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Diagnosis and Treatment of Dyslipidemia

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Introduction

Disorders of lipoprotein metabolism, in conjunction with the prevalence of high-fat diets, obesity, and physical inactivity epidemic of atherosclerotic disease in the United States and other developed countries. The interaction of common disorders of lipoproteins with these adverse environmental factors leads to the premature development of atherosclerotic mortality from coronary artery disease (CAD), particularly in persons younger than 60 years, has been declining since atherosclerotic cardiovascular disease remains the most common cause of death among both men and women.

Formerly, hyperlipidemia was defined as elevation of a lipoprotein level in the population. The recognition that a low level of lipoprotein (HDL) and the presence of small, dense low-density lipoprotein (LDL) are clinically important in the pathogenesis of atherosclerosis has led to the use of the term dyslipidemia to describe a range of disorders that include both abnormally high and low levels of lipoproteins as disorders in the composition of these particles. Dyslipidemias are clinically important, principally because of their association with atherosclerosis. Pancreatitis and fatty liver disease are less common but clinically significant manifestations of lipid disorders.

Lipoprotein Physiology

Lipoprotein Composition and Metabolism

Lipoproteins are spherical macromolecular complexes of lipid and protein [see *Figure 1*]. Clinically important lipids include cholesterol (both unesterified and esterified) and triglyceride (molecules consisting of three fatty acids attached to a glycerol backbone). Lipoproteins have three primary functions: it plays a role in the structure of cell membranes, in the synthesis of steroid hormones, and in the transport of lipids. The major functions of triglyceride are energy storage (in fat) and energy use (by muscle). Because fat cannot readily dissolve in water, cholesterol and triglyceride are made miscible by incorporation into lipoproteins (e.g., very low density lipoprotein [VLDL]). Apolipoproteins are the protein component of lipoproteins; they aid in the lipid transport and delivery process in three ways: as structural elements, as ligands for receptors, and as regulatory cofactors [see *Table 1*].

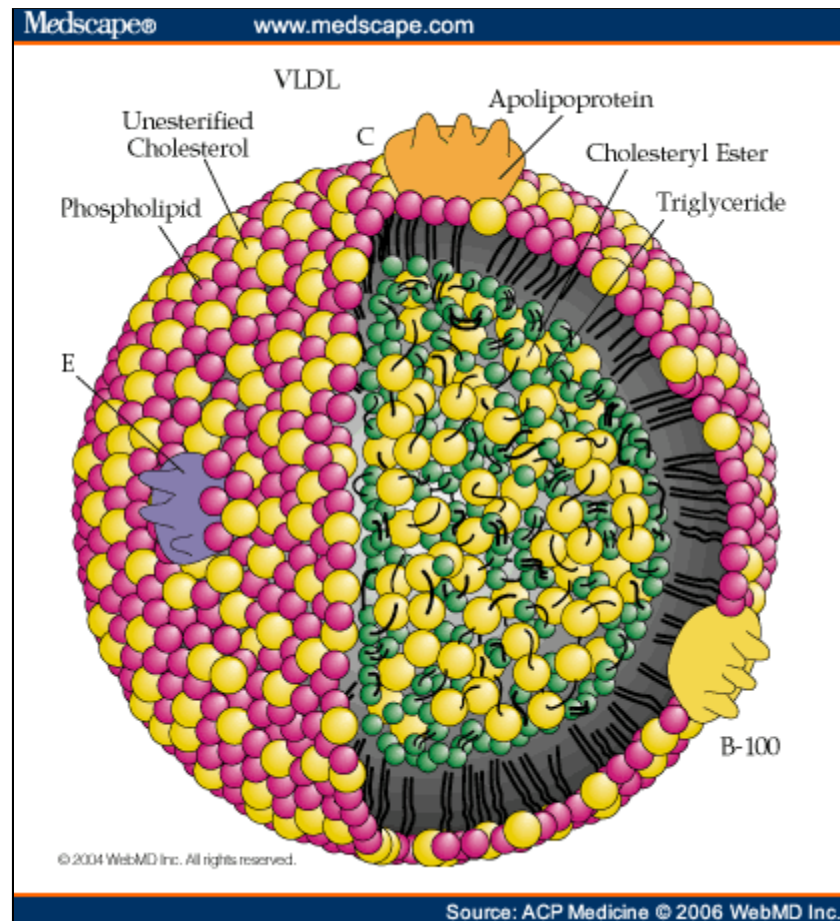


Figure 1.

Lipoproteins transport water-insoluble triglyceride and cholesterol through the bloodstream. All apo B-containing structure similar to that shown for very low density lipoproteins (VLDL). The core is composed of triglyceride and cholesteryl ester, whereas the monolayer surface is composed of phospholipid, unesterified cholesterol, and protein in the form of apolipoproteins. VLDL contains apolipoproteins B-100, C-I, C-II, and E. Low-density lipoprotein (LDL), which transports most of the cholesterol in blood, contains primarily apo B-100.

Lipoprotein Structure and Classification

A mature lipoprotein particle is a sphere consisting of a central core of lipids (triglyceride and cholesteryl ester) surrounded by a surface monolayer of phospholipid, unesterified cholesterol, and apolipoproteins [see *Figure 1*]. Operationally, the lipoproteins are classified based on their size and buoyancy characteristics [see *Figure 2*].

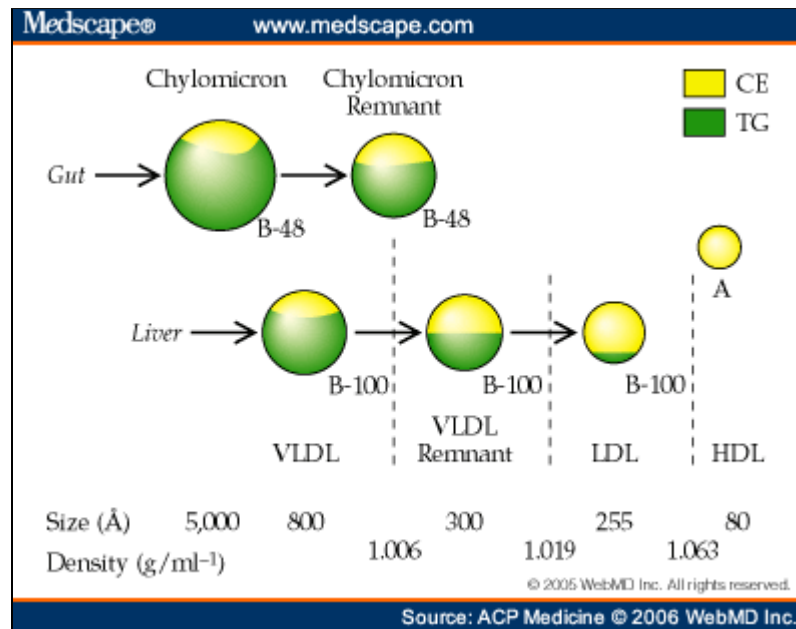


Figure 2.

Size and buoyancy characteristics of lipoproteins. Chylomicrons, which are composed largely of triglyceride, are most buoyant of the lipoproteins. High-density lipoprotein (HDL) particles are substantially smaller and denser, mostly of cholesteryl ester. (CE-cholesteryl ester; TG-triglyceride)

Chylomicron. Chylomicrons are the largest of the lipoprotein particles. The major structural protein is apolipoprotein B-48. The lipid core consists of triglyceride (~80%) and cholesteryl ester (~20%). Synthesized and secreted from the intestine, chylomicrons transport dietary lipids and fat-soluble vitamins absorbed from digested food [see Exogenous Pathway, *below*].

VLDL. This triglyceride-rich particle (~80% of the lipid core consists of triglyceride) is synthesized in the liver, delivers lipids to peripheral tissues, and is the precursor for intermediate-density lipoproteins (IDLs) and LDL. The major structural protein of this lipoprotein is apolipoprotein B-100 [see Endogenous Pathway, *below*].

IDL. The remnant of VLDL is of IDL density. It is formed after triglyceride in VLDL is hydrolyzed by lipoprotein lipase. The core is rich in triglyceride and 50% cholesteryl ester. Approximately half of the body's IDL particles are cleared from the plasma and further processed to form LDL [see Endogenous Pathway, *below*]. In clinical practice, assessment of LDL levels includes measurement of cholesterol in both IDL and LDL fractions.

LDL. This lipoprotein results from the hepatic processing of VLDL remnants. The core is rich in cholesteryl ester and contains cholesterol circulating in the blood. LDL plays a major role in the development of atherosclerosis [see LDL Catabolism, *below*].

HDL. HDL forms from the unesterified cholesterol and phospholipid removed from peripheral tissues and the surface of lipoproteins [see Function and Regulation of HDL, *below*]. The major structural protein is apo A-I; the core is predominantly cholesterol. The return of lipoprotein and tissue cholesterol to the liver for excretion in the process referred to as reverse cholesterol transport. HDL functions is to shuttle apo E and apo C-II to and from chylomicrons and VLDL.

Lipoprotein Assembly and Catabolism

Exogenous Pathway

After a meal, intestinal cells absorb fatty acids and cholesterol, esterify them into triglyceride and cholesteryl ester, and assemble a core of chylomicrons.^[1] Triglyceride greatly predominates over cholesteryl ester in the chylomicron core. The chylomicrons enter the lymphatic system, where apo C-II on the chylomicron surface activates endothelial-bound lipoprotein lipase (LPL). LPL in turn hydrolyzes the triglyceride core of the chylomicron into free fatty acids and glycerol, which are then taken up by peripheral tissues.

core triglyceride and releases free fatty acids, which are taken up by adipose tissue for storage and by muscle for energy. As the chylomicron decreases in size, and some surface components are transferred to HDL; the remaining particle is the chylomicron remnant. This chylomicron remnant next acquires apo E from HDL and is subsequently taken up by the liver after binding to its receptors. The remnant is then degraded, thereby delivering dietary cholesterol to the liver.

Endogenous Pathway

The liver secretes triglyceride-rich VLDL into plasma, where they too acquire apo C-II from HDL. As with chylomicrons on the capillary endothelium, and the core triglyceride is hydrolyzed to provide fatty acids to adipose and muscle tissue. Catabolized VLDL remnants (IDL density) are taken up by hepatic receptors that bind to apo E for degradation; the other particles, depleted of triglyceride relative to cholesteryl ester—are converted by the liver to cholesteryl ester-rich LDL. apo E becomes detached, leaving only one apolipoprotein, apo B-100. Each particle in this cascade from VLDL to LDL has one apo B-100.

In the metabolism of both chylomicrons and VLDL, apo C-II permits the hydrolysis of triglyceride by lipoprotein lipase, and uptake of remnants. A major difference in the metabolism of these particles is that chylomicrons contain a truncated form of apo C-II (apo C-II₃₈), whereas VLDL contains the complete form (i.e., apo C-II₁₀₀). Another difference is that chylomicron remnants are absorbed by the liver, whereas many of the VLDL remnants are most likely processed in the hepatic sinusoids to become IDL.

Regulation of Lipoprotein Metabolism

There are four major clinically significant physiologic steps in the lipoprotein cascade from VLDL to LDL—namely, VLDL secretion, LPL, remnant catabolism, and LDL catabolism [see Figure 3].^[1,2] Defects at any step in the cascade can lead to hyperlipidemia. Defects can be genetic or acquired (i.e., secondary to disease or the effects of drugs) or the result of an interaction of genetic

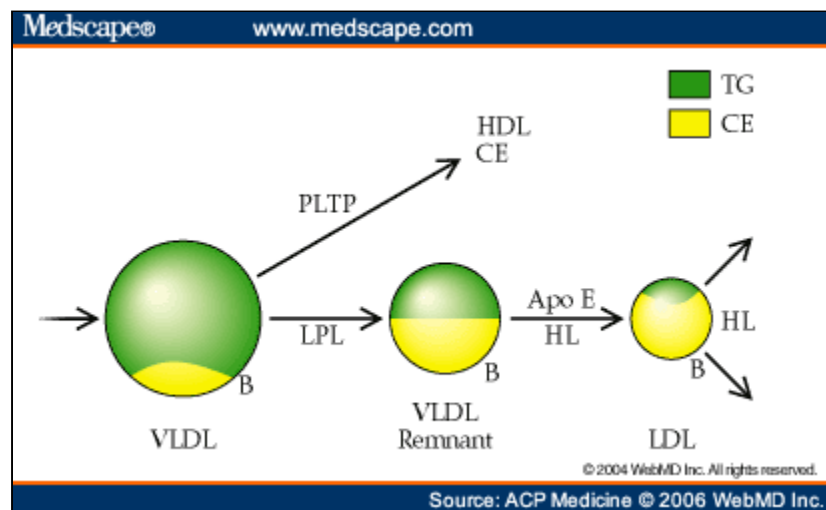


Figure 3.

The apolipoprotein B-100 (apo B-100) cascade. VLDL is secreted from the liver with one apo B on the surface and a core of cholesteryl ester in the core. Core triglyceride is hydrolyzed by lipoprotein lipase and becomes a remnant lipoprotein recognized by the liver—in part, by apo E. The remnant lipoprotein is further processed to form LDL, which has a core of cholesteryl ester and an intact apo B on its surface. The LDL particle can be removed by peripheral or hepatic LDL receptors. When LDL is hydrolyzed, the unesterified cholesterol and phospholipid are transferred to HDL by phospholipid transfer protein, leaving a cholesteryl ester of HDL. (CE—cholesteryl ester; HL—hepatic lipase; LPL—lipoprotein lipase; PLTP—phospholipid transfer protein; TG—triglyceride)

Lipoprotein Assembly

Apo B-100 is synthesized constitutively in the endoplasmic reticulum of the hepatocyte, and much of it is degraded in the liver.

Triglyceride is added to the surviving apo B that will be secreted as VLDL. It is transported to the Golgi complex, where lipid, forming the nascent VLDL particle. This particle is secreted into plasma, where it acquires apolipoproteins (e.g., HDL).^[1]

Abnormalities in VLDL secretion can occur in two genetic forms of hyperlipidemia: familial hypertriglyceridemia (FHTG) hyperlipidemia (FCHL). FHTG is characterized by the overproduction of triglyceride contained within a normal number results in each particle's having an excessive amount of triglyceride. In FCHL, an excessive amount of apo B-100 is particles; these particles tend to be smaller than normal.^[3]

The metabolic syndrome, which is a common condition in the general population, is a component of most cases of FC the residual dyslipidemia seen in patients with type 2 diabetes mellitus who have been treated with insulin or insulin s molecular basis of the hepatic triglyceride or apo B oversecretion in these disorders is unknown.

