cholesterol; HoFH, homozygous familial hypercholesterolemia; LDL, low-density lipoprotein; LDL-C, LDL cholesterol; LPL, lipoprotein lipase; TG, triglyceride; VLDL, very-low-density lipoprotein. to other genetic forms of hypercholesterolemia and can be a clue to the diagnosis. Sitosterolemia should be suspected in a patient with severe hypercholesterolemia without a family history of such or who fails to respond to statin therapy. Sitosterolemia can be diagnosed by a laboratory finding of a substantial increase in plasma sitosterol and/or other plant sterols and should be confirmed by gene sequencing of ABCG5 and ABCG8. It is important to make the diagnosis, because diet, bile acid sequestrants, and cholesterol-absorption inhibitors are the most effective agents to reduce LDL-C and plasma plant sterol levels in these patients. Of note, heterozygosity for mutations in ABCG5 or ABCG8 is now recognized to cause a moderate form of hypercholesterolemia. LYSOSOMAL ACID LIPASE DEFICIENCY (LALD) LALD, also known as cholesteryl ester storage disease, is an autosomal recessive disorder

Myalgias and myopathy, ↑ transaminases, ↑ diabetes risk Elevated transaminases Bloating, constipation, elevated triglycerides 420 mg SC every 1 month (HoFH) 150 mg SC every 2 weeks Injection site reactions ↓ PCSK9 activity due to Ab inhibition → ↑ LDL receptors Injection site reactions ↑ uric acid and gout ↑ cholelithiasis Nausea, diarrhea, increased hepatic fat Injection site reactions, flu-like symptoms, increased hepatic fat Reduced HDL-C levels 600 mg bid 40–160 mg daily depending on product ↑ LPL, ↓ VLDL synthesis Dyspepsia, myalgia, cholelithiasis, elevated transaminases caused by loss-of-function variants in both alleles of the gene LIPA encoding the enzyme lysosomal acid lipase (LAL). LAL is responsible for hydrolyzing neutral lipids, particularly TGs and CEs, after delivery to the lysosome by cell surface receptors such as the LDL receptor. It is particularly important in the liver, which clears large amounts of lipoproteins from the circulation. LALD is characterized by elevated LDL-C, usually in association with low HDL-C and with variably elevated TG levels, together with progressive fatty liver ultimately leading to hepatic fibrosis. Genetic deficiency of LAL results in accumulation of neutral lipid in the hepatocytes, leading to hepatosplenomegaly, microvesicular steatosis, and ultimately fibrosis and end-stage liver disease. The most severe form of this disorder, Wolman's disease, presents in infancy and is rapidly fatal. The etiology of the elevated LDL-C levels is primarily due to impaired LDL receptor-mediated clearance

of LDL. LALD should be suspected in nonobese patients with elevated LDL-C, low HDL-C, and evidence of fatty liver in the absence of overt insulin resistance. The diagnosis can be made with a dried blood spot assay of LAL activity and confirmed by DNA genotyping for the most common mutation, followed if necessary by sequencing of the gene to find the second mutation. Liver biopsy is required to assess the degree of inflammation and fibrosis. LALD is underdiagnosed; it is critically important to suspect it and make the diagnosis because enzyme replacement therapy with sebelipase alfa is now available and is highly effective in treating this condition. The above conditions primarily cause elevations in LDL due to impaired catabolism of LDL from the blood. There are a few forms of primary dyslipidemia that impair the catabolism of "remnant" TRLs (after their processing by LPL) and therefore cause elevations in both cholesterol and TGs due to remnant accumulation. Multifactorial Hypercholesterolemia Most patients with elevated LDL-C do not have

a single-gene disorder, as described above, but instead have a multifactorial etiology that includes genetics and environment. Genetic variation contributes substantially to elevated LDL-C levels in the general population. It has been estimated that at least 50% of variation in LDL-C is genetically determined. Many patients with elevated LDL-C have polygenic hypercholesterolemia due to multiple common genetic variants exerting modest LDL-raising effects. Individuals at the tail of the highest burden of polygenic risk score for LDL-C often have LDL-C levels that are similar to those with FH. In patients who are genetically predisposed to higher LDL-C levels, diet plays a key exacerbating role; indeed, increased saturated and trans fats in the diet shift the entire distribution of LDL-C levels in the population to the right. As described in more detail below, patients with elevated LDL-C should be carefully assessed for their risk of ASCVD and managed with lifestyle modification and LDL-lowering medications as needed to reduce LDL-C and risk of ASCVD. ■

■ **MIXED HYPERLIPIDEMIA (ELEVATED TG AND LDL-C)** Mixed hyperlipidemia can be defined as fasting TGs >150 mg/dL and evidence of elevated cholesterol-containing lipoproteins (such as LDL-C >130 mg/dL or non-HDL-C >160 mg/dL). It is one of the most common types of lipid disorders seen in clinical practice, due both to genetic predisposition and influence of medical conditions and environmental factors (see below). It is generally associated with elevated risk of ASCVD, and therefore, patients with mixed hyperlipidemia should be carefully evaluated and managed to reduce this risk. Primary (Genetic) Causes of Mixed Hyperlipidemia • **FAMILIAL**

DYSBETALIPOPROTEINEMIA (FDBL) FDBL (also known as type III hyperlipoproteinemia) is a recessive disorder characterized by a mixed hyperlipidemia due to the accumulation of remnant lipoprotein particles (chylomicron remnants and VLDL remnants, or IDL). ApoE is present in multiple copies on chylomicron remnants and IDL and mediates their removal via hepatic lipoprotein receptors (Fig. 419-2). The APOE gene is polymorphic in sequence, resulting in the expression of three common isoforms: apoE3, which is the most common (~78% global allele frequency [AF]), apoE4 (~14% global AF), and apoE2 (~8% global AF). The apoE4 allele, which has an arginine instead of a cysteine at position 112, is widely known for being the major genetic risk factor for Alzheimer's disease. It is associated with slightly higher LDL-C levels and increased ASCVD risk but is not associated with FDBL. The apoE2 allele, which has a cysteine at position 158 instead of an arginine, is the cause of FDBL when present on both alleles. ApoE2 has a lower affinity for the LDL receptor; therefore, chylomicron remnants and IDL containing apoE2 are removed from plasma at a slower rate, leading to their accumulation in blood. Approximately 0.5% of the general population are apoE2/E2 homozygotes, but only a small minority of these individuals actually develop hyperlipidemia characteristic of FDBL (which has a prevalence of ~1 in 10,000). Thus, an additional, sometimes identifiable, factor precipitates the development of overt dysbetalipoproteinemia in apoE2/E2 homozygotes. The most common precipitating factors are a high-fat diet,

sedentary lifestyle, obesity, alcohol use, menopause, diabetes mellitus, hypothyroidism, renal disease, HIV infection, or certain drugs. Certain dominant-negative mutations in apoE can cause a dominant form of FDBL where the hyperlipidemia is fully manifest in the heterozygous state, but these mutations are very rare.

