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KEY CONCEPTS

- 1 Hypercholesterolemia, elevated low-density lipoprotein (LDL) levels, and low high-density lipoprotein (HDL) levels are unequivocally linked to increased risk for coronary heart disease and cerebrovascular morbidity and mortality. LDL is the primary target.
- 2 Multiple genetic abnormalities and environmental factors are involved in clinical lipid abnormalities, and routinely used clinical laboratory measurements do not define the underlying abnormalities.
- 3 Initial therapy for any lipoprotein disorder is therapeutic lifestyle changes with restricted intake of total and saturated fat and cholesterol and a modest increase in polyunsaturated fat intake along with a program of regular exercise and weight reduction if needed.
- 4 If pharmacologic therapy is insufficient after therapeutic lifestyle changes, lipid-lowering agents should be chosen based on the specific lipoprotein disorder presentation and the severity of the lipid abnormality.
- 5 Considering compliance, adverse effects, and effectiveness, for patients with hypercholesterolemia statins are the drugs of choice because they are the most potent form of monotherapy and are cost effective in patients with known coronary artery disease or multiple risk factors and in high-risk primary prevention patients.
- 6 Patients who do not respond to statin monotherapy can be treated with combination therapy for hypercholesterolemia but should be monitored closely because of an increased risk for adverse effects and drug interactions.
- 7 Hypertriglyceridemia usually responds well to niacin, gemfibrozil, and fenofibrate. High-dose niacin should be used cautiously in diabetics because of worsening glycemic control. Statins lower triglycerides to a variable extent depending on baseline triglyceride concentration and statin potency.
- 8 Low high-density lipoprotein-cholesterol (HDL-C) levels are addressed with lifestyle modifications, such as smoking cessation and increased exercise. Niacin, gemfibrozil, and fenofibrate can significantly increase HDL-C.
- 9 Lipid-lowering therapy is generally considered cost effective, particularly in secondary intervention and high-risk patients.
- 10 Decreasing elevated total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels reduce coronary heart disease mortality and total mortality; increasing HDL reduces coronary heart disease events as well. Aggressive treatment of hypercholesterolemia results in fewer patients progressing to myocardial infarction, angina, and stroke and reduces the need for interventions such as coronary artery bypass graft and percutaneous transluminal coronary angioplasty.

Cholesterol, triglycerides, and phospholipids are the major lipids in the body. They are transported as complexes of lipid and proteins known as *lipoproteins*. Plasma lipoproteins are spherical particles with surfaces that consist largely of phospholipid, free cholesterol, and protein and cores composed mostly of triglyceride and cholesterol ester (Fig. 23–1). The three major classes of lipoproteins in serum are low-density lipoproteins (LDLs), high-density lipoproteins (HDLs), and very-low-density lipoproteins (VLDLs). VLDL is carried in the circulation as triglyceride and can be estimated by dividing the triglyceride concentration by five. Intermediate-density lipoprotein (IDL) resides between VLDL and LDL and is included in the LDL measurement in routine clinical measurement. Abnormalities of plasma lipoproteins can result in a predisposition to coronary, cerebrovascular, and peripheral vascular arterial disease and constitutes one of the major risk factors for coronary heart disease (CHD). Accumulating evidence over the last decades had linked elevated total cholesterol and low-density lipoprotein-cholesterol (LDL-C) levels and reduced HDL levels to the development of CHD. Premature coronary atherosclerosis, leading to the manifestations of ischemic heart disease (see Chap. 17), is the most common and significant consequence of dyslipidemia. The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) published its third report summarizing these data and giving recommendations for the management of hypercholesterolemia in adults.^{1,2} This report and the later update modify earlier recommendations and provide a new way of risk-stratifying patients based on multiple risk factors, the presence of diabetes, and the metabolic syndrome. The American Heart Association (AHA) also provides guidelines for primary and secondary prevention of CHD.^{3,4}

Total cholesterol and LDL-C increase throughout life in men and women, representing an atherogenic pattern characteristic of westernized society diets.⁵ Based on the National Health and Nutrition Examination Survey (NHANES 1999–2004) and ATP III guidelines, slightly more than 50% or nearly 105 million American adults older than 20 years have total cholesterol levels ≥ 200 mg/dL.⁶ More than half of individuals at borderline to high risk remain unaware that they have hypercholesterolemia, and fewer than half of highest-risk persons (those with symptomatic CHD) are receiving lipid-lowering

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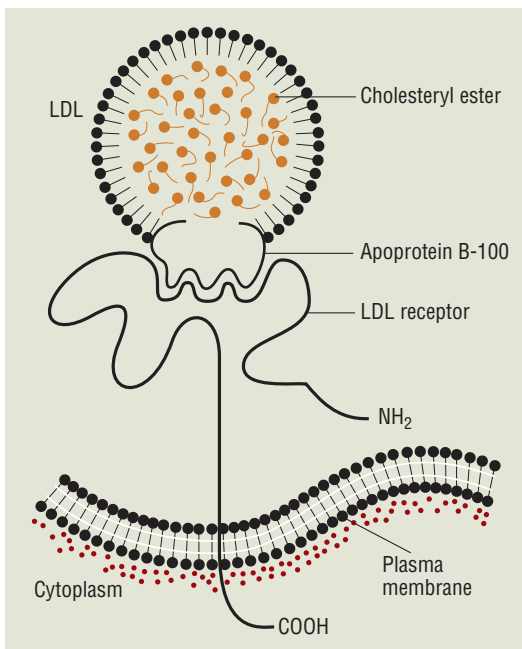


FIGURE 23-1. Diagrammatic representation of the structure of low-density lipoprotein (LDL), the LDL receptor, and the binding of LDL to the receptor via apolipoprotein B-100. (From Ganong WF. *Review of Medical Physiology*, 22nd ed. New York: McGraw-Hill, 2005:303.)

treatment. Approximately one third of treated patients are achieving their LDL goal; fewer than 20% of CHD patients are at their LDL goal.^{6,7} Changes in the NCEP guidelines have increased the number of persons eligible for therapeutic lifestyle changes (TLC) or lipid-lowering therapy by millions. NCEP estimates that only 26% of patients have an optimal LDL-C (<100 mg/dL) and that large numbers of patients either are untreated or undertreated.¹ Unfortunately, those patients at highest risk are less likely to be treated to desirable levels of LDL.⁸ Although these numbers seem staggering in their enormity, substantial progress has been made, and the number of Americans with a desirable blood cholesterol level (<200 mg/dL) has risen to 49% from 45% from the earlier survey (1976–1980), whereas the average total cholesterol in the United States has fallen from 220 mg/dL in 1960–1962 to 203 mg/dL in 2002.⁹ Patients who are at risk but who have not yet experienced their first cardiovascular or cerebrovascular event (e.g., myocardial infarction [MI]) are termed *primary prevention* patients, whereas those with manifest vascular disease are termed *secondary intervention* patients.