A deficiency in lipoproteins containing apo B is referred to as hypobetalipoproteinemia; an absence of apo B is termed Abetalipoproteinemia may occur because of a defect involving both apo B genes that prevents the production of apo B individuals who are homozygous for mutations in the microsomal triglyceride transport protein, which is critical for apo B endoplasmic reticulum. Homozygous hypobetalipoproteinemia and abetalipoproteinemia lead to deficiencies in fat-soluble vitamins. Hypobetalipoproteinemia, which is characterized by apo B levels of 50% normal, can be caused by a defect in a single

Lipoprotein(a). Lipoprotein(a) [Lp(a)] is a specific class of lipoprotein particles that are synthesized in the liver and are similar to that of LDL. Lp(a) differs from LDL by the presence of apolipoprotein(a) [apo(a)], a protein whose structure is similar to plasminogen.^[5] The apo(a) protein is bound by a disulfide linkage to apo B-100 to form Lp(a). High levels of Lp(a) are atherogenic.^[5] Levels of Lp(a) in plasma are almost completely determined by genetic variation in the *Lp(a)* gene.

Lipoprotein Catabolism

Lipoprotein Lipase-mediated Triglyceride Removal. LPL is synthesized in adipose tissue and muscle and then transported to the surface of the endothelial lining of the adjacent capillary, where it acts on triglyceride-rich lipoproteins. The fatty acids released from processing of triglyceride-rich particles (i.e., chylomicrons and VLDL) can be used for energy by muscle, or they can be stored in adipocytes for later use.^[6] Apo C-II, the LPL activator, is carried on the triglyceride-rich lipoproteins.

Genetic defects that result in impaired lipoprotein lipase synthesis or function are rare autosomal recessive causes of these mutations present in neonates or infants as severe hypertriglyceridemia. Heterozygote parents of these children have hypertriglyceridemia. Acquired defects of LPL, such as untreated diabetes or uremia, are more common causes of hypertriglyceridemia. An acquired defect of LPL is associated with a disorder characterized by excessive input of VLDL, marked hypertriglyceridemia, and the coexistence of two or more disorders that independently increase the level of triglycerides in plasma (e.g., FHTG or FCHL). Untreated diabetes can lead to marked hypertriglyceridemia.^[6]

Remnant Catabolism. Both chylomicron and VLDL remnants acquire apo E from HDL before they can bind to hepatic receptors and degradation or further processing to LDL. Three alleles of the *APOE* gene (i.e., *APOE*E2*, *APOE*E3*, and *APOE*E4* combinations). The *APOE*E4* allele product has the greatest affinity for hepatic receptors, followed by the *APOE*E3* allele product has markedly reduced receptor affinity.

Individuals who are homozygous for the *APOE*E2* allele (E2/E2) have marked impairment of hepatic remnant lipoprotein catabolism, resulting in the accumulation of these remnants in the plasma and in very low levels or the absence of LDL. Interestingly, individuals who are homozygous for the *APOE*E2* allele (E2/E2) have either normal or low cholesterol levels because of the paucity of LDL particles characteristic of this disorder.^[7] If an individual is homozygous for the *APOE*E2* allele (E2/E2) has a defect—either inherited or acquired—that causes excessive in-plasma accumulation of VLDL remnants and hyperlipidemia occur. This results in remnant removal disease. Because chylomicrons contain roughly equal amounts of triglyceride and cholesterol, the hyperlipidemia of remnant removal disease is characterized by hypercholesterolemia and hypertriglyceridemia.^[7]

LDL Catabolism. The final step at which a defect in lipoprotein metabolism can occur is in LDL catabolism. Apo B-100 binds to its receptor on the cell surface; LDL is then absorbed into the cell, where it is catabolized [see Figure 4]. After lipids, unesterified cholesterol is used by cells for synthesis of membranes, bile acids, and steroid hormones and for other cellular functions that prevent overaccumulation of cholesterol within the cell. The vast majority of LDL particles in plasma are taken up by the LDL receptor.

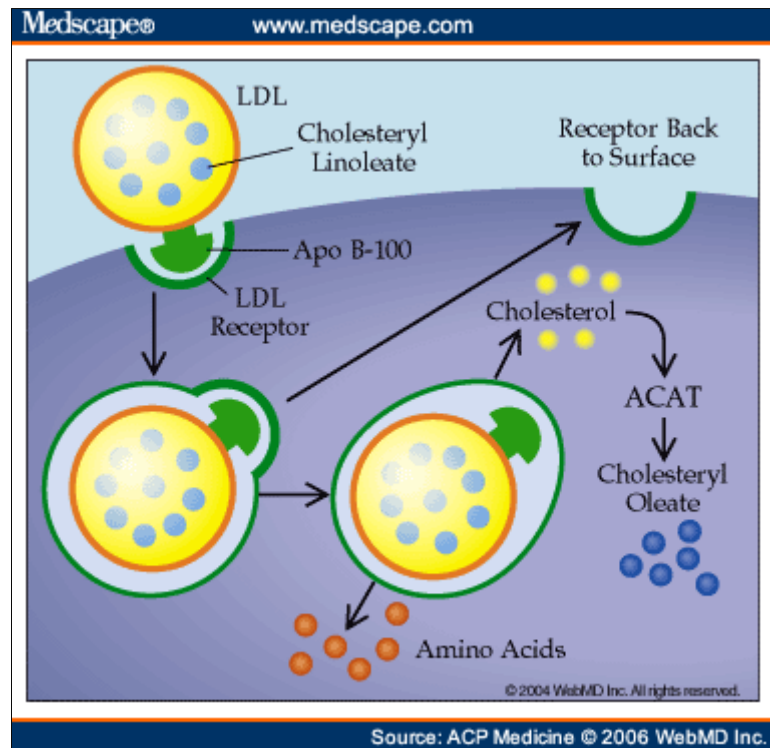


Figure 4.

LDL is absorbed by cells through the LDL receptor. This receptor recognizes apo B-100, the apolipoprotein on the lipoprotein. Once internalized, the lipoprotein is catabolized, releasing cholesterol and amino acids. The free cholesterol is esterified to cholesteryl oleate by the enzyme acyl-coenzyme A: cholesterol acyltransferase (ACAT). The LDL receptor is recycled back to the cell surface.

Mutations of the LDL receptor (as found in familial hypercholesterolemia [FH]) or, less commonly, mutations in the apo B-100 (as found in familial defective apo B-100) lead to an impairment in the interaction of LDL with its receptor; this can result in elevated plasma LDL levels. This process can also be influenced by dietary factors. For example, dietary cholesterol delivered to the liver by chylomicron remnants can saturate LDL receptors, leading to impaired LDL removal from plasma. Dietary saturated fats also may reduce LDL receptor activity and LDL production. Hypothyroidism can also be associated with defective LDL receptor-mediated cholesterol removal.^[8]

Function and Regulation of HDL

The major HDL apolipoproteins are apo A-I and apo A-II, which are formed in the liver and small intestine.^[9] Apo A-I is found on the surface of chylomicrons and VLDL. After LPL hydrolyzes triglyceride in chylomicrons and VLDL, the core lipid component of these particles becomes smaller, and redundancies of unesterified cholesterol and phospholipid occur in the surface layer. These components are transferred to HDL by phospholipid transfer protein. Nascent HDL particles also pick up excess unesterified cholesterol from peripheral tissues via the transporter ABCA1. This HDL cholesterol then undergoes esterification by lecithin-cholesterol acyltransferase (LCAT). LCAT is activated by apo A-I on the HDL surface to esterify free cholesterol, causing it to move into the core. In this process, the particle becomes the larger, more buoyant HDL₂ particle and produces HDL₃ particles.^[9,10] At some point, apo A-II may be added to the HDL₂ particle, which then is directed to deliver cholesterol to the liver via cholesteryl ester transfer protein (CETP). Hepatic lipase activity on the liver surface hydrolyzes the phospholipid and unesterified cholesterol on the HDL₃ particle, promoting the decrease in size and density to HDL₃ and then to even smaller HDL particles.^[10] Recycling of HDL particles to repeat itself [see Figure 5].

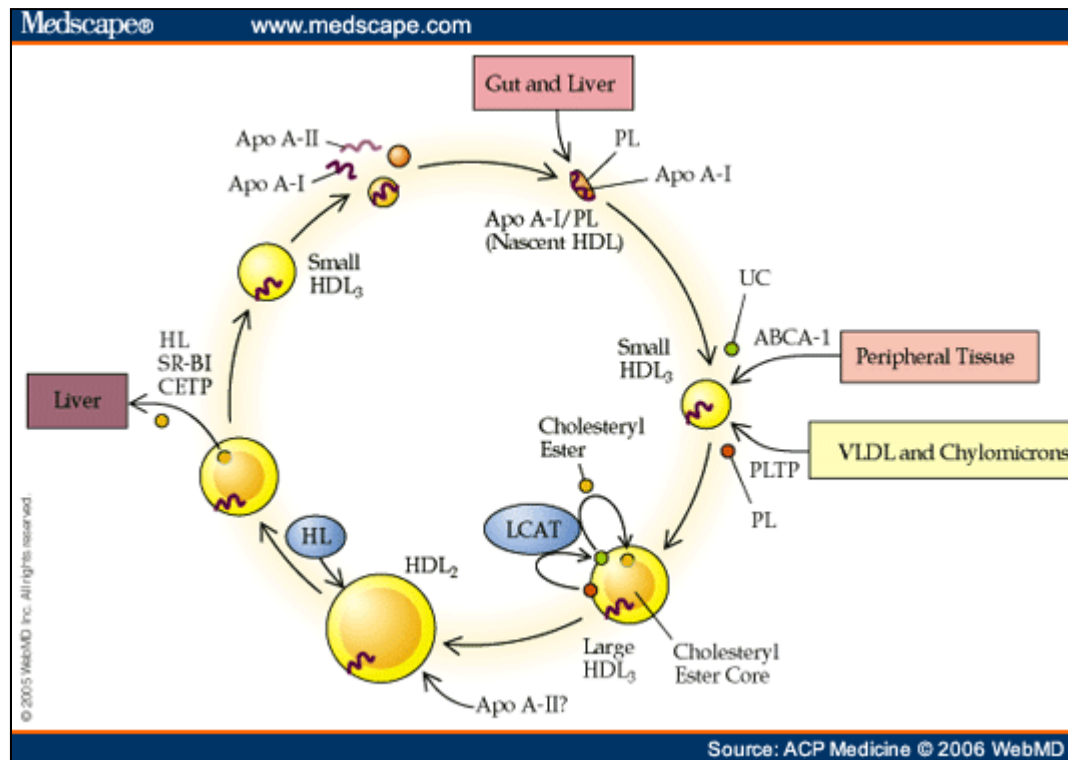


Figure 5.

The circular pathway of HDL formation and degradation.^[11] HDL begins as an apo A-1 phospholipid complex. I cholesterol and phospholipid are added to the nascent HDL via adenosine triphosphate-binding cassette trans phospholipid transfer protein to begin the formation of the smaller HDL₃ particle. LCAT transfers a fatty acid fr unesterified cholesterol to cholesteryl ester, which moves to the HDL core. In this process, the HDL particle be more buoyant HDL₃ particle and progresses to the even larger HDL₂ particle. Cholesteryl ester transfer protein transfer of cholesteryl ester from HDL₂ to the liver and various lipoproteins; with this loss of cholesteryl ester, t shrinks in size. Hepatic lipase hydrolyzes the phospholipid and triglyceride in the HDL₂ particle, promoting the density to HDL₃ and then to even smaller HDL particles, including apo A-1. Recycling of some of the apo A-I c; repeat itself. The role of apo A-II in this process in humans is not clear. (ABCA1-ATP-binding cassette transpo cholesteryl ester transfer protein; LCAT-lecithin-cholesterol acyltransferase; LPL-lipoprotein lipase; PL-phosph phospholipid transfer protein; SR-BI-scavenger receptor BI; UC-unesterified cholesterol)

Abnormally high or low levels of HDL cholesterol may be caused, rarely, by genetic defects. Elevations in the HDL ch from genetic hyperalphalipoproteinemia or CETP deficiency. Markedly reduced HDL cholesterol levels may be cause mutation; homozygosity for mutations in *ABCA1*,^[11] leading to Tangier disease; or homozygosity for mutations in the ϵ LCAT deficiency and fish-eye disease. Factors associated with an increase in HDL levels include female sex, aerobic high-fat diets, and certain drugs (e.g., alcohol, estrogens, fibrates, and nicotinic acid) [see [Table 2](#)]. Factors associate levels include male sex, central obesity, cigarette smoking, low-fat diets, hypertriglyceridemia, uremia, being heterozy and certain drugs (e.g., androgens, progestins, and some antihypertensive agents) [see [Table 2](#)]. Low HDL particle r associated with increased triglyceride levels, as seen in the metabolic syndrome.

Function of Hepatic Lipase

Hepatic lipase is synthesized in the hepatocyte, binds to endothelial surfaces in the liver sinusoids, and acts on lipopr rich VLDL particles exchange triglyceride for the cholesteryl ester in LDL and HDL, hepatic lipase can hydrolyze the p in LDL and HDL [see [Figure 6](#)]. This process leads to the formation of small, dense LDL and converts HDL₂ to HDL₃. by the presence of excessive levels of triglyceride-rich VLDL in the presence of normal hepatic lipase activity or by inc hepatic lipase. Factors such as male sex and the accumulation of intra-abdominal fat predispose to increased hepatic

associated with an increase in small, dense LDL levels and a decrease in HDL₂ levels. Increased hepatic lipase activity is associated with the dyslipidemia of the metabolic syndrome.^[10,12] Hepatic lipase also may facilitate hepatic recognition and uptake of remnant lipoproteins.