Patients with FDBL usually present in adulthood with hyperlipidemia, xanthomas, or premature coronary or peripheral vascular disease. In FDBL, in contrast to other disorders of elevated TGs, the plasma levels of cholesterol and TG are often elevated to a similar degree, and the level of HDL-C

is usually normal. Two distinctive types of xanthomas, tuberoeruptive and palmar, are seen in FDBL patients. Tuberoeruptive xanthomas begin as clusters of small papules on the elbows, knees, or buttocks and can grow to the size of small grapes. Palmar xanthomas (alternatively called xanthomata striata palmaris) are orange-yellow discolorations of the creases in the palms and wrists. Both of these xanthoma types are virtually pathognomonic for FDBL. Subjects with FDBL have premature ASCVD and tend to have more peripheral vascular disease than is typically seen in FH. Disorders of Lipoprotein Metabolism CHAPTER 419 The definitive diagnosis of FDBL can be made either by the documentation of very high levels of remnant lipoproteins or by identification of the apoE2/E2 genotype. A variety of methods are used to identify remnant lipoproteins in the plasma, including “ β -quantification” by ultracentrifugation (ratio of directly measured VLDL cholesterol to total plasma TG >0.30), lipoprotein electrophoresis (broad β band), or nuclear magnetic resonance lipoprotein profiling. The Friedewald formula for calculation of LDL-C is not valid in FDBL because the VLDL particles are depleted in TG and enriched in cholesterol. The plasma levels of LDL-C are actually low in this disorder due to defective metabolism of VLDL to LDL. DNA-based apoE genotyping can be performed to confirm homozygosity for apoE2, which is diagnostic for FDBL. However, absence of the apoE2/E2 genotype does not strictly rule out the diagnosis of FDBL, because other mutations in apoE can (rarely) cause this condition. Because FDBL is associated with increased risk of premature ASCVD, it should be treated aggressively. Other metabolic conditions that can exacerbate the hyperlipidemia (see above) should be managed. Patients with FDBL are typically diet-responsive and can respond favorably to low-cholesterol, low-fat diets and weight reduction. Alcohol intake should be curtailed. Pharmacologic therapy is often required, and statins are the first line in management. In the event of statin intolerance or insufficient control of hyperlipidemia, cholesterol absorption inhibitors, PCSK9 inhibitors, and fibrates are also effective in the treatment of FDBL.

HEPATIC LIPASE DEFICIENCY

Hepatic lipase (HL; gene name LIPC) is a member of the same gene family as LPL and hydrolyzes TGs and phospholipids in remnant lipoproteins and HDL. Hydrolysis of lipids in remnant particles by HL contributes to their hepatic uptake via an apoE-mediated process. HL deficiency is a very rare autosomal recessive disorder caused by biallelic loss-of-function mutations in LIPC. It is characterized by elevated plasma levels of cholesterol and TGs (mixed hyperlipidemia) due to the accumulation of lipoprotein remnants, accompanied by elevated plasma level of HDL-C. The diagnosis is confirmed by confirmation of pathogenic mutations in both alleles of LIPC. Due to the small number of patients with HL deficiency, the association of this genetic defect with ASCVD is not entirely clear, although anecdotally, patients with HL deficiency who have premature CVD have been described. As with FDBL, statin therapy is recommended to reduce remnant lipoproteins and cardiovascular risk.

FAMILIAL COMBINED HYPERLIPIDEMIA (FCHL)

FCHL is one of the most common familial lipid disorders; it is estimated to occur in ~ 1 in 100–200 individuals. FCHL is characterized by elevations in plasma levels of TGs (VLDL) and LDL-C (including especially a small dense form of LDL) and reduced plasma levels of HDL-C. This disorder is an important contributor to premature CHD; $\sim 20\%$ of patients who develop CHD under age 60 have FCHL. FCHL can manifest in childhood but is usually not fully expressed until adulthood. The disease clusters in families, and affected family members typically have one of three possible phenotypes: (1) elevated plasma levels of LDL-C, (2)

elevated plasma levels of TGs due to elevation in VLDL, or (3) elevated plasma levels of both LDL-C and TG. The lipoprotein profile can switch among these three phenotypes in the same individual over time and may depend on factors such as diet, exercise, weight, and insulin sensitivity.

Patients with FCHL have substantially elevated plasma levels of apoB, often disproportionately high relative to the plasma LDL-C concentration, indicating the presence of small dense LDL particles, which are characteristic of this syndrome.

Individuals with this phenotype generally share the same metabolic defect, namely overproduction of VLDL and apoB by the liver. The molecular etiology of this condition remains poorly understood, and no single gene has been identified in which mutations convincingly cause this disorder in a simple Mendelian fashion. It is likely that defects in a combination of genes can cause the condition, suggesting that a more appropriate term for the disorder might be polygenic combined hyperlipidemia. **PART 12 Endocrinology and Metabolism** The presence of a mixed dyslipidemia (plasma TG levels between 150 and 500 mg/dL and total cholesterol levels between 200 and 400 mg/dL, usually with HDL-C levels <40 mg/dL in men and <50 mg/dL in women) and a family history of mixed dyslipidemia and/or premature CHD suggests the diagnosis. Measurement of plasma apoB levels can help support the diagnosis if they are substantially elevated, particularly relative to the LDL-C level. Individuals with this disorder should be treated aggressively due to significantly increased risk of premature CHD, often disproportionate to the LDL-C level. Decreased dietary intake of simple carbohydrates, increased aerobic exercise, and weight loss can all have beneficial effects on the lipid profile. Patients with type 2 diabetes should be aggressively treated to maintain good glucose control. Virtually all patients with FCHL merit lipid-lowering drug therapy to reduce apoB-containing lipoprotein levels and lower the risk of ASCVD. High-intensity statins are first line, but many patients with FCHL require combination therapy that includes ezetimibe, a PCSK9 inhibitor, and/or bempedoic acid. ■ ■ **SECONDARY CONTRIBUTORS TO ELEVATED LEVELS OF APOB-CONTAINING LIPOPROTEINS** There are many “secondary” factors that contribute to dyslipidemia (Table 419-3), often acting in concert with polygenic predisposition as reviewed above. Some primarily affect TGs, some primarily affect LDL-C, and some influence both, with a great deal of variability. Here the major secondary contributors are reviewed. **Secondary Factors That Primarily Elevate TG Levels** • **HIGH CARBOHYDRATE DIET** Dietary carbohydrates are utilized as a substrate for fatty acid synthesis in the liver. Some of the newly synthesized fatty acids are esterified, forming TGs, and secreted in VLDL. Thus, excessive intake of calories as carbohydrates, which is frequent in Western societies, leads to increased hepatic VLDL-TG secretion and elevated TG levels. Reduction in carbohydrate consumption can have a substantial effect in reducing TG levels, although replacing carbohydrates with saturated fat can elevate LDL-C levels. **OBESEITY, INSULIN RESISTANCE, AND TYPE 2 DIABETES** (See also Chaps. 413–415) Obesity, insulin resistance, and type 2 diabetes mellitus are the most frequent contributors to dyslipidemia, primarily by influencing TGs. The increase in adipocyte mass and accompanying decreased insulin sensitivity associated with obesity have multiple effects on lipid metabolism, with one of the major effects being excessive hepatic VLDL production. More free fatty acids are delivered from the expanded and insulin-resistant adipose tissue to the liver, where they are reesterified in hepatocytes to form TGs, which are packaged into VLDLs for secretion into the circulation. In addition, the increased insulin levels promote increased fatty acid synthesis in the liver. In insulin-resistant patients who progress to type 2 diabetes mellitus, dyslipidemia remains common, even when the patient is under relatively good glycemic control. In addition to increased VLDL production, insulin resistance can also result in decreased LPL activity, resulting in reduced catabolism of chylomicrons and VLDLs and more severe HTG. This may be due in part to the effects of tissue insulin resistance leading to reduced transcription of LPL in skeletal muscle and adipose,