① Data from the Framingham study and from other studies demonstrate that the risk for developing cardiovascular disease is related to the degree of total cholesterol and LDL elevation in a graded, continuous fashion.^{10,11} Hypercholesterolemia is additive to the other nonlipid risk factors for CHD, including cigarette smoking, hypertension, diabetes, low HDL levels, and electrocardiographic abnormalities. The presence of established CHD or prior MI increases the risk of MI five to seven times that seen in men or women without CHD, and LDL level is a significant predictor of subsequent morbidity and mortality. Approximately 50% of all MIs and at least 70% of CHD deaths occur in patients with known CHD; therefore, these patients should be targeted for screening, identification, and treatment. Unfortunately, the identification of patients at high risk because of hypercholesterolemia or other lipid disorders is too frequently overlooked because blood lipid levels are not always evaluated in this population even after an event such as MI.

A comparison of the United States to other countries shows similar relationships between total cholesterol, LDL, and an inverse relationship with HDL to coronary artery disease (CAD) mortality.¹⁰

On a positive note, the U.S. mortality rate is midway among the countries studied. The United States has shown the greatest decline in CAD mortality (35%–40%) in men and women over the last 10 years compared to other countries. A decline in the prevalence of hypercholesterolemia in certain segments of the U.S. population parallels these trends in mortality.¹ LDL and the ratio of LDL to HDL also have been used to assess risk, but their use adds little information to total cholesterol alone unless HDL is abnormally high or low. HDL transports cholesterol from lipid-laden foam cells to the liver. HDL has been shown to be protective for the occurrence of CHD, and an inverse relationship exists between CHD and HDL levels.¹²

VLDL, the major lipoprotein associated with triglycerides, is enriched with cholesterol esters. It is smaller, denser, and more atherogenic than less-dense VLDL. Routine measurement of triglycerides cannot distinguish between the types of VLDL present in plasma. Elevation of triglyceride-rich lipoproteins is associated with low HDL, and this ratio predicts increased risk. The 8-year follow-up of the Copenhagen male study found a clear gradient of risk for ischemic heart disease with increasing triglyceride levels within each level of high-density lipoprotein-cholesterol (HDL-C). Compared to the lowest tertile of triglyceride concentrations, the highest tertile had 2.2 relative risk for ischemic heart disease, and the relationship extended across all concentrations of HDL.¹³ The Helsinki Heart Study showed that hypertriglyceridemia and low HDL are associated with obesity (body mass index [BMI] >26 kg/m²), smoking, sedentary lifestyle, blood pressure ≥140/90 mm Hg, and blood glucose >4.4 mmol/L, and that the benefit of gemfibrozil (risk reduction 68%, $P < 0.03$) was largely confined to overweight subjects.¹⁴ Hypertriglyceridemia in certain instances (e.g., diabetes mellitus, nephrotic syndrome, chronic renal disease, and perhaps in women) is associated with increased cardiovascular risk. This is thought to be a consequence of the presence of atherogenic lipoproteins and of hypertriglyceridemia being a marker for them, as triglycerides usually are not independently predictive for CHD.¹⁵

LIPOPROTEIN METABOLISM AND TRANSPORT

As the major plasma lipids, cholesterol and triglycerides are essential substrates for cell membrane formation and hormone synthesis, and they provide a source of free fatty acids.¹⁶ Dyslipidemia can be defined as elevated total cholesterol, LDL-C, or triglycerides level, low HDL-C concentration, or some combination of these abnormalities. Lipids, which are water immiscible, are not present in free form in the plasma but rather circulate as lipoproteins. Hyperlipoproteinemia refers to an increased concentration of the lipoprotein macromolecules that transport lipids in the plasma. The density of plasma lipoproteins is determined by their relative content of protein and lipid. Density, composition, size, and electrophoretic mobility divide lipoproteins into four classes (Table 23–1).

LDL is further divided into LDL₁ (or IDL; density 1.006–1.019 g/mL) and LDL₂ (1.019–1.063 g/mL). LDL₂ is the major LDL component in plasma; it carries 60% to 70% of the total serum cholesterol. HDL has been subdivided into HDL₂ (density 1.063–1.125 g/mL) and HDL₃ (1.125–1.21 g/mL). Fluctuations in HDL usually are caused by alterations in the levels of HDL₂. HDL normally carries approximately 20% to 30% of the total cholesterol. VLDL also has been subdivided into three classes, and it carries approximately 10% to 15% of serum cholesterol and most of the triglyceride in the fasting state. VLDL is the precursor for LDL, and VLDL remnants also may be atherogenic. Table 23–2 lists the characteristics of the protein constituent of lipoproteins known as *apolipoproteins*. The structure of LDL, the LDL receptor, and the binding of LDL to the receptor via apolipoprotein B-100 is shown in Fig. 23–1.

TABLE 23-1 Composition of Lipoprotein Isolated from Normal Subjects

| Lipoprotein Class | Density Range (g/mL) | Diameter (nm) | Protein | Composition (Weight %) | | | |
|-------------------|----------------------|---------------|---------|------------------------|------------------|-------|--------------|
| | | | | Triglyceride | Free Cholesterol | Ester | Phospholipid |
| Chylomicrons | <0.94 | 75–1200 | 1–2 | 80–95 | 1–3 | 2–4 | 3–9 |
| VLDL | 0.94–1.006 | 30–80 | 6–10 | 55–80 | 4–8 | 16–22 | 10–20 |
| LDL | 1.006–1.063 | 18–25 | 18–22 | 5–15 | 6–8 | 45–50 | 18–24 |
| HDL | 1.063–1.21 | 5–12 | 45–55 | 5–10 | 3–5 | 15–20 | 20–30 |

HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein.