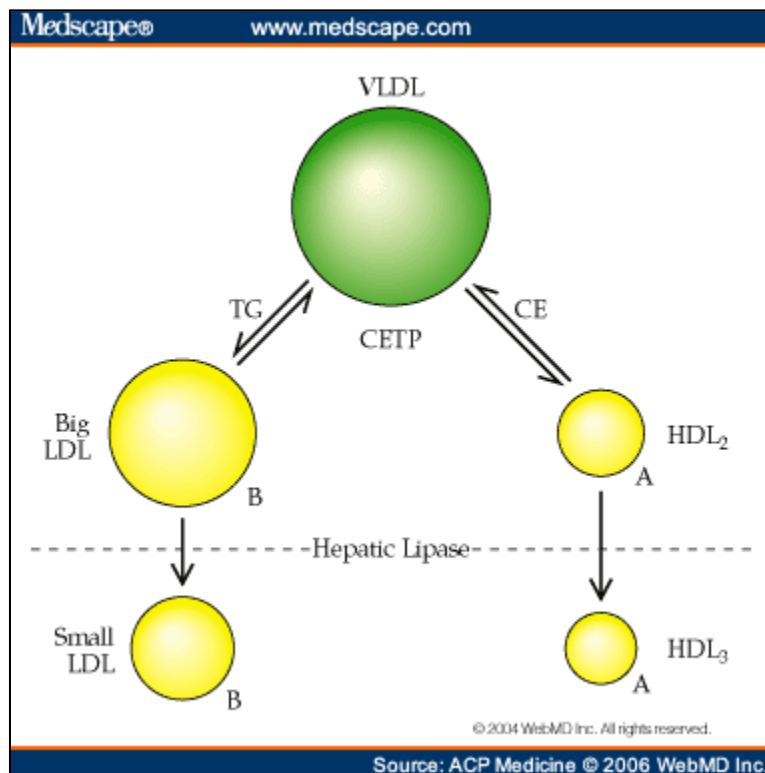


Figure 6.

Dyslipidemia in the metabolic syndrome. Triglyceride-rich VLDL exchanges triglyceride for the cholesteryl ester particles. This change in lipoprotein composition is initiated by cholesteryl ester transfer protein. Hepatic lipase removes triglyceride and phospholipid in large LDL and HDL particles, decreasing the size of each particle. (CE-cholesteryl ester; CETP-cholesteryl ester transfer protein)

Clinical Manifestations of Dyslipidemia

The main clinical consequences of hyperlipidemia are premature atherosclerosis; pancreatitis, which is usually associated with chylomicronemia syndrome; and nonalcoholic fatty liver disease. Atherosclerosis is most clearly associated with elevated cholesterol and reduced levels of HDL cholesterol. In both pancreatitis and fatty liver disease, the underlying lipid disorder

Dyslipidemia in Atherosclerosis

There is consensus that elevated plasma LDL levels and reduced HDL levels are associated with an increased risk of cardiovascular disease. Hypertriglyceridemia as a cardiovascular risk factor is more complex. Hypertriglyceridemia may be a marker for other (e.g., increased levels of small, dense LDL particles; low levels of HDL; or remnant accumulation) that are part of the metabolic syndrome. In these settings, hypertriglyceridemia is associated with premature cardiovascular risk. However, other forms of hypertriglyceridemia may not be associated with premature cardiovascular risk. (e.g., Familial Hypertriglyceridemia, *below*). The precise mechanisms whereby increased levels of LDL result in increased cardiovascular risk are unclear. Very high levels of large, buoyant LDL particles, such as occur in FH and familial defective apo B-100, as well as moderate numbers of small, dense LDL particles, are associated with an increased risk of cardiovascular disease. Accumulation of LDL suggests that LDL needs to be modified before it becomes atherogenic.^[13] Oxidation of LDL may increase its atherogenicity by changing many biologic properties that may cause it to become atherogenic. The atherogenicity of small, dense LDL particles is increased because of their ability to enter the arterial intima, where it is retained by matrix molecules and undergoes oxidation more readily than large

particles. The antiatherogenic properties of HDL are probably related to its role in reverse cholesterol transport, and its anti-inflammatory and antioxidant effects.

Dyslipidemia in the Chylomicronemia Syndrome

Pancreatitis is associated with chylomicronemia, usually with elevated levels of VLDL. The mechanism by which chylomicronemia is associated with pancreatitis is unclear. Pancreatitis is believed to be caused by the release of free fatty acids and lysolecithin from chylomicrons, exceeding their binding capacity in the capillaries of the pancreas by pancreatic lipase.

The chylomicronemia syndrome occasionally occurs when LPL is defective as a result of genetic variation in the enzyme. Much more commonly, chylomicronemia is caused by the coexistence of a genetic form of hypertriglyceridemia combined with a disorder of plasma triglyceride metabolism, the most common being untreated diabetes. Other conditions may be implicated (such as nephrotic syndrome), as may the use of drugs that raise triglyceride levels.

The chylomicronemia syndrome is associated with abdominal pain, eruptive xanthomas, and transient memory loss. Eruptive xanthomas most frequently occur on the buttocks and the extensor surfaces of the upper limb. A reversible loss of memory, particularly peripheral neuropathy, which sometimes mimics the carpal tunnel syndrome, also may occur. The retinal vessels may become occluded (lipemia retinalis). If the chylomicronemia syndrome is not corrected, it may lead to acute pancreatitis. Acute pancreatitis may be recurrent until low triglyceride levels are maintained. The risk of pancreatitis caused by severe hypertriglyceridemia may increase with triglyceride levels over 2,000 mg/dl.

Dyslipidemia in Nonalcoholic Fatty Liver Disease

Fatty liver disease seems to occur in both genetic and acquired hypertriglyceridemia. It usually is caused by the synthesis of triglycerides in amounts that are excessive relative to the amount of apo B that is synthesized; this leads to accumulation of triglycerides in the hepatic secretion of VLDL triglyceride. Fatty liver disease also may occur in heterozygous familial hypobetalipoproteinemia, a disorder characterized by decreased synthesis of hepatic apo B associated with this disorder. Alcoholic fatty liver disease also occurs with increased synthesis in the face of impaired apo B synthesis.^[14] Fatty liver disease has been associated with the metabolic syndrome, central obesity, insulin resistance, and hypertriglyceridemia.

Any severe form of hypertriglyceridemia with defective VLDL catabolism also can be associated with fatty liver and hepatic LPL deficiency—a form of hypertriglyceridemia caused entirely by an extrahepatic defect in triglyceride hydrolysis associated with fatty liver disease; in this setting, fatty liver disease regresses rapidly with restriction of dietary fat. In severe disease, progression to steatohepatitis that is associated with fibrosis and necrosis; the reasons for such a progression or a second insult is needed for these patients to develop nonalcoholic steatohepatitis and then progress to cirrhosis.

Approach to the Patient with Abnormal Lipid Levels

Patients With Isolated Elevation of LDL Cholesterol Levels

A patient's cholesterol level is said to be "above desirable" in an individual with low atherosclerotic risk if the LDL cholesterol level is above 190 mg/dl. High LDL levels are those above 190 mg/dl. The patient's triglyceride level is by definition normal,^[15] and the HDL cholesterol level is often normal. The lipid disorders in these patients are usually discovered through routine cholesterol screening. Observers question the cost-effectiveness of screening men and women older than 20 years, the high prevalence of elevated cholesterol in the United States warrants population screening, as recommended by the National Cholesterol Education Program (NCEP).

Severely elevated cholesterol levels are an indication of FH. The ability to diagnose FH is valuable because affected individuals can be treated with therapy from a relatively young age [see Familial Hypercholesterolemia, *below*].

Isolated hypercholesterolemia may be present intermittently in patients with FCHL. A family history that is strongly positive for cardiovascular disease, or the presence of any of the other criteria for FCHL, should provide clues to the diagnosis of Combined Hyperlipidemia, *below*. Not all cases of mild isolated hypercholesterolemia are indicative of FH or FCHL; such cases may be the result of interactions of acquired and environmental factors, particularly dietary factors, with unknown genetic factors that contribute to hypercholesterolemia.

Most current treatment guidelines are based primarily on LDL cholesterol levels, because reduction of LDL has been shown to reduce the risk of cardiovascular disease by as much as 50%.^[16] Reduction in the consumption of dietary saturated fat and cholesterol results in a reduction in LDL cholesterol levels; such a reduction depends in part on the baseline diet [see *CE:IV Diet and Exercise*].

including diet and weight loss, will suffice in some individuals for reducing LDL cholesterol levels to an acceptable range. Diet and weight loss is unlikely to suffice in patients with familial forms of dyslipidemia, such as FH or FCHL.

In patients with familial forms of the disease or in patients for whom lifestyle measures alone fail to bring LDL cholesterol goals, cholesterol-lowering drugs should be added to the treatment regimen [see Drug Therapy in Dyslipidemia, *below*]. In patients with familial forms of the disease, LDL cholesterol levels an additional 5% to 15% beyond reductions achieved with drugs.^[17] Diet therapy can therefore be used in addition to drug therapy. The major class of drugs used to reduce LDL cholesterol levels are statins. However, bile acid-binding resins and drugs that block cholesterol absorption are of value in patients who do not respond to statins alone, and they can be used in combination with statins and other drugs.

Patients With Isolated Elevation of Triglyceride Levels

An isolated elevation in triglyceride levels may be caused by a primary disorder of lipid metabolism (e.g., FHTG or FCHL) or by the use of therapeutic drugs; or it may be a component of the metabolic syndrome or type 2 diabetes mellitus. Until recently, it has been difficult to determine the level of triglyceride at which the risk of CAD increases or decreases. It is valuable to know the level of hypertriglyceridemia, because the therapeutic approaches may differ.

For example, it is important to distinguish FHTG, which confers no risk of premature CAD, from FCHL, which is associated with premature atherosclerosis.^[17] However, it can be difficult to distinguish these disorders when FCHL is associated with a positive personal or family history of premature atherosclerosis suggests FCHL. In addition, patients with FCHL frequently have other cardiovascular risk factors (i.e., central obesity, hypertension, insulin resistance, impaired glucose tolerance, increased plasminogen activator inhibitor-1, (PAI-1) and increased levels of circulating inflammatory markers). Hypertriglyceridemia present in the presence of increased numbers of small, dense LDL particles and confers an increased risk of premature cardiovascular disease. Hypertriglyceridemia associated with type 2 diabetes mellitus and the metabolic syndrome is an important cardiovascular risk factor. In patients with type 2 diabetes mellitus, the metabolic syndrome, or FCHL, a therapeutic strategy must consider factors beyond the lipid disorder.

Patients with FHTG do not appear to be at significantly increased risk for developing premature CAD. However, they are at increased risk for developing the chylomicronemia syndrome when secondary forms of hypertriglyceridemia are present, such as the hypertriglyceridemia caused by the use of triglyceride-raising drugs. The chylomicronemia syndrome occurs in FCHL in combination with other causes as well. In patients with pancreatitis caused by hypertriglyceridemia, triglyceride levels are above 2,000 mg/dl and care should be taken to maintain plasma triglyceride levels below 2,000 mg/dl to prevent recurrent acute pancreatitis. In patients with hypertriglyceridemia, triglyceride levels should be maintained below 2,000 mg/dl to prevent recurrent acute pancreatitis. In patients with hypertriglyceridemia, triglyceride levels should be maintained below 1,000 mg/dl.

Patients With Elevations in Cholesterol and Triglyceride Levels

Patients with elevations in the levels of both total plasma cholesterol and triglyceride fall into three categories. In the first category, there is an elevation in VLDL and in LDL, as seen in FCHL. In the second category, there is an elevation in VLDL remnants and in LDL, but normal levels of triglyceride, as seen in remnant removal disease. The third category consists of patients with very high triglyceride levels in whom the increase in total cholesterol is the result of the cholesterol in VLDL and chylomicrons.

In patients with FCHL, an increase in triglycerides and in LDL cholesterol is often seen. These patients have elevated levels of small, dense LDL particles. Therapy for these individuals often requires several drugs, one aimed at lowering the triglyceride levels and another aimed at reducing the amount of small, dense LDL particles [see Drug Therapy in Dyslipidemia, *below*].

In patients with remnant removal disease, the levels of plasma cholesterol and triglyceride are often equal. It is important to know the level of remnant removal disease in these circumstances. Therapy in this case is related to decreasing hepatic lipoprotein secretion with statins.

In patients with severe hypertriglyceridemia, the increase in total plasma cholesterol is a result of the cholesterol in VLDL and chylomicrons. Fibrates are often the drug of choice. However, it is very important to determine the etiology of the severe hypertriglyceridemia. If a offending drug [see [Table 2](#)] or treat any secondary cause for the hypertriglyceridemia.

Patients With Low HDL Cholesterol Levels

Many if not most patients with hypertriglyceridemia have a concomitant reduction in HDL cholesterol levels. Therefore, HDL cholesterol levels should be considered in the context of the management of the underlying disorder (e.g., FCHL) [see Patients with Isolated Elevation of Triglyceride Levels, *above*]. Isolated low HDL cholesterol levels of 20 to 30 mg/dl are rare, but such low levels are a risk factor for cardiovascular disease.

the past, these reductions in HDL levels were often not identified; the screening strategies that were employed were based on total cholesterol levels, and total cholesterol levels often are not elevated in patients with isolated reductions in HDL. Measurement of HDL cholesterol is required to identify these patients. The treatment of the rare patients with isolated low levels of HDL is somewhat controversial. There are no currently available drugs that effectively increase HDL cholesterol levels only.^[1] Fibrates decrease VLDL triglyceride levels, also raises HDL cholesterol levels. Many studies of fibrate therapy for atherosclerosis are inconclusive. However, the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) demonstrated a reduction in cardiovascular events.^[19] Nicotinic acid, which acts at many metabolic sites, also raises HDL cholesterol. It decreases the risk of cardiovascular events in the Coronary Drug Project of the 1970s.^[20] Few other studies have evaluated the effect of niacin on atherosclerotic event

Patients With Atherosclerosis and Normal Lipid Levels

On rare occasions, a middle-aged patient with established atherosclerosis is seen to have no detectable lipid or lipoprotein abnormalities in addition to the standard lipid profile, measurement of apo B and Lp(a) will often reveal subtle lipoprotein abnormalities, such as numbers of small, dense LDL particles in these patients. Assessment of nonlipoprotein risk factors (e.g., homocysteinemia, such as C-reactive protein [CRP]) also may be of value in assessing cardiovascular risk factors. Although the levels of these risk factors can be reduced by various strategies (e.g., homocysteine by folate therapy), the use of statins in all categories of high cholesterol, those who have established vascular disease, has been shown to be of benefit, even if lipid levels are apparently normal.