as well as to increased production of the LPL inhibitor apoC-III by the liver. This reduction in LPL activity often exacerbates the effects of increased VLDL production and contributes to the dyslipidemia seen in these patients. The dyslipidemia in this setting is almost invariably associated with low HDL-C levels as well. A cluster of metabolic risk factors are often found together, including obesity, insulin resistance, hypertension, high TGs, and low HDL-C (the so-called “metabolic syndrome,” Chap. 420).

ALCOHOL CONSUMPTION Excessive alcohol consumption inhibits hepatic oxidation of free fatty acids, thus promoting hepatic TG synthesis and VLDL secretion and leading to increased plasma TG levels. Regular alcohol use also raises plasma levels of HDL-C and should be considered in patients with the relatively unusual combination of elevated TGs and normal or elevated HDL-C. A careful history of alcohol use should be taken in patients with elevated TGs. Reduction in alcohol consumption can often have a substantial effect in reducing TG levels.

CHRONIC KIDNEY DISEASE (See also Chap. 322) Chronic kidney disease (CKD) is often associated with mild HTG (150–400 mg/dL) due to the accumulation of VLDLs and remnant lipoproteins in the circulation. TG lipolysis and remnant clearance are both reduced in patients with renal failure. Because the risk of ASCVD is increased in CKD, patients should usually be treated with lipid-lowering agents, particularly statins.

ESTROGEN AND OTHER DRUGS Many drugs have an impact on lipid metabolism and can result in significant alterations in the lipoprotein profile (Table 419-3). Estrogens often elevate TG levels, and TG levels can also increase during pregnancy. In women with HTG, plasma TG levels should be monitored when birth control pills or postmenopausal estrogen therapy is initiated and during pregnancy. Use of low-dose preparations of estrogen or the estrogen patch can minimize the effect of exogenous estrogen on lipids. Isotretinoin therapy for acne can cause substantial elevations in TGs, and TG levels should be checked at baseline and after initiation of therapy. Bexarotene therapy for cutaneous T-cell lymphoma often causes substantial increases in TGs, and patients should be monitored accordingly.

Secondary Factors That Elevate LDL-C Levels

- **DIET HIGH IN SATURATED AND TRANS FATS** Dietary saturated and trans fats act to downregulate LDL receptor expression in the liver, leading to elevation in LDL-C levels and increased ASCVD risk. A careful dietary history should be taken in individuals with elevated LDL-C with a focus on sources of saturated and trans fats. Reduction in consumption of saturated and trans fats can sometimes have a substantial effect in reducing LDL-C levels and is a cornerstone of the initial nonpharmacologic management of hypercholesterolemia.

HYPOTHYROIDISM (See also Chap. 394) Hypothyroidism is the most important medical condition causing elevated LDL-C levels. It causes elevated plasma LDL-C levels due to downregulation of the hepatic LDL receptor, which is normally increased by the action of thyroid hormone. Because hypothyroidism is often subtle and therefore easily overlooked, all patients presenting with elevated plasma levels of LDL-C, especially if there has been an unexplained increase in LDL-C, should be screened for hypothyroidism by measuring thyroid-stimulating hormone (TSH). Thyroid replacement therapy usually reduces LDL-C levels; if not, the patient probably has a primary lipoprotein disorder and may require lipid-lowering drug therapy with a statin.

LIVER DISORDERS (See also Chap. 347) Cholestasis is almost invariably associated with hypercholesterolemia due to elevated LDL-C levels and, if severe, particles called Lp-X. A major pathway by which cholesterol is excreted from the body is via secretion into bile, either directly or after conversion to bile acids, and cholestasis blocks this critical excretory pathway. The increase in hepatocellular cholesterol results in downregulation of the LDL receptor, leading to increased plasma LDL-C levels. In severe cholestasis, excess free cholesterol, coupled with phospholipids, is shed into the plasma as a constituent of a lamellar particle called Lp-X. These unusual particles, which are not lipoproteins, lack apoB, and have an aqueous and not neutral lipid

core, are rich in free cholesterol, and can deposit in the skin, producing xanthomas sometimes seen in patients with cholestasis. Some liver disorders can affect plasma lipid levels in other ways. Viral hepatitis can increase TGs, and liver failure can result in reduction in plasma cholesterol and TGs. NEPHROTIC SYNDROME (See also Chap. 322) Nephrotic syndrome is a classic cause of excessive VLDL production leading to elevation in both TGs and LDL-C. The molecular mechanism of VLDL overproduction remains poorly understood but has been attributed to the effects of hypoalbuminemia leading to increased hepatic protein synthesis. Effective treatment of the underlying renal disease may normalize the lipid profile, but many patients with chronic nephrotic syndrome require lipid-lowering drug therapy with statins and some times additional drugs.

CUSHING'S SYNDROME (See also Chap. 398) Endogenous glucocorticoid excess in Cushing's syndrome is associated with increased VLDL synthesis and secretion leading to dyslipidemia characterized by HTG and elevated LDL-C. Treatment of the underlying cause is often sufficient to manage the dyslipidemia, but sometimes lipid-lowering drug therapy is needed.

IMMUNOSUPPRESSIVE THERAPY AND CORTICOSTEROIDS Several of the immunosuppressants used after solid organ transplantation, including cyclosporin and sirolimus, can cause substantial elevation in LDL-C and TG levels. These patients can present a difficult clinical management problem. Chronic corticosteroid use, whether after transplant or in other inflammatory conditions, can also result in elevations in LDL-C and TG levels, sometimes producing a substantial mixed dyslipidemia. When the immunosuppressant or steroid must be continued, which is often the case, drug therapy with statins may be indicated in certain patients, with careful attention to the potential for untoward muscle-related side effects. ■ ■

DISORDERS ASSOCIATED WITH REDUCED APOB-CONTAINING LIPOPROTEINS Plasma concentrations of LDL-C <60 mg/dL are unusual. Although in some cases, LDL-C levels in this range may be reflective of malnutrition or serious chronic illness, LDL-C <60 mg/dL in an otherwise healthy individual suggests an inherited condition. The major inherited causes of low LDL-C are reviewed here and listed in Table 419-2.