Chylomicrons are large triglyceride-rich particles that contain apolipoproteins B-48, B-100, and E. They are formed from dietary fat solubilized by bile salts in intestinal mucosal cells. Chylomicrons normally are not present in the plasma after a fast of 12 to 14 hours. They are catabolized by lipoprotein lipase (LPL), which is activated by apolipoprotein C-II and in the vascular endothelium and hepatic lipase to form chylomicron remnants. The remnants that contain apolipoprotein E (Fig. 23–2) are taken up by the “remnant receptor,” which may be an LDL receptor–related protein, in the liver. Free cholesterol is liberated intracellularly after attachment to the remnant receptor. Chylomicrons also function to deliver dietary triglyceride to skeletal muscle and adipose tissue. During the catabolism of nascent chylomicrons to remnants, triglyceride is converted to free fatty acids and apolipoproteins A-I, A-II, A-IV (free in plasma), C-I, C-II, and C-III, and phospholipids are transferred to HDL. Apolipoproteins E and C-II are transferred to chylomicrons from HDL and eventually back through these metabolic events. Hepatic VLDL synthesis is regulated in part by diet and hormones and is inhibited by uptake of chylomicron remnants in the liver. VLDL is secreted from the liver and serially converted via LPL to IDL and finally to LDL. VLDL receptors are found in adipose tissue and muscle and bear close homology to the structure of LDL receptors.

LDL, the major cholesterol transport lipoprotein, basically has only apolipoprotein B-100. It is mostly derived from VLDL catabolism and cellular synthesis. When normal subjects fast and consume a low-fat diet, most cholesterol is synthesized and used in the extrahepatic organs; most of the cholesterol carried by LDL is taken

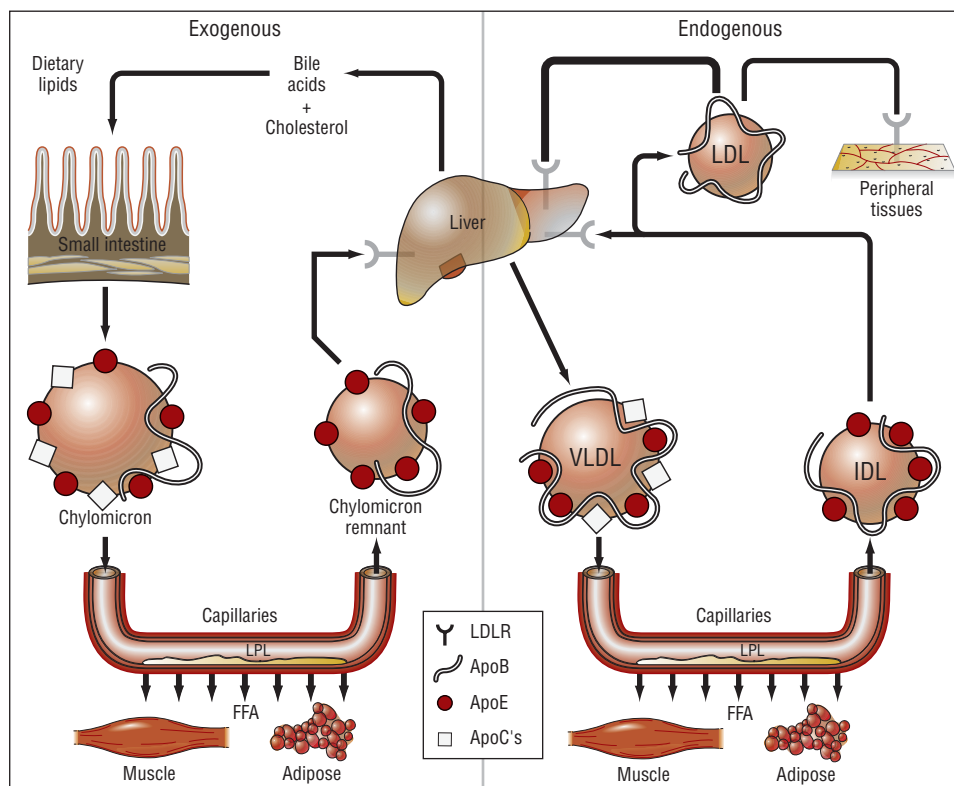
up by the liver for catabolism. In patients with homozygous familial hypercholesterolemia, enhanced synthesis of LDL may occur because LDL clearance is reduced as a consequence of the lack of LDL receptors. LDL is catabolized through interaction of cell surface receptors found on liver, adrenal, and peripheral cells (including fibroblasts and smooth muscle cells). These cells recognize apolipoprotein B-100 on LDL, and, after binding to a receptor on the cell membrane, LDL is internalized and degraded. In the normal fasting state, approximately 70% of LDL is cleared through the receptor-dependent mechanism, although this is highly dependent on the availability and type of saturated and monosaturated or polyunsaturated fat from dietary sources. Ingestion of cholesterol and saturated fatty acids such as C12:0, C14:0, and C16:0 is associated with reduced LDL receptor activity, increased LDL production rate, and elevated LDL plasma concentration. Receptor-independent mechanisms are also involved to a lesser extent in the catabolism of LDL, and these receptors are present in many tissues but are most active in animals in the adrenals and ovary. Increased intracellular cholesterol resulting from LDL catabolism inhibits the activity of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme for intracellular cholesterol biosynthesis (Fig. 23–3). Additional consequences of increased intracellular cholesterol include reduced synthesis of LDL receptors, which limits subsequent cholesterol uptake from the plasma, and accelerated activity of acyl-coenzyme A:cholesterol acyltransferase (ACAT) to facilitate cholesterol storage within cells. LDL-C also may be excreted into bile and become part of the enterohepatic pool or may be lost in the stool.