Genetic Disorders of Lipoprotein Metabolism

Primary disorders of lipoprotein metabolism are those that arise from genetic defects in the metabolic pathways of lipoprotein metabolism (disorders caused by increased hepatic secretion of lipoproteins or by catabolic defects). The disorders that cause increased lipoprotein secretion are the metabolic syndrome, familial combined hyperlipidemia, type 2 diabetes mellitus, and FHTG; elevations of Lp(a) are caused by increased lipoprotein secretion. Disorders of LDL catabolism are FH and familial defective apo B-100. Remnant removal disease is caused by defective catabolism.

Metabolic Syndrome

The metabolic syndrome consists of a central distribution of adiposity or visceral obesity; insulin resistance; elevations of blood pressure; impaired glucose tolerance; hypertension; dyslipidemia; and an abnormal procoagulant state. Many features of the syndrome predispose men and women to premature CAD.^[12]

Etiology and Risk Factors

An accumulation of visceral rather than subcutaneous fat has been observed in individuals with the central body fat distribution of the metabolic syndrome. Men have more visceral fat than premenopausal women, even when matched for body mass index. It has been suggested that these differences in visceral fat and the associated changes in lipoproteins and blood pressure could account for the difference in risk of premature CAD between men and premenopausal women.^[21,22] Increased visceral fat is associated with hyperinsulinemia, low plasma adiponectin, and elevations in plasma free fatty acid levels.^[23] It has been suggested that visceral fat precedes and causes insulin resistance and the resultant hyperinsulinemia, because insulin sensitivity increases when visceral fat is decreased after caloric restriction.^[24]

The levels of insulin, glucose, triglyceride, HDL cholesterol, blood pressure, PAI-1, and other inflammatory markers are usually elevated in patients with the metabolic syndrome. Although these variables are usually shifted to high levels, some are in the high-normal range in some affected individuals. HDL levels tend to be lower than mean normal. Genetic and environmental factors affect the distribution of these variables in both normal persons and those with the metabolic syndrome. Because the metabolic syndrome is associated with multiple cardiovascular risk factors, individuals with the metabolic syndrome are at increased risk for premature CAD. Those who meet the NCEP guidelines for the metabolic syndrome^[25] [see Diagnosis, *below*] are at increased risk for premature CAD. However, type 2 diabetes mellitus and FCHL are specific disorders of which the metabolic syndrome is a component. Type 2 diabetes and FCHL account for at least 40% to 50% of premature CAD and need to be considered in the context of the metabolic syndrome.

The risk of abdominal fat patterning, dyslipidemia, impaired glucose metabolism, and hypertension—the sentinel symptoms of the metabolic syndrome—increases with age.^[26] Central obesity associated with the metabolic syndrome may be evident in young children and adolescent growth; however, it is more typical for central obesity and insulin resistance to manifest in midlife. Whereas elevated cholesterol levels may not predict the onset of atherosclerosis in the elderly, central obesity, hypertension, and insulin resistance are predictors for atherosclerosis, and their prevalence increases with age,^[26–30] possibly because of the metabolic syndrome.

Pathophysiology

Although the association of central obesity and insulin resistance with dyslipidemia is well established, the underlying mechanism that would explain the association of central obesity and insulin resistance with dyslipidemia is an increase in free fatty acids. Such an increase would inhibit hepatic apo B from undergoing degradation in the endoplasmic reticulum, increase the likelihood of apo B undergoing hepatic secretion as triglyceride-containing lipoproteins. This would account for the increased number of VLDL and LDL particles seen in patients in insulin-resistant states.^[31] Another mechanism by which an increase in free fatty acids is to increase hepatic lipase on the surface of hepatic cells. Hepatic lipase hydrolyzes triglyceride and phospholipids, decreasing the size of each particle [see Figure 6].^[12] However, CETP also contributes to this lipoprotein remodeling. Whether hepatic lipase or CETP has the predominant effect on the size and density of LDL and HDL particles depends on the triglyceride secretion rate of VLDL. The differences in LDL particle size and HDL₂ levels between men and premenopausal women are due in part by differences in visceral fat in men and women.

Diagnosis

The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) has suggested five clinical variables for the metabolic syndrome: (1) increased waist circumference, (2) increased triglyceride level, (3) decreased HDL cholesterol, (4) increased blood pressure, and (5) elevated level of fasting plasma glucose [see Table 3].^[15] A diagnosis of the metabolic syndrome is made if more of these clinical variables are present. When these five variables were assessed in a survey of 8,814 adult men, 24% of those surveyed met the diagnostic criteria for diagnosis of the metabolic syndrome.^[32,33] The World Health Organization criteria for the metabolic syndrome. An attempt to harmonize the two sets of criteria is in progress.

Visceral obesity and insulin resistance are major contributors to the dyslipidemia associated with the metabolic syndrome. The abnormalities associated with the metabolic syndrome: increased levels of triglyceride; increased numbers of small, dense LDL particles; increased apo B levels; and decreased levels of HDL cholesterol. However, in normal, randomly selected populations, visceral obesity and insulin resistance were associated with only a slight increase in triglyceride levels and only a slight decrease in HDL cholesterol. In contrast, visceral obesity and insulin resistance can contribute to a more severe dyslipidemia, such as that associated with type 2 diabetes mellitus and FCHL.^[12]

The dyslipidemia of the metabolic syndrome can be diagnosed by demonstrating mild to moderate increases in plasma triglyceride levels, decreased levels of HDL cholesterol, and normal levels of LDL cholesterol. Although the LDL cholesterol level is normal in patients with the metabolic syndrome, the number of LDL particles is generally increased; the predominant form is small, dense LDL particles, which are cholesterol-poor LDL particles. The presence of small, dense LDL particles can be determined by direct measurement of LDL size or by measurement of plasma apo B levels in clinical practice is not necessary for the diagnosis of this disorder; however, apo B levels can indicate the presence of increased numbers of small, dense LDL particles. Similarly, total HDL cholesterol levels reflect the presence of HDL subfractions, indicating that HDL subfractions do not need to be measured.^[34]

Treatment

Aerobic exercise and a diet low in saturated fat are indicated as therapy for most people with the metabolic syndrome. If severe or FCHL or type 2 diabetes mellitus is present, more aggressive therapy is indicated [see CE:IV Diet and Exercise Therapy in Dyslipidemia, below].

Familial Combined Hyperlipidemia

FCHL is an autosomal dominant disorder that accounts for up to half of the familial causes of CAD^[35]; it was first described as a cause of myocardial infarction.^[36–38] FCHL is characterized by elevations in triglyceride or cholesterol levels, or both, in affected individuals. In affected individuals, increases in triglyceride and cholesterol levels, patients with FCHL characteristically have elevations in apo B levels and a high number of small, dense LDL particles.^[39]

Genetic linkage analysis suggests that the inheritance of the lipid phenotype in FCHL involves separate gene effects^[40] and the increased numbers of small, dense LDL particles that are present in FCHL families. Further evidence comes from studies that found that in one third of individuals with FCHL, the activity level of LPL in postheparin plasma is low. Visceral obesity and insulin resistance contribute to the dyslipidemia seen in FCHL but cannot account for the elevations in apo B levels.

In the Familial Atherosclerosis Treatment Study (FATS), intensive lipid-lowering therapy with nicotinic acid or lovastatin plus colestipol led to decreased hepatic lipase activity; decreased numbers of small, dense LDL particles; and elevated levels of HDL cholesterol. Intensive lipid lowering with subsequent regression of CAD, as evidenced by angiography.^[44] Intensive lipid lowering resulted in subsequent regression of atherosclerosis, particularly in individuals with small, dense LDL particles who had FCHL or who had elevated Lp(a) levels.

An aggressive approach to modify reversible cardiovascular risk factors should be undertaken in individuals affected and therapeutic lifestyle modification that includes physical activity should be undertaken [see *CE:IV Diet and Exercise* lowering drug therapy [see *Drug Therapy in Dyslipidemia, below*]^[18] and management of other cardiovascular risk factors depends to some extent on whether the primary lipid manifestation is hypercholesterolemia, hypertriglyceridemia, or elevations of cholesterol and triglyceride. If hypercholesterolemia is the primary manifestation, the approach should be that used for a hypercholesterolemic patient [see *Patients with Isolated Elevation of LDL Cholesterol Levels, above*]. If hypertriglyceridemia is the primary abnormality, the initial approach might be that used for patients with isolated hypertriglyceridemia. However, most patients have both triglyceride and LDL levels and will require combination therapy; regimens may combine a statin and niacin, fibrate [see *Drug Therapy in Dyslipidemia, below*].

Type 2 Diabetes Mellitus

Patients undergoing treatment of type 2 diabetes mellitus characteristically have visceral obesity and insulin resistance. Insulin secretion is present in insulin-resistant individuals who develop hyperglycemia. First-degree relatives of individuals who are centrally obese and insulin resistant or may experience decreased insulin secretion in response to glucose; first-degree relatives who are both centrally obese and who have a defect in insulin secretion invariably develop type 2 diabetes mellitus. Although the pathogenesis of central obesity, insulin resistance, and defective insulin secretion are mostly unknown, type 2 diabetes mellitus is a complex, oligogenic disorder. Determining all of the genes involved will require careful phenotypic characterization of subsets of individuals with type 2 diabetes mellitus.

The dyslipidemia of untreated diabetes mellitus and hyperglycemia is discussed later in this chapter under *Acquired Dyslipidemia That Causes Dyslipidemia, below*. The dyslipidemia of treated type 2 diabetes mellitus is similar to that of FCHL; it is characterized by a mild increase in triglyceride levels, decreased HDL₂ cholesterol levels, and increased LDL particles. Treatment entails diet therapy, increased physical activity, and lipid-lowering drug therapy [see *Drug Therapy in Dyslipidemia, below*].

Familial Hypertriglyceridemia

FHTG is a common inherited disorder, thought to be autosomal dominant, that affects about 1% of the population. FHTG is characterized by an increase in triglyceride synthesis resulting in VLDL particles enriched with triglyceride secreted in normal numbers. Affected individuals have elevated VLDL levels but low levels of LDL and HDL and are generally asymptomatic unless severe hypertriglyceridemia (i.e., >1,000 mg/dl) develops. FHTG does not appear to be associated with an increase in the risk of premature CAD.^[17]

A diagnosis is made by family history and examination of fasting lipoprotein profiles of the patient and relatives. The triglyceride level is usually 250 to 1,000 mg/dl in approximately one half of first-degree relatives; a strong family history of premature CAD usually is present. LDL levels should not be present.

Patients with FHTG should lose weight if necessary, exercise regularly, and reduce their intake of saturated fatty acid and exogenous estrogens, and other drugs that increase VLDL levels might need to be restricted. Diabetes, if present, should be treated. Hypertriglyceridemia in patients with FHTG often responds to these measures. If triglyceride levels exceed 500 mg/dl, nonpharmacologic therapy, drug therapy with a fibrate should be considered^[19]; at levels above 1,000 mg/dl, drug therapy is indicated.

Fibrates are the drugs of choice to reduce elevated triglyceride levels in patients with familial hypertriglyceridemia [see *Dyslipidemia, below*]. In familial combined hyperlipidemia, niacin can be very useful. Niacin has several additional beneficial effects on lipids—it increases HDL cholesterol levels; it reduces levels of small, dense LDL particles; and it may reduce Lp(a) levels. The dramatic effect on triglycerides that fibrates have, statins have been shown to be of value in high-risk patients with moderately increased levels of small, dense LDL particles, such as occur in patients with type 2 diabetes mellitus and FCHL.

Familial Hypercholesterolemia

FH is an autosomal dominant disorder caused by a mutation in the gene encoding the LDL receptor protein. The extreme form of FH has two mutant alleles at the LDL receptor locus, leaving the person with an absolute or nearly absolute inability to clear LDL from circulation by the LDL receptor.^[8] Heterozygotes with FH possess one normal allele, giving them approximately one-half normal activity. Because the LDL receptor contributes to VLDL remnant clearance from the plasma, a deficiency of LDL receptor activity results in accumulation of remnant lipoproteins. High concentrations of LDL result in nonreceptor-mediated uptake of LDL by the liver, including that of the arterial wall, which leads to the formation of xanthomas and atherosclerosis. The heterozygous form of FH has a prevalence of about one in 500 people, making it one of the more common genetic diseases.^[8]

Diagnosis

Hypercholesterolemia can be detected at birth in umbilical cord blood. If FH is not detected at birth, various associate the diagnosis later in life. Tendon xanthomas are a highly specific sign of FH; typically, they begin to appear by 20 years of age; present in up to 70% of older patients. Occasionally, xanthomas are seen on the patellar tendon. Because xanthomas examination of the dorsal hand tendons and Achilles tendon is required for their detection. Xanthelasma (cutaneous xanthomas) and corneal arcus are common in patients with FH after 30 years of age; however, they also occur in normocholesterolemia. Corneal arcus is seen superiorly and inferiorly in the eyes and later becomes totally circumferential.

CAD develops early, with symptoms often manifesting in men in the fourth or fifth decade. Approximately 5% of all cases in patients with heterozygous FH.^[6] Before the development of statin therapy, at least 50% of men with heterozygous FH are symptomatic by 50 years of age; in women, symptoms tend to develop about 10 years later. The total cholesterol level in heterozygous FH is from 350 to 550 mg/dl. The triglyceride level may be mildly elevated, and the HDL cholesterol level is reduced in about 50%. LDL receptor function can be measured only in special laboratories.