Abetalipoproteinemia The synthesis and secretion of apoB-

containing lipoproteins in the enterocytes of the proximal small bowel and in the hepatocytes of the liver involve a complex series of events that coordinate the coupling of various lipids with apoB-48 and apoB-100, respectively. Abetalipoproteinemia is a rare autosomal recessive disease caused by loss-of-function mutations in the gene encoding MTP (gene name MTTP), a protein that transfers lipids to nascent chylomicrons and VLDLs in the intestine and liver, respectively. Plasma levels of cholesterol and TG are extremely low in this disorder, and chylomicrons, VLDLs, LDLs, and apoB are undetectable in plasma. The parents of patients with abetalipoproteinemia (obligate heterozygotes) have normal plasma lipid and apoB levels. Abetalipoproteinemia usually presents in early childhood with diarrhea and failure to thrive due to fat malabsorption. The initial neurologic manifestations are loss of deep tendon reflexes, followed by decreased distal lower extremity vibratory and proprioceptive sense, dysmetria, ataxia, and the development of a spastic gait, often by the third or fourth decade. Patients with abetalipoproteinemia also develop a progressive pigmented retinopathy presenting with decreased night and color vision, followed by reductions in daytime visual acuity and ultimately progressing to near-blindness. The presence of spinocerebellar degeneration and pigmented retinopathy in this disease has resulted in some patients with abetalipoproteinemia being misdiagnosed as having Friedreich's ataxia. Most of the clinical manifestations of abetalipoproteinemia result from defects in the absorption and transport of fat-soluble vitamins. Vitamin E and retinyl esters are normally transported from enterocytes to the liver by chylomicrons, and vitamin E is dependent on VLDL for transport out of the liver and

into the circulation. As a consequence

of the inability of these patients to secrete apoB-containing particles, patients with abetalipoproteinemia are markedly deficient in vitamin E and are also mildly to moderately deficient in vitamins A and K. Patients with abetalipoproteinemia should be referred to specialized centers for confirmation of the diagnosis and appropriate therapy. Treatment consists of a low-fat, high-caloric, vitamin-enriched diet accompanied by large supplemental doses of vitamin E. It is imperative that treatment be initiated as soon as possible to prevent development of neurologic sequelae, which can progress even with high-dose vitamin E therapy. New therapies for this serious, albeit rare, disease are needed. The discovery that genetic loss of MTP causes absent LDL-C led to the development of an MTP inhibitor to treat homozygous FH (see below).

Disorders of Lipoprotein Metabolism CHAPTER 419 Familial Hypobetalipoproteinemia (FHBL) FHBL generally refers to a condition of low total cholesterol, LDL-C, and apoB due to mutations in the APOB gene. Most of the mutations causing FHBL result in a truncated apoB protein, resulting in impaired assembly and secretion of chylomicrons from enterocytes and VLDL from the liver. Any secreted VLDL particles containing a truncated apoB protein are cleared from the circulation at an accelerated rate, which also contributes to the low levels of LDL-C and apoB. Individuals heterozygous for these mutations usually have LDL-C levels <60–80 mg/dL and also tend to have low levels of plasma TG. Many FHBL patients have elevated levels of hepatic fat (due to reduced VLDL export) and some times have increased levels of liver transaminases, although it appears that these patients infrequently develop associated hepatic inflammation and fibrosis. Truncating mutations in both apoB alleles cause homozygous FHBL, an extremely rare disorder resembling abetalipoproteinemia with nearly undetectable LDL-C and apoB. The neurologic defects in homozygous hypobetalipoproteinemia are similar to those seen in abetalipoproteinemia but tend to be less severe. Homozygous hypobetalipoproteinemia can be distinguished from abetalipoproteinemia by examining the inheritance pattern of the plasma LDL-C level. The levels of LDL-C and apoB are normal in the parents of patients with abetalipoproteinemia, a classic recessive condition, and low in those of patients with homozygous hypobetalipoproteinemia, a co-dominant condition. The discovery that truncating mutations in apoB reduce LDL-C led to the development of an antisense oligonucleotide to treat HoFH (see below). Familial PCSK9 Deficiency Another inherited cause of low LDL-C results from loss-of-function mutations in PCSK9. PCSK9 is a secreted protein that binds to the extracellular domain of the LDL receptor in the liver and promotes the degradation of the receptor. Heterozygosity for nonsense mutations in PCSK9 that interfere with the synthesis of the protein are associated with increased hepatic LDL receptor activity and reduced plasma levels of LDL-C. Such mutations are more frequent in individuals of African descent. Individuals who are heterozygous for a loss-of-function mutation in PCSK9 have an ~30–40% reduction in plasma levels of LDL-C and have a substantial protection from CHD relative to those without a PCSK9 mutation, presumably due to having lower plasma cholesterol levels since birth. Homozygotes for these nonsense mutations have been reported and have extremely low LDL-C levels (<20 mg/dL) but appear otherwise healthy. A sequence variation of somewhat higher frequency (R46L) is found predominantly in individuals of European descent. This mutation impairs, but does not completely destroy, PCSK9 function. As a consequence, the plasma levels of LDL-C in individuals carrying this mutation are more modestly reduced (~15–20%); individuals with these mutations have a 45% reduction in CHD risk. The discovery of this condition led to the development of therapies that antagonize or silence PCSK9, thus reducing LDL-C levels and risk of

CHD (see below). Familial Combined Hypolipidemia Nonsense mutations in both alleles of the gene angiopoietin-like 3 (ANGPTL3) lead to low plasma levels of all three major lipid fractions—TG, LDL-C, and

HDL-C—a phenotype termed familial combined hypolipidemia.

ANGPTL3 is a protein synthesized by the liver and secreted into the bloodstream. It inhibits LPL, thus delaying clearance of TRLs from the blood and increasing TRL blood concentrations. Deficiency of ANGPTL3, therefore, raises LPL activity and lowers blood TG; it also lowers LDL-C and raises HDL-C levels apparently related to the effects of ANGPTL3 on endothelial lipase. ANGPTL3 deficiency is associated with a reduced risk for CHD. The discovery of this condition led to the development of therapies that antagonize or silence ANGPTL3 to reduce LDL-C and TG levels (see below).