TABLE 23-2 Characteristics and Functions of Apolipoproteins

| Apolipoprotein | Lipoprotein Density Class | Approximate Plasma Concentration (mg/dL) | Approximate Molecular Weight (kDa) | Reported Functions | Major Site of Synthesis |
|----------------|---------------------------|--|------------------------------------|--|-------------------------|
| A-I | Chylomicrons, HDL | 120 | 28 | Cofactor with LCAT, structural protein on HDL, ligand for HDL receptor | Liver, intestine |
| A-II | Chylomicrons, HDL | 35 | 17 | Structural protein for HDL, ligand for HDL receptor | Liver |
| A-IV | Chylomicrons, 1.21B | 15 | 46 | Possibly facilitates transfer of other apolipoproteins between HDL and chylomicrons | Intestine |
| Lp(a) | LDL, HDL | 10 | 500± | Bound to B-100, high homology with plasminogen, may prevent LDL uptake by B, E receptor | Liver |
| B-100 | VLDL, LDL, IDL | 100 | 540 | Necessary for assembly and secretion of VLDL from liver, structural protein of VLDL, IDL, LDL, ligand for LDL receptor | Liver |
| B-48 | Chylomicrons | Trace | 264 | Necessary for assembly and secretion of chylomicrons from small intestine | Intestine |
| C-I | Chylomicrons, VLDL, HDL | 7 | 6.6 | Cofactor with LCAT; may inhibit hepatic uptake of chylomicron and VLDL remnants | Liver |
| C-II | Chylomicrons, VLDL, HDL | 4 | 8.9 | Activator of LPL | Liver |
| C-III | Chylomicrons, VLDL, HDL | 13 | 8.8 | Inhibitor with LPL; may inhibit hepatic uptake of chylomicron and VLDL remnants | Liver |
| D | HDL | 6 | 32 | ? | ? |
| E2-E4 | Chylomicrons, VLDL, HDL | 5 | 34 | Ligand for several lipoproteins to LDL receptor, LRP and possibly to a separate hepatic apolipoprotein E receptor | Liver |

IDL, intermediate-density lipoprotein; LCAT, lecithin-cholesterol acyltransferase; LRP, LDL receptor–related protein. Other abbreviations are in Table 23–1.

FIGURE 23-2. Simplified diagram of lipoprotein systems for transporting lipids in humans. In the exogenous system, chylomicrons rich in triglycerides of dietary origin are converted to chylomicron remnants rich in cholesteryl esters by the action of lipoprotein lipase (LPL). In the endogenous system, very-low-density lipoproteins (VLDL) rich in triglycerides are secreted by the liver and converted to intermediate-density lipoproteins (IDL) and then to low-density lipoproteins (LDL) rich in cholesteryl esters. Some of the LDLs enter the subendothelial space of arteries, are oxidized, and then are taken up by macrophages, which become foam cells. The letters on the chylomicrons, chylomicron remnants, VLDL, IDL, and LDL identify the primary apoproteins (ApoB, ApoC, ApoE) found in them. (LDLR, low-density lipoprotein receptor.) (From Kasper DL, Braunwald E, Fauci AS, et al., eds. *Harrison's Principles of Internal Medicine*, 16th ed. New York, McGraw-Hill, 2005, p. 2289.)



Lipoprotein(a) is a cholesterol-rich lipoprotein similar in composition and density to LDL and with close homology to fibrinogen. It is reported to be an important independent risk factor for the development of premature cardiovascular disease.

Nascent HDL is derived from liver and gut synthesis primarily in the form of apolipoprotein A-I phospholipid discs.¹² Esterification of free cholesterol in nascent HDL and from peripheral tissues to cholesteryl esters by lecithin-cholesterol acyltransferase (LCAT) results in the production of HDL₃. Further addition of tissue cholesterol to HDL₃ results in the formation of HDL₂. HDL₂ can also be formed from remodeling of chylomicrons and VLDL catabolism. HDL₂ can be converted back to HDL₃ by the action of hepatic lipase and by the transfer of cholesteryl esters to the liver, LDL, and VLDL. Apolipoprotein A-I production is increased by estrogens, leading to higher HDL levels in women and in individuals receiving estrogen. Transfer of excess cholesterol from peripheral tissues by HDL is called *reverse cholesterol transport*. Putative HDL receptors in peripheral cells facilitate the uptake of cholesterol by HDL, which transfers cholesterol to either VLDL and LDL or to the liver for secretion into bile or conversion into bile acids. These processes rid peripheral tissue (e.g., coronary arteries) of excessive amounts of cholesterol and account for some of the protective effects noted with increasing HDL in women and other factors that elevate HDL levels. Variants of the cholesterol ester transfer protein (CETP) have been demonstrated in humans, and the B1B1 genotype is associated with lower HDL and progression of coronary atherosclerosis. Inhibition of CETP leads to elevations in HDL. However, CETP inhibitors tested in clinical trials did not induce regression of atherosclerotic plaque and were associated with higher blood pressure and CHD events.^{17–19}

The “response-to-injury” hypothesis states that risk factors such as oxidized LDL, mechanical injury to the endothelium (e.g., percutaneous transluminal angioplasty), excessive homocysteine, immunologic attack, and infection-induced (e.g., *Chlamydia*, herpes simplex virus 1) changes in endothelial and intimal function lead to endothelial dysfunction and a series of cellular interactions that culminate in atherosclerosis. C-reactive protein is an acute phase reactant and a

marker for inflammation; it may be useful in identifying patients at risk for developing CAD.²⁰ The eventual outcomes of this atherogenic cascade are clinical events such as angina, MI, arrhythmias, stroke, peripheral arterial disease, abdominal aortic aneurysm, and sudden death. Atherosclerotic lesions are thought to arise from transport and retention of plasma LDL-C through the endothelial cell layer into the extracellular matrix of the subendothelial space. Once in the artery wall, LDL is chemically modified through oxidation and nonenzymatic glycation. Mildly oxidized LDL then recruits monocytes into the artery wall, and the monocytes become transformed into macrophages. Macrophages have tremendous potential for accelerating LDL oxidation and apolipoprotein B accumulation and altering the receptor-mediated uptake of LDL into the artery wall from the usual LDL receptor to a “scavenger receptor” not regulated by cell content of cholesterol. Oxidized LDL increases plasminogen inhibitor levels (promotion of coagulation), induces expression of endothelin (vasoconstrictive substance), inhibits expression of nitric oxide (a vasodilator and platelet inhibitor), and is toxic to macrophages if highly oxidized. As oxidation of biologically active lipids proceeds, other lipids such as lysophosphatidylcholine, hydroperoxides, aldehydic breakdown products of fatty acids, and oxysterol are formed and continue the reaction within the tissue. These events lead to a massive accumulation of cholesterol. The cholesterol-laden cells are called *foam cells*, which are the earliest recognized cells of the arterial fatty streak.