Heterozygous FH should be suspected when severe hypercholesterolemia from elevated LDL is detected. If tendon xanthomas are present, diagnosis is virtually certain. If tendon xanthomas are absent, secondary causes of hypercholesterolemia (e.g., hypothyroidism) should be sought, but the diagnosis of familial hypercholesterolemia is not excluded. A comprehensive family history should reveal premature CAD and hypercholesterolemia without hypertriglyceridemia; the disorder affects approximately one half of first-degree relatives. The presence of hypercholesterolemia and tendon xanthomas in a parent or sibling is virtually diagnostic, as is hypercholesterolemia in a family. Careful screening of family members is mandatory, because 50% of first-degree relatives will be affected and early treatment with lowering therapy.^[18,46]

Treatment

Management of FH requires both dietary intervention and drug therapy. The goal of therapy is to lower the LDL cholesterol to <100 mg/dl, or even lower if the patient exhibits CAD. In patients with heterozygous FH, effective treatment is possible with statins, niacin, and ezetimibe. Because LDL cholesterol levels tend to be very high, combination therapy is required, and three drugs may be necessary [see Drug Therapy in Dyslipidemia, *below*]. Although diet therapy alone is insufficient in heterozygous FH, reducing saturated fatty acid and cholesterol intake will lower LDL levels and reduce the amount of atherogenic lipoproteins. This is particularly important in children and adolescents before initiation of drug therapy. Tendon xanthomas have been reported to regress when LDL levels are maintained in a desirable range. Aggressive reduction of LDL cholesterol in men and women who have FH can cause a regression of coronary atherosclerosis.

Familial Defective Apolipoprotein B-100

A mutation in apo B-100 that inhibits its binding to the LDL receptor is another genetic cause of elevations in the LDL cholesterol. The disorder is unknown but is estimated to be 5% to 10% that of FH. LDL receptor structure and function are normal. A functional apo B-100 molecule is produced with a single amino acid substitution; this results in apo B that binds poorly to LDL receptors, leading to its clearance from the plasma.

Affected individuals are clinically indistinguishable from patients with heterozygous FH: they may present with severe tendon xanthomas, and premature atherosclerosis. Treatment with statins appears to lower LDL cholesterol levels in affected individuals. Specialized tests available only in selected research laboratories are required to distinguish affected people with defective LDL receptors.

Increased Levels of Lipoprotein(a)

Lp(a) is a specific class of lipoprotein particles synthesized in the liver.^[5] An important component of Lp(a) is apo(a), which is homologous with plasminogen, a key protein in the coagulation cascade. Plasma concentrations of Lp(a) vary markedly, ranging from undetectable to 200 mg/dl. Lp(a) plasma concentration is strongly controlled by genetic factors.

Most epidemiologic studies suggest that Lp(a) is a risk factor for CAD and stroke. If Lp(a) is atherogenic, it may be because of its properties: Lp(a) has been shown to undergo endothelial uptake and oxidative modification and to promote foam cell formation. Because Lp(a) has a high degree of homology with plasminogen, it may play a role in thrombosis by interfering with the binding of plasminogen to fibrin. Elevated Lp(a) levels appear to increase the atherogenicity of other cardiovascular risk factors, with earlier onset of CAD.

Data suggest that reducing LDL cholesterol levels in patients with high levels of Lp(a) may be an effective strategy to reduce atherosclerosis and to prevent coronary events. The Lp(a) level itself can be reduced with high-dose niacin, estrogen, or LDL apheresis. Insufficient data exist regarding the efficacy of lowering the Lp(a) level per se to inhibit atherosclerosis.

events.^[5]

Remnant Removal Disease

Remnant removal disease, also called type III hyperlipoproteinemia, dysbetalipoproteinemia, and broad-beta disease, is characterized by the presence of VLDL particles that migrate in the beta position on electrophoresis (normal VLDL particles migrate in the pre-beta I position). The beta particles are chylomicron and VLDL remnants.

Remnant removal disease is caused in part by a mutation in the *APOE* gene^[7] [see Regulation of Lipoprotein Catabolism]. This mutation leads to an impairment in the hepatic uptake of apo E-containing lipoproteins and stops the conversion of VLDL and IDL to LDL. In the presence of additional genetic, hormonal, or environmental factors, remnants do not accumulate to a degree sufficient to cause disease because they are cleared by hepatic receptors that also bind, with less avidity, to apo B-48 and apo B-100. Remnant removal disease occurs when an apo E defect (almost always the E2/E2 genotype) occurs in conjunction with a second genetic or acquired defect, such as overproduction of VLDL (such as occurs with FCHL) or a reduction in LDL receptor activity (such as occurs in heterozygous hypothyroidism). The E2/E2 genotype is found in 1% of the white population and in virtually all persons with remnant removal disease.

Diagnosis

Persons with remnant removal disease have elevations in both cholesterol and triglyceride levels and are likely to develop cardiovascular disease. For reasons that are not understood, these patients are at particularly increased risk for peripheral vascular disease. Hypertension may develop before adulthood. Palmar xanthomas (xanthoma striata palmaris)—orange-yellow discolorations of the palmar creases—are pathognomonic for genetic remnant removal disease, but they are not always present. Palmar xanthomas may be difficult to see and should be carefully sought using good lighting. Tuberoeruptive xanthomas are occasionally found at pressure sites, particularly the knees.

The diagnosis of remnant removal disease should be suspected in a person with elevated total cholesterol and triglyceride levels and IDL cholesterol levels, and reduced LDL and HDL cholesterol levels. Cholesterol and triglyceride levels range from 100 to 400 mg/dL and are roughly equal, except during an acute exacerbation, at which time hypertriglyceridemia tends to predominate. Beta migration on electrophoresis, although this test is seldom used today. Ultracentrifugation demonstrates that the ratio of VLDL cholesterol to triglyceride is greater than 0.3. Definitive diagnosis is made by detecting the E2/E2 phenotype by isoelectric focusing or by genotype by gene analysis.

Treatment

Generally, therapy for remnant removal disease is the same as that for other forms of hypertriglyceridemia. A low-fat diet and exercise can have a major effect on lipid levels. Fibrates, statins, and nicotinic acid have been used successfully in the treatment of this disease. Agents that increase triglyceride levels, such as bile acid-binding resins, must be avoided.

Rare Disorders

Severe hypertriglyceridemia can present in childhood as a result of LPL deficiency or, extremely rarely, as apo C-II deficiency. Patients at risk for acute pancreatitis with severe hypertriglyceridemia and must be treated with moderate to severe dietary-fat restriction. If triglyceride levels are below 1,000 to 2,000 mg/dL, treatment is not necessary.

Homozygous FH is extremely rare and leads to severe hypercholesterolemia, atherosclerosis, and death, often in the second decade of life. Patients with homozygous FH may benefit from LDL apheresis. At the other extreme, the absence of apo B-containing lipoproteins, from defects in the synthesis of apo B (e.g., homozygous hypobetalipoproteinemia) or from defects in the transport of apo B from the endoplasmic reticulum. Individuals with very low apo B levels are not at risk for atherosclerosis.

The absence of HDL can occur in persons with homozygosity for defects in the cholesterol and phospholipid transporters. A heterozygous state is an uncommon cause of isolated low-HDL cholesterol¹¹ (i.e., hypoalphalipoproteinemia).

Miscellaneous Common Dyslipidemias

Polygenic hypercholesterolemia was once thought to be common. Polygenic hypercholesterolemia is a term used to describe mild elevations in LDL cholesterol in the apparent absence of a familial form of dyslipidemia or of dyslipidemia of secondary origin. The prevalence of polygenic hypercholesterolemia continues to shrink as LDL variants such as Lp(a) and small, dense LDL particles are discovered.

Mild to moderate hypertriglyceridemia may occur in the presence of modest defects in LPL. Typically, it presents as a conjunction with a decrease in HDL cholesterol levels. It is seen in the obligate heterozygote parents of children with I may predispose to premature CAD.

Secondary Disorders of Lipoprotein Metabolism

Secondary dyslipoproteinemias are caused by acquired defects in lipoprotein metabolism that result in hypercholesterolemia, hypertriglyceridemia, or combined hyperlipidemia; the HDL level may or may not be low. Secondary hypertriglyceridemia, a common genetic form of hypertriglyceridemia may be severe enough to cause chylomicronemia with pancreatitis. It may be caused by selected medications.

Endocrine Disorders That Cause Dyslipidemia

Untreated Hyperglycemia

Untreated hyperglycemia in patients with diabetes mellitus causes an increase in VLDL synthesis, a reduction in VLDL clearance, and an accompanying reduction in LPL activity, or both. These abnormalities result in hypertriglyceridemia and a reduction in HDL level usually is normal. Fasting chylomicronemia occurs when there is a coexisting primary form of hypertriglyceridemia that competes to interact with LPL, and both lipoproteins may accumulate. A low HDL level results from impaired lipolysis of lipoproteins, which supply lipid components for HDL development. These defects occur in both untreated type 1 and type 2 diabetes mellitus. Lipid levels should approach normal with comprehensive treatment of diabetes; if they fail to do so, additional treatment is indicated [see Genetic Disorders of Lipoprotein Metabolism, *above*]. In diabetic patients with persistent moderate to severe hypertriglyceridemia, niacin is suitable because it reduces the secretion of VLDL and enhances the activity of LPL. Nicotinic acid may be used in patients with type 2 diabetes mellitus, because it may exacerbate hyperglycemia.^[47] Statins are effective in reducing hypertriglyceridemia in diabetic patients.^[45]

Hypothyroidism

Hypothyroidism may cause a severe elevation of LDL levels because of reduced LDL receptor activity; in addition, it may cause hypertriglyceridemia and an associated reduction in the HDL level as a result of reduced LPL activity. Remnants of chylomicrons also accumulate and unmask remnant removal disease. The dyslipoproteinemia that occurs with hypothyroidism is corrected by thyroid hormone replacement.

Dyslipidemia Secondary to Estrogen and Progestin Therapy

Oral contraceptives that contain a combination of estrogen and progestin can have variable effects on lipoproteins, depending on the combination used. Estrogen tends to raise VLDL and HDL levels and lower LDL levels. Progestins tend to lower VLDL and HDL levels, but the effect varies considerably. Postmenopausal estrogen replacement therapy lowers LDL levels and raises HDL levels, but the addition of progesterone to protect the uterus lessens these effects but does not eliminate them.^[48] Estrogen may increase triglyceride levels in women who have an underlying primary triglyceride disorder, leading to pancreatitis; therefore, triglyceride levels should be monitored in these patients.^[6] Oral combination therapy with estrogen and progesterone was associated with a mild increase in breast cancer risk in the Women's Health Initiative Study. In this randomized study of 16,608 women, use of oral hormone replacement therapy was associated with an excess rate of breast cancer. In women who have undergone hysterectomies, estrogen therapy has been shown to be associated with an increase in breast cancer risk [see Managing Dyslipidemia in Women, *below*].^[49] These studies have led to a decrease in the use of postmenopausal hormone therapy.

Renal Disorders That Cause Dyslipidemia

Nephrotic Syndrome

The nephrotic syndrome causes enhanced hepatic secretion of apo B-100-containing lipoproteins (i.e., VLDL) in response to increased levels of and other proteins in the urine. Hepatic synthesis of cholesterol is also increased. The LDL level is typically elevated, and the VLDL level elevation may be associated with a reduction in the HDL level as lipolysis becomes impaired. Patients with the nephrotic syndrome are at increased risk for CAD, and the lipid disorder should be treated aggressively. Dietary changes and exercise may improve lipoprotein levels, but pharmacologic therapy is necessary to achieve desirable lipoprotein levels. Niacin is effective in the treatment of this disorder because it inhibits hepatic secretion of apo B-100-containing lipoproteins; however, it has not been studied extensively for this use. The statins are useful in lowering LDL cholesterol levels in patients with the nephrotic syndrome. Drug therapy with statins, nicotinic acid, fibrates, or ezetimibe may be necessary for the reduction of LDL cholesterol levels.

Drug Therapy in Dyslipidemia, *below*]. Studies are needed to evaluate the effects of various drug combinations on ca

Chronic Renal Failure

Chronic renal failure produces hypertriglyceridemia as a result of a decrease in LPL and hepatic triglyceride lipase.^[50] range from 150 to 750 mg/dl, and the HDL level is usually low; the risk of CAD is increased. Dietary measures should treatment is being considered. Gemfibrozil, a drug that enhances LPL activity, has been shown to be effective in low patients with renal insufficiency.^[51] Gemfibrozil is preferred over other fibrates (e.g., fenofibrate and clofibrate) in this ; is partly cleared by the liver; as such, it carries a lower risk of drug-induced myopathy than do fibrates that are cleared. Nonetheless, because gemfibrozil is partially excreted renally, the drug should be administered in the lowest effective statins have been less well studied in this condition. Combination therapy with nicotinic acid, statins, or gemfibrozil may therapeutic goal.

Gastrointestinal Disorders That Cause Dyslipidemia

Primary biliary cirrhosis is the most significant gastrointestinal cause of dyslipidemia. In the early stages of primary bil hepatocellular function remains, mild elevations of VLDL and LDL levels occur because of elevations in the levels of r HDL. Terminal liver disease with cirrhosis results in severe elevation in cholesterol levels because of increased produ abnormal lipoprotein particle containing albumin and other plasma components that is rich in free cholesterol and pho terminal disorder requires liver transplantation.

Other Causes of Secondary Dyslipidemia

Many commonly used drugs have adverse effects on lipoproteins [see [Table 2](#)]. Discontinuance of the drug often will increase in VLDL, LDL, and HDL cholesterol levels can result from the use of drugs for the prevention of rejection afte Pravastatin is the drug of choice for lowering LDL levels because of its unique catabolic pathways. Immunosuppressiv cyclosporine compete with atorvastatin and simvastatin for the cytochrome P-450 3A4 system. The use of antifungal ; with the metabolism of these statins. The predominant dyslipidemia that is seen in patients with AIDS is similar to the patients with the metabolic syndrome; mild hypertriglyceridemia is common, and low HDL cholesterol is seen in some extreme hypertriglyceridemia can result from the use of HIV drugs, and the resultant hypertriglyceridemia may be ass The etiology of dyslipidemia in AIDS is complex: excessive free fatty acid mobilization is seen, along with the develop insulin resistance. In addition, AIDS patients typically use dyslipidemia-causing drugs. The specific therapy in each pa individualized.