DISORDERS ASSOCIATED WITH REDUCED HIGH-DENSITY LIPOPROTEINS Low levels of HDL-C, generally defined as <50 mg/dL in women and <40 mg/dL in men, are very common in clinical practice. Low HDL-C is an important independent predictor of increased cardiovascular risk and has been used regularly in standardized risk calculators. As an independent risk factor, it has clinical value in the assessment of cardiovascular risk, and a patient with low HDL-C should generally be considered at higher risk of ASCVD. However, it is now considered doubtful that low HDL-C is directly causal for the development of ASCVD. Thus, while HDL-C remains an important biomarker for assessing cardiovascular risk, it is no longer considered a target for therapeutic intervention to raise HDL-C levels in order to reduce cardiovascular risk. **PART 12 Endocrinology and Metabolism** HDL metabolism is strongly influenced by TG metabolism, insulin resistance, and inflammation, among other environmental and medical factors. Thus, the HDL-C measurement integrates a number of cardiovascular risk factors, potentially explaining its strong inverse association with ASCVD. The majority of patients with low HDL-C have some combination of genetic predisposition and secondary factors. Variants in hundreds of genes have been shown to influence HDL-C levels. Even more important quantitatively, obesity and insulin resistance have strong suppressive effects on HDL-C, and low HDL-C in these conditions is widely observed. Furthermore, the vast majority of patients with elevated TGs have reduced levels of HDL-C due to the substantial interplay between the metabolism of TRLs and HDL (see above). Most patients with low HDL-C who have been studied in detail have accelerated catabolism of HDL and its associated apoA-I protein as the physiologic basis for the low HDL-C. Single-gene Mendelian disorders that reduce HDL-C have been described (Table 419-2) but are rare; the vast majority of patients with low HDL-C have a polygenic predisposition with secondary factors like obesity, insulin resistance, or HTG. ■ ■ **PRIMARY (GENETIC) CAUSES OF LOW HDL-C** Mutations in three key genes encoding proteins that play critical roles in HDL synthesis and catabolism result in hypoalphalipoproteinemia (primary low levels of HDL-C). Unlike the genetic forms of hypercholesterolemia, which are invariably associated with premature coronary atherosclerosis, genetic forms of hypoalphalipoproteinemia are usually not associated with clearly increased risk of ASCVD. Nevertheless, in the clinical setting of an HDL-C level <20 mg/dL without accompanying severe HTG, these rare conditions should be considered. **Gene Deletions and Missense Mutations in APOA1** Complete genetic deficiency of apoA-I due to a complete deletion of the APOA1 gene results in the virtual absence of circulating HDL, proving the critical role of apoA-I in HDL biogenesis. The APOA1 gene is part of a gene cluster on chromosome 11 that includes APOA5, APOC3, and APOA4. Some patients with no apoA-I have large genomic

deletions that include other genes in the cluster. The rare patient lacking apoA-I may have cholesterol deposits in the cornea and in the skin, and in contrast to the other genetic disorders of low HDL-C, premature CHD has been reported. Heterozygotes for apoA-I deletions have reduced HDL-C levels but no obvious clinical sequelae. More common, but still rare, are heterozygous missense mutations in the APOA1 gene associated with low plasma levels of HDL-C. The first example reported, and still the best known, is an Arg173Cys substitution in apoA-I (so-called apoA-IMilano), found in multiple residents of a town in northern Italy. Heterozygotes for this mutation have very

low plasma levels of HDL-C (<25 mg/dL) due to impaired LCAT activation and accelerated clearance of the HDL particles containing the abnormal apoA-I. Despite having very low plasma levels of HDL-C, these individuals do not appear to have an increased risk of premature CHD (neither are they protected against CHD as was initially believed). Multiple other rare APOA1 missense mutations causing low HDL-C have been reported. A few of these mutations in APOA1 (as well as some mutations in APOA2) promote the formation of amyloid fibrils, causing systemic amyloidosis. Tangier Disease (ABCA1 Deficiency) Tangier disease is a rare autosomal co-dominant form of extremely low plasma HDL-C levels that is caused by mutations in the ABCA1 gene encoding ABCA1, a cellular transporter that facilitates efflux of unesterified cholesterol and phospholipids from cells to apoA-I as an acceptor (Fig. 419-3). Through transporting cellular lipids, ABCA1 in the hepatocytes and intestinal enterocytes promotes the extracellular lipidation of the apoA-I secreted from the basolateral membranes of these tissues. In the genetic absence of ABCA1, the nascent, poorly lipidated apoA-I is rapidly cleared from the circulation. Thus, patients with Tangier disease (both ABCA1 alleles mutated) have extremely low circulating plasma levels of HDL-C (<5 mg/dL) and apoA-I (<5 mg/dL). Cholesterol accumulates in the reticuloendothelial system of these patients, resulting in hepatosplenomegaly and pathognomonic enlarged, grayish yellow or orange tonsils. An intermittent peripheral neuropathy (mononeuritis multiplex) or a sphingomyelia-like neurologic disorder can also be seen in this disorder. Tangier disease may be associated with some increased risk of ASCVD, although the association is not as robust as might have been anticipated, given the extremely low levels of HDL-C in these patients. Patients with Tangier disease also have low plasma levels of LDL-C, which may attenuate the atherosclerotic risk. Heterozygotes for ABCA1 mutations have moderately reduced plasma HDL-C levels (~15–40 mg/dL), and the effect on risk of ASCVD remains uncertain. Familial LCAT Deficiency This rare autosomal recessive disorder is caused by mutations in LCAT, an enzyme synthesized in the liver and secreted into the plasma, where it circulates associated with lipoproteins (Fig. 419-3). As reviewed above, the enzyme is activated by apoA-I and mediates the esterification of cholesterol to form CEs. Consequently, in familial LCAT deficiency, the proportion of free cholesterol in circulating lipoproteins is greatly increased (from ~25% to

“ 70% of total plasma cholesterol). Deficiency in this enzyme interferes with the maturation of HDL particles and results in rapid catabolism of circulating apoA-I. Two genetic forms of familial LCAT deficiency have been described in humans: complete deficiency (also called classic LCAT deficiency) and partial deficiency (also called fish eye disease). Progressive corneal opacification due to the deposition of free cholesterol in the cornea, very low plasma levels of HDL-C

(usually <10 mg/dL), and variable HTG are characteristic of both disorders. In partial LCAT deficiency, there are no other known clinical sequelae. In contrast, patients with complete LCAT deficiency have hemolytic anemia and progressive renal insufficiency that eventually leads to end-stage renal disease. Remarkably, despite the extremely low plasma levels of HDL-C and apoA-I, premature ASCVD is not a consistent feature of either LCAT deficiency or fish eye disease. The diagnosis can be confirmed in a specialized laboratory by assaying plasma LCAT activity or by sequencing the LCAT gene.

Primary Hypoalphalipoproteinemia

Primary hypoalphalipoproteinemia is defined as a plasma HDL-C level below the tenth percentile in the setting of relatively normal cholesterol and TG levels, no apparent secondary causes of low plasma HDL-C, and no clinical signs of LCAT deficiency or Tangier disease. A family history of low HDL-C suggests an inherited condition and may trigger an evaluation of one of the Mendelian causes of hypoalphalipoproteinemia. However, most patients with isolated low HDL do not have an identifiable single-gene disorder and likely have a polygenic etiology, possibly exacerbated by a secondary factor. The physiologic defect appears to be accelerated catabolism of HDL and its apolipoproteins. Several kindreds with

primary hypoalphalipoproteinemia and an increased incidence of premature CHD have been described, although it is not clear if the low HDL-C level is the cause of the accelerated atherosclerosis in these families. ■ ■

SECONDARY FACTORS THAT

REDUCE HDL-C LEVELS

Hypertriglyceridemia Low HDL-C is very commonly found in association with elevated TG levels. The lipolysis of TRLs generates lipids that transfer to HDL, and therefore, any impairment of lipolysis (the most common cause of elevated TGs) leads to reduced HDL biosynthesis. In settings of elevated TGs, where the HDL-C is not reduced, alternative explanations (e.g., FDBL, alcohol, estrogens) should be considered. Conversely, an isolated low HDL-C in the presence of normal TGs should prompt consideration of a primary genetic etiology (as above) or specific secondary factors (see below).