Oxidized LDL provokes an inflammatory response that is mediated by a number of chemoattractants and cytokines. Examples that appear to be involved at different stages of lesion development include monocyte chemoattractant protein 1 (MCP-1); monocyte colony stimulating factor (M-CSF); *gro*; vascular cell adhesion molecule (VCAM-1); E-selectin (endothelial-leukocyte adhesion molecule [ELAM]-1); intercellular adhesion molecule (ICAM-1); platelet-derived growth factor (PDGF); vascular endothelial growth factor (VEGF); transforming growth factors (TGF- α and TGF- β); interleukin (IL)-1 and IL-6; and the ratio of IL-10 and IL-12. Some of these factors (e.g., MCP-1 and M-CSF) appear to participate early in the

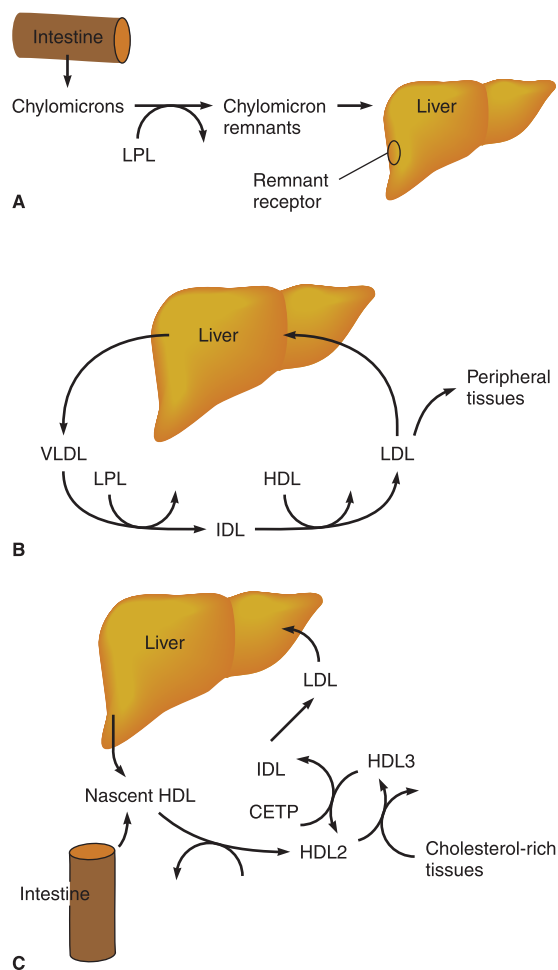


FIGURE 23-3. Biosynthetic pathway for cholesterol. The rate-limiting enzyme in this pathway is 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase). (CETP, cholesterol ester transfer protein; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LPL, lipoprotein lipase; VLDL, very-low-density lipoprotein.) (Modified from Breslow JL. Genetic basis of lipoprotein disorders. *J Clin Invest* 1989; 84:373.)

process of monocyte-macrophage attachment and transmigration across the endothelium, whereas others (PDGF and VCAM-1) promote later lesion growth.¹⁸ Based on murine model studies, the extent of oxidation and the inflammatory response is under genetic control of a major gene termed *Ath-1*. The process of aging may lead to lipoproteins that are more susceptible to oxidation and have longer resident time in the vascular compartment. Two proteins associated with HDL (apolipoprotein J and paraoxonase) appear to play important roles in minimizing oxidation of LDL-C.^{21,22} Increased recognition of the role of these growth regulatory molecules provides the possibility of future directions for antagonists to regulatory molecules such as PDGF, TGF- β , and the interleukins. Repeated injury and repair within an atherosclerotic plaque eventually leads to the formation of a fibrous cap that protects the underlying core of lipids, collagen, calcium, and inflammatory cells such as T-lymphocytes. Maintenance of the fibrous plaque is critical to preventing plaque rupture and subsequent coronary thrombosis. An imbalance between plaque synthesis and degradation may lead to a weakened or vulnerable plaque prone to rupture. The fibrous cap may become weakened through decreased synthesis of the extracellular matrix or increased degradation of the matrix. The cytokine interferon- γ , produced by T lymphocytes, inhibits the ability of smooth muscle cells to synthesize collagen, a structurally important component of the fibrous cap. A family of enzymes known as *matrix*

TABLE 23-3 Fredrickson-Levy-Lees Classification of Hyperlipoproteinemia

| Type | Lipoprotein Elevation |
|------|-------------------------|
| I | Chylomicrons |
| IIa | LDL |
| IIb | LDL + VLDL |
| III | IDL (LDL ₁) |
| IV | VLDL |
| V | VLDL + Chylomicrons |

IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein.

metalloproteinases can degrade all major constituents of the vascular extracellular matrix: collagen, elastin, and proteoglycans.²³

Lipoprotein disorders are classified into six categories, which are commonly used for phenotypical description of dyslipidemia (Table 23-3). **2** Specific genetic defects with disrupted protein, cell, and organ function give rise to several disorders within each family of lipoproteins (Table 23-4). An elevated cholesterol level does not necessarily equate with familial hypercholesterolemia or type IIa, as cholesterol may be elevated in other lipoprotein disorders and the lipoprotein pattern does not describe the underlying genetic defect. The preceding discussion focused on primary or genetic dyslipoproteinemia; however, secondary forms exist, and several drugs may elevate lipid levels (Table 23-5). The secondary forms of hyperlipidemia initially should be managed by correcting the underlying abnormality, including modification of drug therapy when appropriate.

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

Familial LPL deficiency is a rare, autosomal recessive trait characterized by massive accumulation of chylomicrons and corresponding increase in plasma triglycerides or a type I lipoprotein pattern. VLDL concentration is normal. Presenting manifestations include repeated attacks of pancreatitis and abdominal pain, eruptive cutaneous xanthomatosis, and hepatosplenomegaly beginning in childhood. Symptom severity is proportional to dietary fat intake and consequently to the elevation of chylomicrons. LPL is normally released from vascular endothelium or by heparin and hydrolyzes chylomicrons and VLDL (see Fig. 23-2). Diagnosis is based on low or absent enzyme activity with normal human plasma or apolipoprotein C-II, a cofactor of the enzyme. Accelerated atherosclerosis is not associated with the disease. Abdominal pain, pancreatitis, eruptive xanthomas, and peripheral polyneuropathy characterize type V (VLDL and chylomicrons). Symptoms may occur in childhood, but usually the disorder is expressed at a later age. The risk of atherosclerosis is increased with the disorder. Patients commonly are obese, hyperuricemic, and diabetic, and alcohol intake, exogenous estrogens, and renal insufficiency tend to be exacerbating factors.