Prevention and Treatment of Coronary Artery Disease

Primary Prevention

The treatment of lipid disorders in individuals who do not have clinical evidence of CAD is considered primary prevent based on the assumption that modification of lipid risk factors will alter the natural history of the untreated condition—; hypothesis. An association between cholesterol and CAD has been known since the early 1950s; however, it was not Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) in 1984 that there were data to support the lipi

The LRC-CPPT enrolled almost 4,000 men with moderate hypercholesterolemia; patients were followed for 7 years. 1 prescribed cholestyramine, which resulted in LDL cholesterol levels being 12.6% lower than those of the control subje placebo. The cholestyramine group had a 19% reduction in CAD deaths and nonfatal myocardial infarcts ($P < 0.05$), a mortality was observed.^[53] Further analysis demonstrated that the extent of benefit depended upon the achieved redu (reflecting drug compliance). Use of a proportional hazards model indicated that a 25% decrease in total cholesterol c cholesterol would be expected to decrease the risk of a CAD event by 50%.^[54]

The Helsinki Heart Study used the fibrate gemfibrozil to treat dyslipidemic men without CAD. After 6 years of follow-up events was seen in the treatment group, compared with the group receiving placebo.^[55] Again, no decrease in CAD n

In both the Helsinki Heart Study and the LRC-CPPT, the sample size was calculated on the power to detect CAD eve alone. As such, the lack of an effect on mortality was not surprising, but an increase (not statistically significant) in noi treatment groups of both these studies was troublesome^[53–55] and confounded the recommendations for primary prev hypercholesterolemic patients. These concerns were not completely addressed until 1995, when results of the West c Prevention Study (WOSCOPS) were published.^[56]

The WOSCOPS trial evaluated the effect of 5 years of treatment with pravastatin on the incidence of nonfatal myocardial deaths in 6,595 men. The men were middle-aged (45 to 64 years of age) and moderately hypercholesterolemic (LDL 190 mg/dl). The treatment group manifested a 20% reduction in total cholesterol, a 26% reduction in LDL cholesterol, a 12% increase in HDL cholesterol, as compared with the control group. On the basis of intention-to-treat principle associated with a 31% risk reduction in nonfatal MI or CAD deaths ($P < 0.001$), a 32% risk reduction in all cardiovascular mortality, and a 22% risk reduction in total mortality ($P = 0.051$). In addition, coronary interventions (i.e., angiography, angioplasty, aortocoronary surgery) were reduced 31% to 37% ($P < 0.01$).

The reduction in clinical events began within 6 months of randomization and were independent of other risk factors, such as blood pressure, family history of CAD, and the ratio of total cholesterol to HDL cholesterol.^[57] Although there was no decrease in LDL cholesterol, a decrease in LDL cholesterol of approximately 24% was adequate to see the full benefit. The treatment effect was proportionately the same regardless of baseline lipid levels and the reduction in LDL cholesterol alone did not account for all the benefits of treatment with pravastatin.^[58] Importantly, there was no increase in noncardiovascular mortality reported in earlier primary preventive trials.

The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) was the first large primary intervention trial to evaluate the effects of cholesterol lowering in individuals with average cholesterol levels.^[59] That is, the mean total and LDL cholesterol levels were close to the average value for the general population (221 mg/dl and 150 mg/dl, respectively). In addition, it was the first large study to evaluate the effects of treatment in a total of 6,605 patients. Lovastatin was the treatment agent in this randomized, placebo-controlled trial. LDL cholesterol follow-up was 5 years. The total absolute benefit was 2%, meaning that 50 patients had to be treated for 5 years to prevent one cardiovascular event. The treatment group had a 28% reduction in cardiovascular hospitalizations, a 23% decrease in angioplasty, and a 32% reduction in coronary surgery. An analysis of the cost-effectiveness of lovastatin treatment demonstrated a 27% (or \$524 per patient) reduction in care costs for the lovastatin group, as compared with the group that received placebo.^[60]

Persons with average cholesterol levels were also evaluated in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Intervention (LLA).^[61] Nearly 20,000 hypertensive patients were randomized to one of two antihypertensive regimens. The lipid-lowering intervention randomized 10,305 patients with total cholesterol levels of 251 mg/dl or lower to treatment with atorvastatin or placebo. A significant benefit was observed in the treatment group. Median follow-up was 3.3 years. The study demonstrated statistically significant reductions in cardiovascular or all-cause mortality; however, significant reductions were seen in cardiovascular events and procedures, and stroke.^[61]

The effect of atorvastatin (10 mg/day) on primary prevention of cardiovascular disease in diabetic patients was examined in the Atorvastatin Diabetes Study (CARDS).^[45] CARDS randomized almost 3,000 diabetic patients with LDL levels of 160 mg/dl or higher, and at least one of the following: retinopathy, albuminuria, smoking habit, or hypertension. The atorvastatin group demonstrated a 36% reduction in cardiovascular mortality, a 36% reduction in coronary revascularization procedures, a 48% decrease in stroke, and a 27% reduction in all-cause death compared with the placebo group.

These studies support lipid-lowering therapy as primary prevention for patients with high LDL and average LDL values. They also support lipid-lowering therapy on primary prevention in patients with other lipid abnormalities, such as isolated low HDL cholesterol levels or elevated triglyceride levels.

Secondary Prevention

Lipid-lowering therapy in patients with documented CAD is considered secondary prevention. Lipid levels have a significant impact on death rates in those with and without CAD; however, the impact is significantly greater in patients with established CAD.

Several trials have investigated the effect of aggressive lifestyle intervention in patients with CAD. The Saint Thomas Study (STARS) randomized men with CAD and total cholesterol levels above 232 mg/dl to conventional care or a low-fat diet. Despite relatively modest changes in lipid levels (the intervention group had an LDL cholesterol average of 162 mg/dl compared with 190 mg/dl in the control group), the rate of regression increased in the intervention group. Angina symptoms also improved.^[63]

The effects of a Mediterranean diet (increased α -linoleic acid) were compared with those of a prudent Western diet in the Lyon Diet Heart Study.^[64] All study participants had had a first MI. Those consuming the Mediterranean diet had lower rates of primary (death or unstable angina, stroke, heart failure) end points than those on the prudent Western diet at 27 months. This effect persisted through 5 years of follow-up. The group on the Mediterranean diet had a rate of combined primary and secondary end points of 2.59 events per 100 patients per year, compared with 9.03 events per 100 patients per year in the group on the prudent diet.^[65]

A variety of pharmacologic agents have been used alone and in combination in secondary prevention trials. Some trials

end points in assessing progression or regression of CAD, whereas others have used clinical end points. The Familia Study (FATS) examined the effect of several lipid-reducing regimens in men with elevated apo B levels. The two most (nicotinic acid-colestipol and lovastatin-colestipol) were equally effective; both regimens were associated with delayed 25%, respectively, versus 46% in the placebo-colestipol group) and an increased likelihood of regression of coronary 39%, respectively, versus 11% in the placebo-colestipol group). Clinical end points (death, MI, worsening angina, and also reduced in the more aggressively treated groups (4.2% and 6.5%, respectively, versus 19% in the placebo-coles first major study to document the regression of CAD with aggressive lipid-lowering therapy. A subsequent analysis of the change in CAD severity with therapy-induced changes in LDL buoyancy and hepatic lipase activity.^[66]

The Scandinavian Simvastatin Survival Study (4S) evaluated 4,444 patients with known CAD and moderate to severe baseline (total cholesterol concentration ranging from 212 to 309 mg/dl).^[67] Patients were randomized to a regimen of plus placebo. At 5.4 years, there was a significant reduction in total mortality (8% on simvastatin versus 12% on place (19% versus 28%), CAD deaths (42% reduction), and cerebrovascular events (2.7% versus 4.3%). The reduction in c correlated with total cholesterol and LDL cholesterol levels and with changes from baseline.^[68]

The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial randomized approximately 9,000 men of recent MI or unstable angina to receive either placebo or pravastatin.^[69] The study was stopped prematurely at 60 significant benefit associated with pravastatin therapy. CAD death was reduced in the treatment arm of the study (6.4 total mortality (11% versus 14%), stroke (20% relative decrease), need for bypass surgery (8.9% versus 11.3%), and The benefit was primarily related to changes in lipid levels and was seen in all predefined subgroups. The greatest re was seen in those patients thought to be at highest risk, as assessed by concomitant risk factors.^[70]

The Cholesterol and Recurrent Events (CARE) trial evaluated 4,159 patients with relatively low lipid levels. The average was 209 mg/dl, and the average LDL cholesterol level was 139 mg/dl. Treatment with pravastatin over 5 years resulted coronary death or nonfatal myocardial infarction (10.2% versus 13.2% for placebo), need for revascularization (14.1% frequency of stroke (2.6% versus 3.8%).^[71] However, in contrast to the results seen with 4S and LIPID, the absolute c LDL had little relationship to coronary events.^[72] The benefits were seen only in patients with LDL levels above 125 m

The Heart Protection Study enrolled over 20,000 persons with a history of cardiovascular disease (coronary, cerebrovascular disease), diabetes, or treated hypertension.^[73] As such, it was a mixture of primary and secondary interventional individuals had baseline LDL cholesterol levels below 116 mg/dl, and 25% had initial LDL levels ranging from 116 to 1 randomized to receive simvastatin or placebo. After an average follow-up of 5.5 years, the lipid-lowering group showed cardiovascular events, an 18% reduction in cardiovascular deaths, and a 13% reduction in all-cause mortality, as compared group. The percentage reductions in events were similar in all three tertiles of baseline LDL cholesterol levels and in patients levels below 100 mg/dl at baseline. These results differ from those reported in the CARE study, but they are consistent and LIPID trials. The results of the Heart Protection Study also suggest that there may not be a threshold beyond which therapy ceases to improve outcome, at least in patients at high risk for recurrent coronary events.

Aggressive LDL-lowering therapy appears to be more effective than standard lipid-lowering treatment. The Pravastatin and Infection Therapy (PROVE-IT) trial compared standard LDL-lowering treatment (pravastatin, 40 mg daily) with intensive treatment (atorvastatin, 80 mg daily) in more than 4,000 patients recently hospitalized with an acute coronary syndrome up was 24 months. The median LDL cholesterol level achieved with atorvastatin was 62 mg/dl, compared with 96 mg/dl pravastatin. The primary composite end point was death from any cause, MI, unstable angina not requiring hospitalization, revascularization, and stroke. The rate of reaching the primary end point was 22.4% in the atorvastatin group and 26. The benefit of aggressive therapy with atorvastatin was apparent as early as 30 days after initiating therapy and was

The Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial also compared moderate LDL-lowering (40 mg daily) with more intensive LDL-lowering therapy (atorvastatin, 80 mg daily).^[75] The study used coronary intravascular sensitive means of measuring plaque volume, as a baseline measurement and primary end point. The median percent volume was -0.4% in the atorvastatin group, compared with +2.7% in the pravastatin group. This finding correlated with levels of 79 mg/dl in the atorvastatin group and 110 mg/dl in the pravastatin group. These results gave further support that LDL-lowering therapy is superior to standard LDL-lowering therapy.

Few studies have examined the benefit of raising HDL cholesterol levels in the secondary prevention of CAD. The VA patients with known CAD and with LDL cholesterol levels below 140 mg/dl, HDL cholesterol levels of 40 mg/dl or above 300 mg/dl or below.^[19] The patients were randomized to receive gemfibrozil or placebo. The subsequent mean HDL cholesterol in the gemfibrozil group was 6% higher than that in the placebo group, and the mean triglyceride level in the gemfibrozil group mean LDL cholesterol levels were 113 mg/dl in both groups. The combined primary end point of cardiac death and nonfatal was 17% in the gemfibrozil group and 22% in the placebo group (relative risk reduction, 22%). The beneficial effect of

apparent until 2 years after randomization.

Combination therapy using a statin to lower LDL cholesterol levels and niacin to raise HDL cholesterol levels has been increased cardioprotection. In one study, patients were randomized to one of four groups: simvastatin plus niacin, vitamin E plus antioxidants, or placebos. At entry, the HDL cholesterol level was below 35 mg/dl, and the LDL cholesterol level was above 190 mg/dl. Mean LDL and HDL cholesterol levels were unaltered in the antioxidant and placebo groups but were changed significantly in the niacin groups (mean LDL cholesterol level reduced by 42% and mean HDL cholesterol level raised by 26%). At 3 years, clinical events in the simvastatin and niacin groups was greater than that which is usually reported in studies of statins (0.4 compared with placebo), suggesting that a benefit may be associated with the elevation of HDL cholesterol levels. However, there was no additional benefit and may even have attenuated the benefits of combination therapy.^[76]

Risk Stratification

CAD risk factors seldom occur in isolation, and the risk associated with each varies widely in combination with other risk factors. This risk prompted the NCEP ATP III to standardize guidelines for risk assessment of CAD. Over time, the guidelines were made more aggressive lipid-lowering targets as a means of reducing CAD risk. This evolution in guidelines is the result of our understanding that extend our understanding of dyslipidemia, associated risk factors and their relationship to CAD, and the utility of treatment.

The ATP III guidelines focus primarily on LDL cholesterol levels as the major lipid risk factor. More recently, low HDL cholesterol level and the metabolic syndrome were added to risk assessment. In ATP III, the metabolic syndrome was added as a risk factor in an attempt to assess risk for CAD in patients who have modest elevations in triglyceride levels, low HDL cholesterol levels, and small, dense LDL particles, as well as FCHL. In an effort to better identify those at highest risk for CAD events, the NCEP recognizes several CAD equivalents: diabetes mellitus, peripheral arterial disease, abdominal aortic aneurysm, symptomatic carotid artery disease, and myocardial infarction. The presence of these CAD equivalents requires a level of therapeutic aggressiveness recommended for patients with established CAD.^[15]

The American College of Physicians (ACP) has adopted a somewhat less aggressive recommendation for treatment of patients with type 2 diabetes mellitus. The ACP reserves the use of statins for patients with type 2 diabetes and other CAD risk factors.^[77] The ACP does not differentiate between the risk of CAD in patients with type 1 diabetes and that in patients with type 2 diabetes. An aggressive approach to the CAD risk is greater in type 2 diabetes and that treatment guidelines should differentiate between these entities.