Very-Low-Fat Diet Dietary fat is positively associated with HDL-C levels. Individuals who eat very-low-fat vegan diets or who have anorexia or severe fat malabsorption often have low levels of HDL-C that are secondary to low dietary fat. In this setting, LDL-C levels are also usually low as well. There is no known harm to low HDL-C levels in this setting and no indication for liberalizing the diet solely for the purpose of raising the HDL-C.

Sedentary Lifestyle and Obesity Physical activity is known to have a (generally modest) effect in raising HDL-C levels, and conversely, a sedentary lifestyle is often associated with low HDL-C levels. Concordant with that observation, obesity is frequently associated with low HDL-C levels even when overt insulin resistance or HTG is not present. Increased physical activity and weight loss usually have some effect in raising HDL-C, which is not the primary reason for recommending these interventions but can have a motivating influence on the patient.

ANABOLIC STEROIDS AND TESTOSTERONE Anabolic steroids have a well-established effect on lowering HDL-C levels, sometimes quite dramatically. Testosterone supplementation can also reduce HDL-C levels, although not to the degree caused by anabolic steroids. In a young male patient who presents with unexplained very low HDL-C, a careful history of medication and supplement use should be taken.

APPROACH TO THE PATIENT Lipoprotein Disorders The major goals in the diagnosis and clinical management of lipoprotein disorders are (1) prevention of CVD and related cardiovascular events and (2) prevention of acute pancreatitis in patients with severe HTG. Given the high prevalence of dyslipidemia and the proven clinical benefits of early diagnosis and initiation of therapy, it is essential that physicians screen lipids systematically, rule out secondary causes of dyslipidemia, suspect inherited disorders of lipoprotein metabolism where appropriate, actively promote family-based screening, carefully assess risk for ASCVD and consider additional risk stratification approaches, and be knowledgeable about the wide range of existing therapeutic options for dyslipidemia. The field of clinical lipidology has matured and is moving toward a more systematic clinical application of genomic medicine. Diagnostic DNA sequencing or genotyping in patients with suspected FCS, FPLD, FH, and FDBL has the potential to enhance molecular diagnosis, facilitate appropriate therapeutic interventions, and promote family-based cascade screening based on genetic diagnosis. **DIAGNOSIS** A critical first step in managing a lipoprotein disorder is to attempt to determine the class or classes of lipoproteins that are increased or decreased in the patient. Once the dyslipidemia is accurately classified, efforts should be directed to identify or rule out any possible secondary causes (Table 419-3). A careful social, medical, and family history

should be obtained. In patients with elevated TG levels (>150 mg/dL), a fasting glucose and/or hemoglobin A1c should be obtained to rule out diabetes. In patients with elevated LDL-C levels (>160 mg/dL), a TSH should be obtained to rule out hypothyroidism and consideration should be given to the possibility of liver or kidney disease. Once secondary causes have been ruled out, attempts should be made to diagnose a primary lipid disorder, because the underlying genetic defect can provide important prognostic information regarding the risk of pancreatitis in severe HTG and the risk of ASCVD in other dyslipidemias, as well as impact on the choice of drug therapy and the screening of other family members. Obtaining the correct diagnosis often requires a detailed family history, lipid analyses in family members, and sometimes specialized or genetic testing. **Severe Hypertriglyceridemia** If the fasting plasma TG level is

“ 500 mg/dL, the patient has severe HTG and may be at risk for pancreatitis. If the TG levels are persistently severely elevated, especially if they are >1000 mg/dL, and the total cholesterol-to-TG ratio is >8 , FCS should be considered, and genetic testing of an FCS gene panel may be indicated (Table 419-2). If central obesity, insulin resistance, and/or fatty liver disease are also present, consideration should be given to the possibility of FPLD, and an FPLD gene panel may be indicated (Table 419-2). However, most individuals with severe HTG do not have a single-gene disorder but have increased polygenic risk for high TGs often exacerbated by secondary factors (e.g., diet, alcohol, obesity, insulin resistance, medications). Such patients are still at risk for acute pancreatitis and should be treated to reduce their TG levels and thus their risk of pancreatitis (see below). **Hypercholesterolemia** If the LDL-C levels are >190 mg/dL, the patient has severe hypercholesterolemia and is at risk for premature ASCVD. In absence of secondary causes, FH should be considered, particularly if there is a family history of hypercholesterolemia and/or premature CHD, and genetic testing of an FH gene panel may be indicated (Table 419-2). The Centers for

Disease Control and Prevention has identified FH as a Tier 1 condition for implementation of public health genomics. While FH is ultimately a clinical diagnosis, a finding of a causal mutation may appropriately result in earlier and more aggressive therapy to lower LDL-C and should also promote family-based cascade screening. Recessive forms of severe hypercholesterolemia are rare, but if a patient with severe hypercholesterolemia has parents with normal cholesterol levels, ARH, sitosterolemia, and LALD should be considered, and genetic testing may be indicated (Table 419-2). Patients without an identified genetic variant or who have more moderate hypercholesterolemia are likely to have polygenic hypercholesterolemia but should still be considered at risk and eligible for treatment (see below).

Mixed Hyperlipidemia Patients with elevations in fasting plasma levels of both TGs (>150 mg/dL) and LDL-C (>130 mg/dL), often accompanied by reduced levels of HDL-C (<40 mg/dL in men and <50 mg/dL in women), are common and such patients are often diagnosed as having “mixed hyperlipidemia.” Most such patients are at increased risk of ASCVD and merit consideration of lifestyle and often pharmacologic interventions. Secondary factors, particularly obesity, insulin resistance, and type 2 diabetes, are common in such patients, who often also have increased polygenic risk for dyslipidemia. The presence of palmar or tuberous xanthomas or an unusual lipid profile of total cholesterol and TG levels in the same range with an HDL-C that is not reduced should prompt consideration of FDBL, or type III hyperlipidemia, and can be diagnosed by advanced lipoprotein testing or genetic testing for the APOE2 genotype. FDBL patients should be managed aggressively due to substantially increased risk of ASCVD. More commonly, patients with mixed hyperlipidemia, particularly those with family histories of dyslipidemia or premature ASCVD, have familial combined hyperlipidemia (FCHL). ApoB should be measured in such patients, and the finding of substantially elevated apoB levels can help identify patients with FCHL, who are at especially increased risk of ASCVD and require more aggressive treatment.

Disorders of Lipoprotein Metabolism CHAPTER 419

TREATMENT Severe Hypertriglyceridemia There is a well-established observational relationship between severe HTG, particularly chylomicronemia, and acute pancreatitis; however, there has never been a clinical trial designed or powered to definitively prove that intervention to reduce TGs reduces the risk of pancreatitis. Nevertheless, it is generally considered appropriate medical practice to intervene in patients with TGs >500 mg/dL in order to reduce the risk of pancreatitis. It remains uncertain whether chylomicronemia increases risk for ASCVD per se. Importantly, moderate HTG (TG 150–500 mg/dL) is associated with increased ASCVD risk; management of these patients is focused on reducing risk of ASCVD and on reducing LDL-C, non-HDL-C, and apoB.