Patients with familial type III hyperlipoproteinemia (also called *dysbetalipoproteinemia*, *broad-band*, or β -VLDL) develop the fol-

TABLE 23-4 Lipoprotein Disorders

| Lipid Phenotype | Plasma Lipid Levels [mmol/L (mg/dL)] | Lipoproteins | | Clinical Signs |
|---|--|-----------------------|-----------|--|
| | | Elevated | Phenotype | |
| Isolated hypercholesterolemia | | | | |
| Familial hypercholesterolemia | Heterozygotes TC = 7–13 (275–500) | LDL | IIa | Usually develop xanthomas in adulthood and vascular disease at 30–50 years |
| | Homozygotes TC >13 (>500) | LDL | IIa | Usually develop xanthomas in adulthood and vascular disease in childhood |
| Familial defective Apo B-100 | Heterozygotes TC = 7–13 (275–500) | LDL | IIa | |
| Polygenic hypercholesterolemia | TC = 6.5–9 (250–350) | LDL | IIa | Usually asymptomatic until vascular disease develops; no xanthomas |
| Isolated hypertriglyceridemia | | | | |
| Familial hypertriglyceridemia | TG = 2.8–8.5 (250–750) | VLDL | IV | Asymptomatic; may be associated with increased risk of vascular disease |
| Familial LPL deficiency | TG >8.5 (750) | Chylomicrons, VLDL | I, V | May be asymptomatic; may be associated with pancreatitis, abdominal pain, hepatosplenomegaly |
| Familial Apo C-II deficiency | TG >8.5 (>750) | Chylomicrons, VLDL | I, V | As above |
| Hypertriglyceridemia and hypercholesterolemia | | | | |
| Combined hyperlipidemia | TG = 2.8–8.5 (250–750) TC = 6.5–13 (250–500) | VLDL, LDL | IIb | Usually asymptomatic until vascular disease develops; familial form may present as isolated high TG or isolated high LDL cholesterol |
| Dysbetalipoproteinemia | TG = 2.8–8.5 (250–750); TC = 6.5–13 (250–500) | VLDL, IDL; LDL normal | III | Usually asymptomatic until vascular disease develops; may have palmar or tuberous xanthomas |

Apo, apolipoprotein; LPL, lipoprotein lipase; TC, total cholesterol; TG, triglycerides. Other abbreviations as in Table 23-1.

lowing clinical features after age 20 years: xanthoma striata palmaris (yellow discolorations of the palmar and digital creases); tuberous or tuberous xanthomas (bulbous cutaneous xanthomas); and severe atherosclerosis involving the coronary arteries, internal carotids, and abdominal aorta. A defective structure of apolipoprotein E does not allow normal hepatic surface receptor binding of remnant particles derived from chylomicrons and VLDL (known as IDL). Aggravating factors such as obesity, diabetes, and pregnancy may promote overproduction of apolipoprotein B-containing lipoproteins. Although homozygosity for the defective allele (E_2/E_2) is common (1:100), only 1 in 10,000 express the full-blown picture, and interaction with other genetic or environmental factors, or both, is needed to produce clinical disease.

Familial combined hyperlipidemia is characterized by elevations in total cholesterol and triglycerides, decreased HDL, increased apolipoprotein B, and small, dense LDL.²⁴ It is associated with premature CHD and may be difficult to diagnose because lipid levels do not consistently display the same pattern.

Type IV hyperlipoproteinemia is common and occurs in adults, primarily in patients who are obese, diabetic, and hyperuricemic and do not have xanthomas. It may be secondary to alcohol ingestion and can be aggravated by stress, progestins, oral contraceptives, thiazides, or β -blockers. Two genetic patterns that occur in type IV hyperlipoproteinemia are familial hypertriglyceridemia, which does not carry a great risk for premature CAD, and familial combined hyperlipidemia, which is associated with increased risk for cardiovascular disease.

Rare forms of lipoprotein disorders include hypobetalipoproteinemia, abetalipoproteinemia, Tangier disease, LCAT deficiency (fish eye disease), cerebrotendinous xanthomatosis, and sitosterolemia. Most of these rare lipoprotein disorders do not result in premature atherosclerosis, with the exceptions of familial LCAT deficiency, cerebrotendinous xanthomatosis, and sitosterolemia with xanthomatosis. Treatment consists of dietary restriction of plant sterols (sitosterolemia with xanthomatosis) and chenodeoxycholic acid (cerebrotendinous xanthomatosis), or, potentially, blood transfusion (LCAT deficiency).

TABLE 23-5 Secondary Causes of Lipoprotein Abnormalities

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

ISA, intrinsic sympathomimic activity.

CLINICAL PRESENTATION**General**

- Most patients are asymptomatic for many years before disease is clinically evident
- Patients with the metabolic syndrome may have three or more of the following: abdominal obesity, atherogenic dyslipidemia, increased blood pressure, insulin resistance with or without glucose intolerance, prothrombotic state, or proinflammatory state

Symptoms

- None to severe chest pain, palpitations, sweating, anxiety, shortness of breath, loss of consciousness or difficulty with speech or movement, abdominal pain, sudden death

Signs

- None to severe abdominal pain, pancreatitis, eruptive xanthomas, peripheral polyneuropathy, high blood pressure, body mass index >30 kg/m² or waist size >40 inches in men (35 inches in women)

Laboratory Tests

- Elevations in total cholesterol, LDL, triglycerides, apolipoprotein B, C-reactive protein
- Low HDL

Other Diagnostic Tests

- Lipoprotein(a), homocysteine, serum amyloid A, small dense LDL (pattern B), HDL subclassification, apolipoprotein E isoforms, apolipoprotein A-1, fibrinogen, folate, *Chlamydia pneumoniae* titer, lipoprotein-associated phospholipase A₂, omega-3 index²⁵
- Various screening tests for manifestations of vascular disease (ankle-brachial index, exercise testing, magnetic resonance imaging) and diabetes (fasting glucose, oral glucose tolerance test)