The ATP III guidelines use the Framingham scoring system for estimating the 10-year risk of CAD. Some studies indicate that the Framingham score overestimates risk in Japanese-American and Hispanic men, Native-American women, and some European men. It also has been suggested that the Framingham score weights age too heavily as a risk factor. The Pravastatin in Elderly Subjects Study (PROSPER) study, which is the only prospective study to assess statin therapy in men and women aged 70 years and older, demonstrated that statin therapy was of no benefit in those without preexisting atherosclerosis.^[81] Any age bias present in the Framingham scoring system is eliminated when the system is used to predict risk in nonelderly patients.

A multicenter, international study confirmed the validity of risk stratification. In this study of over 15,000 patients with a 10-year risk of CAD, over 90% of the population-attributable risk could be accounted for by nine potentially modifiable risk factors.^[82] Most important were an elevated apo B to apo A1 ratio, smoking, hypertension, and diabetes. These risk factors were more important in women than in men. As such, principles of cardiovascular disease prevention are similar worldwide and have the potential to reduce the burden of CAD.

Drug Therapy in Dyslipidemia

Drugs Used to Lower LDL Cholesterol Levels

Several classes of drugs lead to a reduction in LDL cholesterol levels [see [Table 4](#)].^[16] Before the introduction of statins, the major drugs used for this purpose were the bile-acid sequestrants and niacin. The introduction of statins, with their powerful cholesterol-lowering effects, their tolerability, and their relative lack of toxicity, provided a significant advance in the management of patients with hypercholesterolemia. The introduction of intestinally active drugs has provided additional approaches both for monotherapy and for combination therapy in individuals who are unable to tolerate statins—and, more particularly, for combination therapy.

Statins. Several statins are now available, and new ones continue to be introduced. To date, statins have been highly effective in reducing clinical events, including stroke. Although some of the benefits of statins have been attributed to the so-called pleiotropic effects of the class of drugs, the extent of reduction in LDL cholesterol levels nonetheless appears to be the major determinant of risk reduction.

Intestinally Active Compounds. Bile-acid sequestrants were among the earliest drugs to become available for the treatment of hypercholesterolemia.

hypercholesterolemia, and they were the first class of drugs to demonstrate that the reduction of LDL cholesterol was risk of CAD; however, their use was limited by their very poor tolerability and their modest effect in reducing LDL cholesterol levels tend to increase with their use in patients with high baseline plasma triglyceride levels. The introduction of bile acid sequestrants, colestyramine, resulted in improved compliance with this class of drugs, especially when used in combination with very high LDL cholesterol levels (e.g., for patients with FH).

Unlike bile-acid sequestrants, the intestinally active drug ezetimibe directly inhibits cholesterol absorption. Although it appears ezetimibe is able to reduce LDL cholesterol by approximately 20%, whether used as monotherapy or in combination with other lipid-lowering agents.^[83] In addition, ezetimibe does not cause an increase in plasma triglyceride levels, as occurs with bile acid sequestrants. Ezetimibe has not yet been reported in clinical trials with cardiovascular end points.

Drugs Used Primarily to Lower Triglyceride Levels

The preferred drugs for treatment of hypertriglyceridemia are the fibrates and niacin. Niacin is the best drug currently available for reducing triglyceride levels. It also produces modest reductions in LDL and reduces apo B levels, but because it worsens insulin resistance, its use in patients with type 2 diabetes mellitus is limited. Fibrates are the drugs of choice for patients with marked hypertriglyceridemia. The primary goal of therapy is the prevention of pancreatitis and other features of the chylomicronemia syndrome. They are also useful in hypertriglyceridemic states (e.g., the familial forms of hypertriglyceridemia and in some patients with diabetic dyslipidemia) in which triglyceride levels are more than mildly elevated. Fibrates also have a modestly beneficial effect on HDL cholesterol levels. Niacin is useful in combination therapy, primarily with statins.

Omega-3 fatty acids (e.g., those found in marine oils) have been used for the treatment of hypertriglyceridemia, especially in patients in whom other therapies have failed to reduce markedly elevated levels of triglycerides.

Combination Therapy

Combinations of drugs often need to be used when both LDL cholesterol and triglyceride levels are elevated. Combination monotherapy, especially with statins, fails in achieving target lipid and lipoprotein levels, especially LDL cholesterol. Combination therapies include statins and fibrates—although little is known of their additive benefit in reducing clinical events—statins and bile-acid sequestrants also are a useful combination, and the use of the new cholesterol absorption inhibitors, particularly statins, is likely to be of value. In some cases, triple therapy (e.g., statins, niacin, and an intestinally active bile acid sequestrant) may be necessary.

Special Issues in the Management of Dyslipidemia

Screening for Hypercholesterolemia in Children

Numerous autopsy studies demonstrate that coronary atherosclerosis begins in childhood and adolescence and that it is consistently associated with the extent of such atherosclerosis. Children in families with FH and early CAD have high childhood cholesterol levels and are significant predictors of adult levels. However, a significant proportion of children and adolescents with mildly elevated cholesterol levels will not as adults develop cholesterol levels high enough to warrant intervention; screening for elevated cholesterol would risk labeling many young people as diseased. All children older than 2 years would benefit from a goal of reducing total cholesterol to less than 170 mg/dL; this goal should be a part of any population strategy for controlling epidemic atherosclerosis. However, the safety and efficacy of drug therapy have not been established in this age group, and treatment must be approached cautiously.

Considering these and other issues, the recommendations of the NCEP's Expert Panel on Blood Cholesterol Levels in Children seem appropriate.^[84] Physicians should advise patients younger than 55 years who have a known CAD or a lipid disorder and their grandchildren should undergo regular cholesterol testing, and patients with a genetically well-defined lipid disorder should undergo genetic counseling. Physicians who care for patients younger than 20 years who have markedly elevated LDL cholesterol levels should consider interventions before considering medications. If such measures are ineffective, resins should be used, and referral to a lipid specialist should be considered.

Treatment of young adults with elevated cholesterol levels is controversial. The strategy of matching the intensity of intervention to the risk of atherosclerosis has been proposed, but for young adults, a short-term (e.g., 10-year) risk assessment may be difficult. The potential benefit of cholesterol lowering is unclear. It is incorrect to argue that all treatment can be safely deferred to later life to prevent an atherosclerotic event. Population-level prevention and lifestyle interventions should still be favored for young adults. Advances in technology that better enable the identification of asymptomatic patients (of any age) who should take steps to reduce their risk of atherosclerosis may make it possible to reliably identify or quantify vulnerable plaques; markers of inflammation; or new markers of endothelial dysfunction.

Managing Dyslipidemia in Women

Before menopause, women have a lower incidence of CAD than men of the same age. Although rare, CAD does occur in women, usually in association with multiple genetic and environmental risk factors, such as in patients with familial hypercholesterolemia or in diabetic patients who smoke cigarettes.

After menopause, some women develop the metabolic syndrome, characterized by visceral obesity, insulin resistance, and dyslipidemia.^[21] There is some evidence that estrogen replacement therapy can reverse these findings. However, the Women's Health Initiative Study demonstrated that combined oral estrogen and progesterone did not protect women from CAD and that in fact the estrogen-alone component of the Women's Health Initiative Study indicated that estrogen therapy carried a modest increase in CAD death; the study was halted prematurely because of increased risk of stroke.^[49]

Managing Dyslipidemia in Older Patients

Age is the most significant risk factor for the development of atherosclerosis. CAD is currently a major cause of disability in older populations; however, the relative risk associated with any single coronary risk factor decreases with age because of noncardiovascular mortality that affect an aging population. One implication of the complex relationships between risk factors in the pathogenesis of coronary-related events in the elderly is represented by the multiple effects of treatment such as the decrease in LDL cholesterol levels and inflammation markers yielded by statins. A growing body of evidence indicates that statin therapy is effective in the elderly; lipid-lowering therapy is probably indicated in this population in patients with atherosclerosis or who have preexisting atherosclerosis.^[73,81] Primary intervention with drug therapy in persons without atherosclerosis is controversial. In the PROSPER trial of persons older than 70 years, no benefit was seen with statin therapy in those with preexisting clinical atherosclerosis. Indeed, there was a suggestion of increased gastrointestinal cancer with statin therapy in these patients.^[81] Attention to other concomitant diseases and the nutritional state, as well as to capabilities of the elderly, are important in the management of older patients with dyslipidemia.^[86]

Table 1.

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<i>Table 1</i> Major Apolipoproteins and Their Functions	
<i>Apolipoprotein</i>	<i>Function</i>
Apo A-I	Structural protein of HDL; activates lecithin-cholesterol acyltransferase
Apo A-II	Structural protein of HDL
Apo B-48	Structural protein of chylomicron
Apo B-100	Structural protein of VLDL, IDL, and LDL; ligand for LDL receptor
Apo C-II	Activator of LPL
Apo C-III	Potential inhibitor of apo C-II and apo E functions
Apo E	Ligand for chylomicron remnant receptor and LDL receptor
Apo(a)	Function unknown; antagonizes plasminogen

HDL—high-density lipoprotein IDL—intermediate-density lipoprotein
 LDL—low-density lipoprotein LPL—lipoprotein lipase VLDL—very low density lipoprotein

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Table 2.

Medscape® www.medscape.com			
Table 2 Effects of Selected Drugs on Lipoprotein Levels			
Drug	VLDL	LDL	HDL
Alcohol*	+	0	+
Estrogens, estradiol*	+	-	+
Androgens, testosterone	+	+	-
Progestins	-	+	-
Glucocorticoids*	+	0	+
Cyclosporines	+	+	+
Tacrolimus	+	+	+
Thiazide diuretics*	+	+	-
Beta blockers*	+	0	-
Calcium channel blockers	0	0	0
Angiotensin-converting enzyme inhibitors	0	0	0
Sertraline*	Possible+	+	0
Protease inhibitors*	+	0	0
Valproate and related drugs	+	0	-
Isotretinoin*	+	0	-

*Can cause severe hypertriglyceridemia and chylomicronemia syndrome in patients with a familial form of hypertriglyceridemia or type 2 diabetes mellitus.

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Table 3.

Medscape® www.medscape.com	
Table 3 Clinical Features of the Metabolic Syndrome ¹⁵	
The presence of three or more variables indicates a diagnosis of metabolic syndrome	
Abdominal obesity: waist circumference > 35 in (women) or > 40 in (men)	
Triglycerides \geq 150 mg/dl	
HDL cholesterol < 50 mg/dl (women) or < 40 mg/dl (men)	
Blood pressure \geq 130/85 mm Hg	
Fasting plasma glucose \geq 110 mg/dl	

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Table 4.

Medscape®		www.medscape.com	
Table 4 Drug Treatment of Lipid Disorders			
Drug	Dosage	Cost per Month	Comment
Bile acid-binding resins	Start with one packet (2 g for colestipol tabs) b.i.d., increase over 1–2 wk to desired dose		For elevated LDL, normal triglycerides 1 hr before or 4 hr after nicotinic acid, statins, or fibrates
Cholestyramine	Maximum 24 g/day b.i.d. or t.i.d.	\$69	
Colestipol	Maximum 30 g/day b.i.d. or t.i.d.	\$305	t.i.d. more effective
Colestipol tablets	Maximum 16 g/day	\$267	
Colesevelam	Three 625 mg tablets b.i.d. with meals or six tablets/day with a meal; maximum seven tablets/day	\$142	Better tolerated than other resins
Ezetimibe	10 mg/day	\$72	Can reduce LDL cholesterol by increasing plasma triglycerides
Fenofibrate	200 mg/day	\$73	For elevated triglycerides and both LDL and triglycerides
Gemfibrozil	600 mg b.i.d. before meals	\$17	used with bile acid-binding resins; decrease dose with severe liver disease
Niacin	Start with 250 mg q.d. with meals; increase to 1.5–2.0 g/day; maximum 6 g/day	\$28	For elevated LDL, triglyceride used with bile acid-binding resins
Statins			For elevated LDL; possibly useful in whom both LDL and triglycerides may be used with bile acid-binding resins
Atorvastatin	Start with 10 mg/day; maximum 80 mg/day	\$95	
Fluvastatin	Start with 20 mg b.i.d. or at bedtime; maximum 80 mg/day	\$68	
Lovastatin	Start with 20 mg b.i.d. or with dinner; maximum 80 mg/day	\$126	
Pravastatin	Start with 10 mg at bedtime; maximum 40 mg/day	\$120	May be used with drugs that inhibit CYP3A4
Simvastatin	Start with 10 mg at bedtime; maximum 40 mg/day	\$124	

Source: ACP Med

References

1. Havel R, Kane J: Introduction: structure and metabolism of plasma lipoproteins. The Metabolic and Molecular Bases of Inherited Disease, 8th ed. Scriver CR, Beaudet AL, Sly WS, et al, Eds. McGraw-Hill Book Co, New York, 2001
2. Brunzell JD, Chait A, Bierman EL: Pathophysiology of lipoprotein transport. *Metabolism* 27:1109, 1978
3. Brunzell JD, Albers JJ, Chait A, et al: Plasma lipoproteins in familial combined hyperlipidemia and monogenic hypertriglyceridemia. *J Lipid Res* 24:147, 1983
4. Kane JP, Havel RJ: Disorders of the biogenesis and secretion of lipoproteins containing the B apolipoproteins. *Molecular Bases of Inherited Disease*, 8th ed. Scriver CR, Beaudet AL, Sly WS, et al, Eds. McGraw-Hill Book Co, New York, 2001
5. Utermann G: Lipoprotein (a). *The Metabolic and Molecular Bases of Inherited Disease*, 8th ed. Scriver CS, Beaudet AL, Sly WS, et al, Eds. McGraw-Hill Book Co, New York, 2001
6. Brunzell J, Deeb S: Familial lipoprotein lipase deficiency, apo CII deficiency, and hepatic lipase deficiency. *The Metabolic and Molecular Bases of Inherited Disease*, 8th ed., Vol 2. Scriver CR, Beaudet AL, Sly WS, et al, Eds. McGraw-Hill Book Co, New York, 2001
7. Mahley R, Rall S: Type III hyperlipoproteinemia (dysbetalipoproteinemia): the role of apolipoprotein E in normal lipoprotein metabolism. *Metabolism* 27:1109, 1978