PART 12 Endocrinology and Metabolism LIFESTYLE AND MODIFIABLE FACTORS In patients with severe HTG, lifestyle modification can be associated with a significant reduction in plasma TG level. Importantly, certain medications can exacerbate HTG (Table 419-3). Patients who drink alcohol should be encouraged to decrease or preferably eliminate their intake. Patients with severe HTG often benefit from a formal dietary consultation with a dietician intimately familiar with counseling

patients on the dietary management of high TGs. Dietary fat intake should be restricted to reduce the formation of chylomicrons in the intestine. The excessive intake of simple carbohydrates should be discouraged because insulin drives TG production in the liver. Aerobic exercise and even increase in regular physical activity can have a positive effect in reducing TG levels and should be strongly encouraged. For patients who are overweight, weight loss can help to reduce TG levels. In extreme cases, bariatric surgery has been shown to not only produce effective weight loss but also substantially reduce plasma TG levels. Many patients with diabetes have HTG, and better control of diabetes can result in lowering of TGs. GLP-1 agonists prescribed for diabetes or obesity can reduce TG levels.

PHARMACOLOGIC THERAPY Despite lifestyle interventions, many patients with severe HTG require pharmacologic therapy (Table 419-4). Patients who persist in having fasting TG >500 mg/dL despite active lifestyle management are candidates for pharmacologic therapy. The two major classes of drugs used for management of these patients are fibrates and omega-3 fatty acids (fish oils). In addition, statins can reduce plasma TG levels and also reduce ASCVD risk and should be used in patients with severe HTG who are at increased risk of ASCVD.

Fibrates Fibrates, fibric acid derivatives, or fibrates, are agonists of PPAR α , a nuclear receptor involved in the regulation of lipid metabolism. Fibrates stimulate LPL activity (enhancing TG hydrolysis), reduce apoC-III synthesis (enhancing lipoprotein remnant clearance), promote β -oxidation of fatty acids, and may reduce VLDL TG production. Fibrates reduce TG levels by ~30% in individuals with severe HTG and are often used as first-line therapy. They do not reduce and sometimes modestly raise LDL-C levels. Fibrates are generally well tolerated but can cause myopathy, especially when combined with statins, can raise creatinine, and are associated with an increase in gallstones. Fibrates can potentiate the effect of warfarin and certain oral hypoglycemic agents.

Omega-3 Fatty Acids (Fish Oils) Omega-3 fatty acids, or omega-3 polyunsaturated fatty acids (n-3 PUFAs), commonly known as fish oils, are present in high concentration in fish and in flaxseed. The n-3 PUFAs used for the treatment of HTG are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). n-3 PUFAs have been concentrated into capsules and, in doses of 3–4 g/d, are effective at lowering fasting TG levels by ~30%. Fish oils can cause an increase in plasma LDL-C levels in some patients. Icosapent ethyl is an EPA-only product that has been shown to reduce cardiovascular events in patients with HTG. In general, fish oils are well tolerated, with

the major side effect being dyspepsia. They appear to be safe, at least at doses up to 3–4 g, but can be associated with a prolongation in the bleeding time. Fish oils can be first-line therapy for the treatment of severe HTG or can be used in combination with fibrates.

APOC3 Silencing ApoC-III inhibits LPL and TRL uptake, and genetic variants in the APOC3 gene reduce TG levels and risk of ASCVD. Volanesorsen is an antisense oligonucleotide (ASO) targeted to the APOC3 mRNA in the liver; it significantly reduces plasma apoC-III and TG levels and is approved in Europe for patients with FCS. It has been associated with severe thrombocytopenia. Additional therapeutic approaches to APOC3 and other targets for TG lowering (e.g., ANGPTL3) are in development.

Hypercholesterolemia (Elevated LDL-C with or without Elevated TG) There are abundant and compelling data that intervention to reduce LDL-C substantially reduces the risk of ASCVD, including myocardial infarction and stroke, as well as total mortality. Thus, it is imperative that patients with hypercholesterolemia be carefully assessed for cardiovascular risk and need for intervention. It is also worth emphasizing that patients with or at high risk for ASCVD who have plasma LDL-C levels in the “normal” or average range also benefit from intervention to reduce LDL-C levels.

LIFESTYLE AND MODIFIABLE FACTORS In patients with elevated LDL-C, lifestyle modifications can be effective but are often less effective than in HTG. Patients should receive

dietary counseling to reduce the content of saturated fats and trans fats in the diet. Obese patients should make an effort to lose weight. Regular aerobic exercise has relatively little impact on reducing plasma LDL-C levels, although it has cardiovascular benefits independent of LDL-C lowering. Patients with hypothyroidism should be optimally controlled. Finally, certain medications can elevate LDL-C levels (Table 419-3). **PHARMACOLOGIC THERAPY** The decision to use LDL-lowering drug therapy (Table 419-4)—with a statin being first-line therapy—depends on the presence of ASCVD or, if absent, the level of LDL-C as well as the level of cardiovascular risk. In patients with established ASCVD, drug therapy to reduce LDL-C is well supported by clinical trial data to reduce LDL-C as long as it remains >70 mg/dL, using combination drug therapy if necessary. In the absence of ASCVD, patients with FH must be treated to reduce the very high lifetime risk of ASCVD, and treatment should be initiated as early as possible, ideally during childhood. Otherwise, the decision to initiate LDL-lowering drug therapy is generally determined by the level of cardiovascular risk. For patients >40 years old without clinical CVD, the ASCVD pooled cohort risk calculator can be used to determine the 10-year absolute risk for CVD, and current guidelines suggest that a 10-year risk

“ 7.5% merits consideration of statin therapy regardless of plasma LDL-C level. For younger patients, the assessment of lifetime risk of CVD may help inform the decision to start a statin, as well as a careful assessment of family history of ASCVD. In patients for whom the decision to start a statin is uncertain due to borderline ASCVD risk and/or borderline LDL-C levels, additional risk stratification might be considered. Blood tests that predict ASCVD risk beyond traditional risk factors include apoB, Lp(a), and high-sensitivity C-reactive protein (hs-CRP). In patients who are of a sufficient age (men >40 years and women >50 years), a coronary artery calcium (CAC) score has been shown to provide independent information about risk of future CAD. Elevated levels of one or more of these biomarkers or an elevated CAC score might be used to justify initiation of statin therapy in primary prevention for patients who are in a borderline zone with regard to treatment. Finally, given the strong polygenic contribution to ASCVD, there is increasing interest in

the concept that a polygenic risk score for CAD might eventually be of clinical utility in lifetime risk assessment and decision-making regarding statin therapy in primary prevention. **HMG-CoA Reductase Inhibitors (Statins)** Statins inhibit HMGCoA reductase, a key enzyme in cholesterol biosynthesis. By inhibiting cholesterol synthesis in the liver, statins lead to a counterregulatory increase in the expression of the LDL receptor and thus accelerated clearance of circulating LDL, resulting in a dose-

dependent reduction in plasma levels of LDL-C. The magnitude of LDL-C lowering associated with statin treatment (~ 30 – 55%) varies by statin and among individuals, but once a patient is on a statin, the doubling of the statin dose produces a $\sim 6\%$ further reduction in the level of plasma LDL-C. An extensive body of randomized clinical trials has clearly established that statin therapy significantly reduces major cardiovascular events (and in some cases total mortality) in both primary and secondary prevention settings. The seven statins currently available differ in their LDL-