PATIENT EVALUATION

A fasting lipoprotein profile including total cholesterol, LDL-C, HDL-C, and triglycerides should be measured in all adults 20 years and older at least once every 5 years.¹ If the profile is obtained in the nonfasted state, only total cholesterol and HDL-C will be usable because LDL-C usually is a calculated value. If total cholesterol is ≥ 200 mg/dL or HDL-C is <40 mg/dL, a followup fasting lipoprotein profile should be obtained. After a lipid abnormality is confirmed (Table 23-6), major components of the evaluation are the history (including age, gender, and, if female, menstrual and hormone replacement status), physical examination, and laboratory investigations. A complete history and physical examination should assess (a) presence or absence of cardiovascular risk factors (Table 23-7) or definite cardiovascular disease in the individual; (b) family history of premature cardiovascular disease or lipid disorders; (c) presence or absence of secondary causes of lipid abnormalities, including concurrent medications (see Table 23-5); and (d) presence or absence of xanthomas or abdominal pain, or history of pancreatitis, renal or hepatic disease, peripheral vascular disease, abdominal aortic aneurysm, or cerebral vascular disease (carotid bruits, stroke, or transient ischemic attack). In an important change in the ATP III guidelines, diabetes mellitus is regarded as a CHD risk equivalent.¹ The presence of diabetes in patients without known CHD is associated with the same level of risk as in patients without diabetes but with confirmed CHD.^{26,27} ATP III identifies four categories of risk that modify the goals and modalities of LDL-lowering therapy (Table 23-8).² The

TABLE 23-6 Classification of Total, LDL, and HDL Cholesterol, and Triglycerides

| | |
|--------------------------|-----------------------|
| Total cholesterol | |
| <200 | Desirable |
| 200–239 | Borderline high |
| ≥ 240 | High |
| LDL cholesterol | |
| <100 | Optimal |
| 100–129 | Near or above optimal |
| 130–159 | Borderline high |
| 160–189 | High |
| ≥ 190 | Very high |
| HDL cholesterol | |
| <40 | Low |
| ≥ 60 mg/dL | High |
| Triglycerides | |
| <150 | Normal |
| 150–199 | Borderline high |
| 200–499 | High |
| ≥ 500 | Very high |

All values are given in milligrams per deciliters.

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

highest category is known CHD or CHD risk equivalents, which is defined as the risk for major coronary events equal to or greater than established CHD, that is, $>20\%$ per 10 years (2% per year). The next category is moderately high risk, consisting of patients with multiple (2+) risk factors in which 10-year risk for CHD is 10% to 20%. Moderate risk is defined as ≥ 2 risk factors and a 10-year risk of $\geq 10\%$. The lowest risk category is persons with a risk factor of 0 to 1. Risk is estimated from Framingham risk scores²⁸ and is estimated based on the patient's age, LDL-C or total cholesterol level, blood pressure, presence of diabetes, and smoking status (Table 23-7). This approach for a single patient is referred to as a *case finding* or *patient-based approach*, whereas large-scale screening and recommendations for the general populace, health care providers, and the food industry are called a *population-based approach*.

Measurement of plasma cholesterol (which is approximately 3% lower than serum determinations), triglyceride, and HDL-C levels after a fast of 12 hour or longer is important, as triglycerides may be elevated in nonfasted individuals; total cholesterol is only modestly affected by fasting. Analytic and biologic variability can have a major impact on the measurement and interpretation of cholesterol level (or any other laboratory test). Analytic variability can be minimized through the use of adequate quality control procedures, including internal training, routine calibration and monitoring, and external proficiency testing. Even with these measures, the coefficient of variability in the best procedures can acceptably be up to 5%, and,

TABLE 23-7 Major Risk Factors (Exclusive of LDL Cholesterol) That Modify LDL Goals^a

| |
|--|
| Age |
| Men: ≥ 45 years |
| Women: ≥ 55 years or premature menopause without estrogen replacement therapy |
| Family history of premature CHD (definite myocardial infarction or sudden death before age 55 years in father or other male first-degree relative, or before age 65 years in mother or other female first-degree relative) |
| Cigarette smoking |
| Hypertension ($\geq 140/90$ mm Hg or taking antihypertensive medication) |
| Low HDL cholesterol (<40 mg/dL) ^b |

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

^aDiabetes is regarded as a coronary heart disease (CHD) risk equivalent.

^bHDL cholesterol ≥ 60 mg/dL counts as a "negative" risk factor; its presence removes one risk factor from the total count.

TABLE 23-8 LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

| Risk Category | LDL Goal (mg/dL) | LDL Level at Which to Initiate TLC (mg/dL) | LDL Level at Which to Consider Drug Therapy (mg/dL) |
|---|---------------------------|--|--|
| High risk: CHD or CHD risk equivalents (10-year risk >20%) | <100 (optional goal: <70) | ≥100 | ≥100 (<100 mg/dL; consider drug options) ^a |
| Moderately high risk: 2+ risk factors (10-year risk >10%–20%) | <130 | ≥130 | ≥130 (100–129: consider drug options) |
| Moderate risk: 2+ risk factors (10-year risk <10%) | <130 | ≥130 | ≥160 |
| Lower risk: 0–1 risk factor ^b | <160 | ≥160 | ≥190 (160–189: LDL-lowering drug optional) |

CHD, coronary heart disease; LDL, low-density lipoprotein.

^aSome authorities recommend use of LDL-lowering drugs in this category if LDL cholesterol <100 mg/dL cannot be achieved by therapeutic lifestyle changes (TLC). Others prefer to use drugs that primarily modify triglycerides and high-density lipoprotein, e.g., nicotinic acid or fibrates. Clinical judgement also may call for deferring drug therapy in this subcategory.

^bAlmost all people with 0–1 risk factor have a 10-year risk <10%; thus, 10-year risk assessment in people with 0–1 risk factor is not necessary.

when combined with average biologic variability, total variability may be as high as approximately 22%. Analytic variability with desktop equipment generally is greater in the fingerstick capillary blood methods, usually yielding measurements less than those from a clinical laboratory; this technology should be considered for use only as a screening method. Reliance on desktop methods can result in misclassification of 7% to 14% of patients if capillary blood is used. Two determinations, 1 to 8 weeks apart, with the patient on a stable diet and weight and in the absence of acute illness, are recommended to minimize variability and obtain a reliable baseline.¹ If total cholesterol is >200 mg/dL, a second determination is recommended, and if the values are more than 30 mg/dL apart, the average of three values should be used. Familiarity with the method and quality control procedures used by local laboratories are essential for interpretation of reported values. If the physical examination and history are insufficient to diagnose a familial disorder, then agarose-gel lipoprotein electrophoresis is useful to determine which class of lipoproteins is affected. If triglyceride levels are <400 mg/dL and neither type III hyperlipidemia nor chylomicrons are detected by electrophoresis, then VLDL and LDL concentrations can be calculated as follows: VLDL = Triglycerides/5; LDL = Total cholesterol – (VLDL + HDL).