- metabolism. *The Metabolic and Molecular Bases of Inherited Disease*, 8th ed. Scriver CR, Beaudet AL, Sly W Book Co, New York, 2001
8. Goldstein JL, Hobbs HH, Brown MS: Familial hypercholesterolemia. *The Metabolic and Molecular Bases of Inherited Disease*, 8th ed. Scriver CS, Beaudet AL, Sly WS, et al, Eds. McGraw-Hill Book Co, New York, 2001
 9. Tall A, Breslow J, Rubin E: Genetic disorders affecting plasma high-density lipoproteins. *The Metabolic and Molecular Bases of Inherited Disease*, 8th ed. Scriver CS, Beaudet AL, Sly WS, et al, Eds. McGraw-Hill Book Co, New York, 2001
 10. Deeb SS, Zambon A, Carr MC, et al: Hepatic lipase and dyslipidemia: interactions among genetic variants, obesity, and insulin resistance. *Lipid Res* 44:1279, 2003
 11. Frikke-Schmidt R, Nordestgaard BG, Jensen GB, et al: Genetic variation in ABC transporter A1 contributes to general population. *J Clin Invest* 114:1343, 2004
 12. Carr MC, Brunzell JD: Abdominal obesity and dyslipidemia in the metabolic syndrome: importance of type 2 diabetes. *J Clin Endocrinol Metab* 89:2601, 2004
 13. Griffin BA: Lipoprotein atherogenicity: an overview of current mechanisms. *Proc Nutr Soc* 58:163, 1999
 14. Steinberg D, Pearson TA, Kuller LH: Alcohol and atherosclerosis. *Ann Intern Med* 114:967, 1991
 15. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on treatment of high blood cholesterol in adults (adult treatment panel III). Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA* 285:2486, 2001
 16. Brown CD, Higgins M, Donato KA, et al: Body mass index and the prevalence of hypertension and dyslipidemia. *Am J Hypertens* 13:1092, 2000
 17. Austin MA, McKnight B, Edwards KL, et al: Cardiovascular disease mortality in familial forms of hypertriglyceridemia: a prospective study. *Circulation* 101:2777, 2000
 18. Knopp RH: Drug treatment of lipid disorders. *N Engl J Med* 341:498, 1999
 19. Rubins HB, Robins SJ, Collins D, et al: Gemfibrozil for the secondary prevention of coronary heart disease in patients with hypertriglyceridemia. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med* 341:410, 1999
 20. Coronary Drug Project Research Group: Clofibrate and niacin in coronary heart disease. *JAMA* 231:360, 1975
 21. Carr MC: The emergence of the metabolic syndrome with menopause. *J Clin Endocrinol Metab* 88:2404, 2003
 22. Lemieux S, Despres JP, Moorjani S, et al: Are gender differences in cardiovascular disease risk factors explained by differences in body fat distribution? *Diabetologia* 37:757, 1994
 23. Nieves D, Cnop M, Retzlaff B, et al: The atherogenic lipoprotein profile associated with obesity and insulin resistance is attributable to intra-abdominal fat. *Diabetes* 52:172, 2003
 24. Purnell JQ, Kahn SE, Albers JJ, et al: Effect of weight loss with reduction of intra-abdominal fat on lipid metabolism. *J Clin Endocrinol Metab* 85:977, 2000
 25. Grundy SM: Approach to lipoprotein management in 2001 National Cholesterol Guidelines. *Am J Cardiol* 90:11B, 2001
 26. Cefalu WT, Wang ZQ, Werbel S, et al: Contribution of visceral fat mass to the insulin resistance of aging. *Metabolism* 47:401, 1998
 27. Bermudez OI, Tucker KL: Total and central obesity among elderly Hispanics and the association with type 2 diabetes. *Am J Hypertens* 14:1092, 2001
 28. Lempiainen P, Mykkanen L, Pyorala K, et al: Insulin resistance syndrome predicts coronary heart disease even in men. *Circulation* 100:123, 1999
 29. Mykkanen L, Kuusisto J, Haffner SM, et al: Hyperinsulinemia predicts multiple atherogenic changes in lipoprotein profiles. *Arterioscler Thromb Vasc Biol* 14:518, 1994
 30. Cefalu WT, Werbel S, Bell-Farrow AD, et al: Insulin resistance and fat patterning with aging: relationship to metabolic syndrome. *Metabolism* 47:401, 1998
 31. Ginsberg HN: Insulin resistance and cardiovascular disease. *J Clin Invest* 106:453, 2000
 32. Ford E, Giles W, Dietz W: Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA* 287:356, 2002
 33. Alexander CM, Landsman PB, Teutsch SM, et al: NCEP-defined metabolic syndrome, diabetes, and prevalence of cardiovascular disease among NHANES III participants age 50 years and older. *Diabetes* 52:1210, 2003
 34. Lamarche B, Moorjani S, Cantin B, et al: Associations of HDL₂ and HDL₃ subfractions with ischemic heart disease. *Thromb Vasc Biol* 17:1098, 1997
 35. Williams RR, Hopkins PN, Hunt SC, et al: Population-based frequency of dyslipidemia syndromes in coronary artery disease. *Arch Intern Med* 150:582, 1990
 36. Goldstein JL, Hazzard WR, Schrott HG, et al: Hyperlipidemia in coronary heart disease. I. Lipid levels in 500 subjects with myocardial infarction. *J Clin Invest* 52:1533, 1973
 37. Goldstein JL, Schrott HG, Hazzard WR, et al: Hyperlipidemia in coronary heart disease. II. Genetic analysis of the disorder and delineation of a new inherited disorder, combined hyperlipidemia. *J Clin Invest* 52:1544, 1973
 38. Hazzard WR, Goldstein JL, Schrott MG, et al: Hyperlipidemia in coronary heart disease. III. Evaluation of lipoprotein subfractions in genetically defined survivors of myocardial infarction. *J Clin Invest* 52:1569, 1973
 39. Ayyubi AF, McGladdery SH, McNeely MJ, et al: Small, dense LDL and elevated apolipoprotein B are the common features of three major lipid phenotypes of familial combined hyperlipidemia. *Arterioscler Thromb Vasc Biol* 23:1289, 2003
 40. Jarvik GP, Brunzell JD, Austin MA, et al: Genetic predictors of FCHL in four large pedigrees. Influence of apolipoprotein B genotype and LDL subclass phenotype. *Arterioscler Thromb Vasc Biol* 14:1687, 1994
 41. Austin MA, Horowitz H, Wijsman E, et al: Bimodality of plasma apolipoprotein B levels in familial combined hyperlipidemia. *J Clin Invest* 94:1092, 1994

- hyperlipidemia. *Atherosclerosis* 92:67, 1992
42. Babirak SP, Brown BG, Brunzell JD, et al: Familial combined hyperlipidemia and abnormal lipoprotein lipase. *JAMA* 273:1176, 1992
 43. Purnell JQ, Kahn SE, Schwartz RS, et al: Relationship of insulin sensitivity and ApoB levels to intra-abdominal combined hyperlipidemia. *Arterioscler Thromb Vasc Biol* 21:567, 2001
 44. Brown G, Albers JJ, Fisher LD, et al: Regression of coronary artery disease as a result of intensive lipid-lowering with high levels of apolipoprotein B. *N Engl J Med* 323:1289, 1990
 45. Colhoun HM, Betteridge DJ, Durrington PN, et al: Primary prevention of cardiovascular disease with atorvastatin. Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 361:569, 2003
 46. Marks D, Thorogood M, Neil HA, et al: A review on the diagnosis, natural history, and treatment of familial hypercholesterolaemia. *Atherosclerosis* 168:1, 2003
 47. Grundy SM, Vega GL, McGovern ME: Efficacy, safety, and tolerability of once-daily niacin for the treatment of type 2 diabetes: results of the assessment of diabetes control and evaluation of the efficacy of Niaspan trial. *Diabetes Care* 25:1568, 2002
 48. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women: the Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial. *JAMA* 273:199, 1995
 49. Anderson GL, Limacher M, Assaf AR, et al: Effects of conjugated equine estrogen in postmenopausal women. Women's Health Initiative randomized controlled trial. *JAMA* 291:1701, 2004
 50. Joven J, Villabona C, Vilella E, et al: Abnormalities of lipoprotein metabolism in patients with the nephrotic syndrome. *Nephron* 323:579, 1990
 51. Samuelsson O, Attman PO, Knight-Gibson C, et al: Effect of gemfibrozil on lipoprotein abnormalities in chronic kidney disease: a controlled study in human chronic renal disease. *Nephron* 75:286, 1997
 52. Khovidhunkit W, Memon RA, Feingold KR, et al: Infection and inflammation-induced proatherogenic changes in lipoproteins. *Diabetes* 49:181:S462, 2000]
 53. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. *JAMA* 251:351, 1984
 54. The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. *JAMA* 251:365, 1984
 55. Frick MH, Elo O, Haapa K, et al: Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 317:1237, 1987
 56. Shepherd J, Cobbe SM, Ford I, et al: Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med* 333:1301, 1995
 57. Baseline risk factors and their association with outcome in the West of Scotland Coronary Prevention Study. The West of Scotland Coronary Prevention Study Group. *Am J Cardiol* 79:756, 1997
 58. Influence of pravastatin and plasma lipids on clinical events in the West of Scotland Coronary Prevention Study. *Am J Cardiol* 97:1440, 1998
 59. Downs JR, Clearfield M, Weis S, et al: Primary prevention of acute coronary events with lovastatin in men and women with hypercholesterolemia: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 285:2081, 2001
 60. Gotto AM, Boccuzzi SJ, Cook JR, et al: Effect of lovastatin on cardiovascular resource utilization and costs in the Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). AFCAPS/TexCAPS Research Group. *Am J Cardiol* 88:1000, 2002
 61. Sever PS, Dahlof B, Poulter NR, et al: Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 361:1149, 2003
 62. Pekkanen J, Linn S, Heiss G, et al: Ten-year mortality from cardiovascular disease in relation to cholesterol level without preexisting cardiovascular disease. *N Engl J Med* 322:1700, 1990
 63. Watts GF, Lewis B, Brunt JN, et al: Effects on coronary artery disease of lipid-lowering diet, or diet plus cholesterol-lowering drugs. Atherosclerosis Regression Study (STARS). *Lancet* 339:563, 1992
 64. de Lorgeril M, Salen P, Martin JL, et al: Effect of a Mediterranean type of diet on the rate of cardiovascular coronary artery disease: insights into the cardioprotective effect of certain nutrients. *J Am Coll Cardiol* 28:111, 1996
 65. de Lorgeril M, Salen P, Martin JL, et al: Mediterranean diet, traditional risk factors, and the rate of cardiovascular myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation* 99:779, 1999
 66. Zamboni A, Hokanson JE, Brown BG, et al: Evidence for a new pathophysiological mechanism for coronary artery disease: hepatic lipase-mediated changes in LDL density. *Circulation* 99:1959, 1999
 67. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 344:1383, 1994
 68. Pedersen TR, Olsson AG, Faergeman O, et al: Lipoprotein changes and reduction in the incidence of major cardiovascular events in the Scandinavian Simvastatin Survival Study (4S). *Circulation* 97:1453, 1998
 69. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a low cholesterol level. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. *N Engl J Med* 339:977, 1998
 70. Simes RJ, Marschner IC, Hunt D, et al: Relationship between lipid levels and clinical outcomes in the Long-term Pravastatin in Ischemic Disease (LIPID) Trial: to what extent is the reduction in coronary events with pravastatin

- lipid levels? *Circulation* 105:1162, 2002
71. Sacks FM, Pfeffer MA, Moya LA, et al: The effect of pravastatin on coronary events after myocardial infarction on cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med* 335:1001, 1996
 72. Sacks FM, Moya LA, Davis BR, et al: Relationship between plasma LDL concentrations during treatment with coronary events in the Cholesterol and Recurrent Events trial. *Circulation* 97:1446, 1998
 73. MCR/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized controlled trial. Heart Protection Study Collaborative Group. *Lancet* 360:7, 2002
 74. Cannon CP, Braunwald E, McCabe CH, et al: Intensive versus moderate lipid lowering with statins after acute myocardial infarction. *N Engl J Med* 350:1495, 2004
 75. Nissen SE, Tuzcu EM, Schoenhagen P, et al: Effect of intensive compared with moderate lipid-lowering therapy on coronary atherosclerosis: a randomized controlled trial. *JAMA* 291:1071, 2004
 76. Brown BG, Zhao XQ, Chait A, et al: Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of atherosclerotic disease. *N Engl J Med* 345:1583, 2001
 77. Snow V, Aronson MD, Hornbake ER, et al: Lipid control in the management of type 2 diabetes mellitus: a clinical practice guideline. *Ann Intern Med* 140:644, 2004
 78. D'Agostino RB, Grundy S, Sullivan LM, et al: Validation of the Framingham coronary heart disease prediction equations: the Framingham Heart Study. *JAMA* 286:180, 2001
 79. Liu J, Hong Y, D'Agostino RB, et al: Predictive value for the Chinese population of the Framingham CHD risk score: results from the Chinese Multi-Provincial Cohort Study. *JAMA* 291:2591, 2004
 80. Brindle P, Emberson J, Lampe F, et al: Predictive accuracy of the Framingham coronary risk score in British men: a prospective study. *BMJ* 327:1267, 2003
 81. Shepherd J, Blauw GJ, Murphy MB, et al: Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomized controlled trial. *Lancet* 360:1623, 2002
 82. Yusuf S, Hawken S, Ounpuu S, et al: Effect of potentially modifiable risk factors associated with myocardial infarction in INTERHEART study: case-control study. *Lancet* 364:937, 2004
 83. Davidson MH, McGarry T, Bettis R, et al: Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. *Am J Cardiol* 40:2125, 2002
 84. Cholesterol in childhood. American Academy of Pediatrics, Committee on Nutrition. *Pediatrics* 101:141, 1998
 85. Rossouw JE, Anderson GL, Prentice RL, et al: Risks and benefits of estrogen plus progestin in healthy postmenopausal women: results from the Women's Health Initiative randomized controlled trial. *JAMA* 288:321, 2002
 86. Carlsson CM, Carnes M, McBride PE, et al: Managing dyslipidemia in older adults. *J Am Geriatr Soc* 47:1458, 2002

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