C-reducing potency (Table 419-4). Current recommendations are to use high-intensity statin therapy in patients with ASCVD or deemed at high risk of ASCVD. Statins also modestly reduce plasma TGs in a dose-dependent fashion roughly proportional to their LDL-C-lowering effects. Statins, taken in tablet form once a day, are remarkably safe and well tolerated. The most important side effect associated with statin therapy is muscle pain, or myalgia, which occurs in 3–5% of patients, some of whom are unable to tolerate any statin. Severe myopathy (associated with an increase in plasma creatine kinase [CK]) and even rhabdomyolysis can occur rarely with statin treatment. The risk of statin-associated myalgia or myopathy is increased by the presence of older age, frailty, renal insufficiency, and coadministration of drugs that interfere with the metabolism of certain statins, such as erythromycin and related antibiotics, antifungal agents, immunosuppressive drugs, and fibric acid derivatives (particularly gemfibrozil). In the event of muscle symptoms, a plasma CK level may be obtained to differentiate myopathy from myalgia. Serum CK levels need not be monitored on a routine basis in patients taking statins because an elevated CK in the absence of symptoms does not predict the development of myopathy and does not necessarily suggest the need for discontinuing the drug. Statins can result in elevation in liver transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), but it is usually mild and transient and generally does not require discontinuation. Finally, meta-analyses of large randomized controlled clinical trials with statins indicate a slight excess in incident type 2 diabetes, an observation as yet not fully understood. However, the cardiovascular benefits associated with statin therapy far outweigh the slight increase in incident diabetes. Based on their safety and extensively documented benefit with regard to cardiovascular outcomes, statins are the clear drug class of choice for LDL-C reduction and are by far the most widely used class of lipid-lowering drugs. Cholesterol Absorption Inhibitor Cholesterol within the lumen of the small intestine is derived from the diet (about one-third) and the bile (about two-thirds) and is actively absorbed by the enterocyte through a process that involves the protein NPC1L1. Ezetimibe (Table 419-4) is a cholesterol absorption inhibitor that binds directly to and inhibits NPC1L1 and blocks the intestinal absorption of cholesterol. Ezetimibe (10 mg taken once daily) inhibits cholesterol absorption by almost 60%, resulting in a reduction in delivery of dietary sterols in the liver and a compensatory increase in hepatic LDL receptor expression. The mean reduction in plasma LDL-C on ezetimibe (10 mg) is 18%, and the effect is additive when used in combination with a statin. Effects on TG and HDL-C levels are negligible. Ezetimibe added to a statin has been shown to significantly reduce major cardiovascular events compared with statin alone. It is generally considered the second-line option for adding to a statin in order to achieve further LDL-C reduction. Ezetimibe

is very safe and well-tolerated. When used in combination with a statin, monitoring of liver transaminases is recommended. The only roles for ezetimibe in monotherapy are in patients who do not tolerate statins and in some patients with sitosterolemia.

PCSK9 Inhibitors Circulating PCSK9 targets the LDL receptor for lysosomal degradation, thus reducing its recycling and abundance at the surface of the hepatocyte. Genetic loss of function of PCSK9 results in low levels of LDL-C and protection from CAD. Antibodies to PCSK9 (Table 419-4) sequester it and functionally increase the number of LDL receptors available to remove LDL from the blood. They are highly effective in lowering LDL-C, with an ~60% reduction in LDL-C. They also reduce plasma levels of Lp(a) modestly. Both PCSK9 antibodies have been shown to significantly reduce cardiovascular events when added to a statin in patients with existing CAD. These antibodies are administered subcutaneously every 2 weeks. They are generally well tolerated, with a side effect being injection site reactions. They are generally indicated as second-line (added to

statin) or third-line (added to statin plus ezetimibe) therapy in patients with FH or ASCVD in whom LDL-C is not reduced to acceptable levels with a statin (with or without ezetimibe) alone. An alternative approach to silencing PCSK9, inclisiran, is a therapeutic siRNA molecule that targets the PCSK9 mRNA in the liver. In contrast to the antibodies, it is administered subcutaneously every 6 months. It is effective in reducing LDL-C by ~60% and appears to be well tolerated and safe; cardiovascular outcomes trials are ongoing.

Disorders of Lipoprotein Metabolism CHAPTER 419

ATP Citrate Lyase Inhibitor Bempedoic acid

Bempedoic acid is a first-in-class competitive inhibitor of ATP citrate lyase (ACL), which acts on mitochondrial-derived citrate to generate production of acetylCoA, which is subsequently used for cholesterol synthesis. Thus, it reduces cholesterol synthesis through a different mechanism than statins, ultimately upregulating the hepatic LDL receptor. Bempedoic acid is a prodrug that requires activation by very-long-chain acyl-CoA synthetase-1 (ACSL1), which is not expressed in skeletal muscle, potentially explaining why it has less association with myalgias than statins; indeed, it has been shown to be relatively well tolerated in patients with statin-induced myalgias. In phase 3 trials, bempedoic acid 180 mg daily reduced LDL-C by ~18% when added to a statin and by ~23% as monotherapy. In a large cardiovascular outcomes trial in statin-intolerant patients, bempedoic acid 180 mg daily was shown to significantly reduce (by 13%) a four-component composite of major adverse cardiovascular events. It is also available in a fixed-dose combination with ezetimibe, which reduced LDL-C by ~36%, for patients who are statin intolerant. It can be used in combination with statins but should not be used with simvastatin in a dose >20 mg. Bempedoic acid is associated with increased uric acid levels and gout as well as with increased liver enzymes and cholelithiasis. Unlike statins, it is not associated with increased incidence of diabetes.

Bile Acid Sequestrants (Resins)

Bile acid sequestrants (BAS) bind bile acids in the intestine and promote their excretion rather than reabsorption in the ileum. To maintain the bile acid pool size, the liver diverts cholesterol to bile acid synthesis. The decreased hepatic intracellular cholesterol content results in upregulation of the LDL receptor and enhanced LDL clearance from the plasma. BAS, including cholestyramine, colestipol, and colesevelam (Table 419-4), primarily reduce plasma LDL-C levels but can cause an increase in plasma TGs. Therefore, patients with HTG generally should not be treated with bile acid-binding resins. Cholestyramine and colestipol are insoluble resins that must be suspended in liquids. Colesevelam is available as tablets but generally requires up to six to seven tablets per day for effective LDL-C lowering. BAS are effective in combination with statins and in combination with ezetimibe. Side effects of resins are limited to the gastrointestinal tract and include bloating and constipation. Because BAS are not systemically absorbed, they are very safe and are the cholesterol-lowering drug

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