Because total cholesterol is composed of cholesterol derived from LDL, VLDL, and HDL, determination of HDL is useful when total plasma cholesterol is elevated. HDL may be elevated by moderate alcohol ingestion (fewer than two drinks per day), physical exercise, smoking cessation, weight loss, oral contraceptives, phenytoin, and terbutaline. Smoking, obesity, a sedentary lifestyle, and use of drugs such as β -blockers lower HDL. Only exercise and smoking cessation can be recommended as interventions for low HDL concentrations. Niacin and gemfibrozil increase HDL concentrations.

The range of lipid concentrations represents a population mean ± 2 SD and does not define the risk of disease. Reference values for plasma total, LDL, and HDL-C concentrations for men and women, as well as various ethnic groups, are available from the NHANES III.⁵ Levels of Cholesterol and triglycerides increase throughout life until about the fifth decade for men and the sixth decade for women. Past these ages, total cholesterol and LDL plateau and fall slightly. HDL tends to fall slightly with time and more rapidly after menopause in women. Institution of a population-based approach for cholesterol reduction should shift the entire curve to the left, and the potential reduction in cardiovascular mortality would be proportional to mean reductions at any cholesterol concentration.

Based on a careful review of the experimental pathologic, genetic, and epidemiologic evidence relating to the relationship between blood cholesterol levels and CHD, the adult treatment panel III of the NCEP recommends use of a fasting lipoprotein profile and risk factor assessment in the initial classification of adults.^{1,29} If total cholesterol is <200 mg/dL, then the patient has a *desirable blood cholesterol level* (Table 23–6). Cholesterol levels between 200 and 239

mg/dL are classified as *borderline–high blood cholesterol levels*, and assessment of risk factors (Table 23–7) is needed to more clearly define disease risk. Blood cholesterol levels ≥ 240 mg/dL are classified as *high blood cholesterol levels*. If total cholesterol is <200 mg/dL and HDL is >40 mg/dL, no further followup is recommended for patients without known CHD who have fewer than two risk factors. In patients with evidence of CHD or other clinical atherosclerotic disease, the LDL goal is <100 mg/dL, and most patients will require diet and/or drug intervention. In patients with very high risk (known CHD and multiple risk factors), the LDL goal may be set <70 mg/dL based on evidence from newer studies.²⁹ Decisions regarding classification and management are based on the LDL-C levels listed in Table 23–8. An increasing number of persons have the metabolic syndrome, which is characterized by abdominal obesity, atherogenic dyslipidemia (elevated triglycerides, small LDL particles, low HDL-C), increased blood pressure, insulin resistance (with or without glucose intolerance), and prothrombotic and proinflammatory states. ATP III recognizes the metabolic syndrome as a secondary target of risk reduction therapy after LDL-C has been addressed, and, if the metabolic syndrome is present, the patient is considered to have a CHD risk equivalent. Other lipid targets include non-HDL goals for patients with triglycerides >200 mg/dL. Non-HDL is calculated by subtracting HDL from total cholesterol, and the targets are 30 mg/dL greater than for LDL at each risk stratum. Non-HDL takes into consideration atherogenic particles such as remnant lipoproteins and IDL, which are not measured in routine clinical laboratory testing.³⁰ HDL raising has potential benefit, but the current guidelines do not set any specific goals, and evidence in support of aggressively increasing HDL levels is modest.³¹

The Expert Panel on Children and Adolescents of the NCEP recommends screening of higher-risk children (positive family history or parental high blood cholesterol ≥ 240 mg/dL).^{32,33} The rationale for this approach is based partly on the recognition that atherosclerosis begins in the childhood and adolescent years, as documented in the Pathobiologic Determinants of Atherosclerosis in Youth (PDAY) and the Bogalusa studies.³⁴ Similarly, if children with high blood lipids or lipoprotein levels are identified but the levels in the parents are unknown, the parents should be screened because they likely are at high risk. Racial and gender differences do exist in the determination of lipoprotein fractions and should be considered in screening. Use of the serum cholesterol level alone may be of insufficient specificity or sensitivity, depending on the cut points used in screening, and other discretionary factors, such as hypertension, smoking, obesity, high-fat diet, and use of cholesterol-raising medication, may be needed to correctly identify children at risk. Presently, children older than 10 years are candidates for drug therapy if a trial of diet (6 months to 1 year) proves to be inadequate and LDL-C remains >190 mg/dL, or >160 mg/dL if two or more risk factors or CHD is present in the child or adolescent, or if patient has a history of premature CHD. The Dietary Intervention Study in

Children (DISC) found that a fat-restricted diet in pubertal children modestly lowered LDL-C and maintained psychologic well-being, and that dietary changes are acceptable to children.^{35,36} Although bile acid sequestrants have been the recommended drugs for this population, clinical trials now demonstrate that statin therapy is effective and well tolerated in pediatric populations.^{37,38} The long-term consequences of drug therapy in this population are unknown. In special instances, familial hypercholesterolemia (particularly the homozygous form) or the existence of CHD or two or more risk factors in the child prompts earlier institution of drug therapy after a trial of dietary intervention.

TREATMENT

■ DESIRED OUTCOMES

The goals of therapy expressed as LDL-C levels and the level of initiation of TLC and drug therapy are given in Tables 23–8 and 23–9 for adults and children, respectively. Although these goals are surrogate end points, the primary reason for instituting TLC and drug therapy is to reduce the risk of first events or recurrent events such as MI, angina, heart failure, ischemic stroke, and other forms of peripheral arterial disease, such as carotid stenosis and abdominal aortic aneurysm.

■ GENERAL APPROACH¹

Establishing targeted changes and outcomes with consistent reinforcement of goals and measures at followup visits to attain goals are important to reduce barriers for optimizing TLC and pharmacologic therapy. **3** TLC should be implemented in all patients prior to considering drug therapy. The components of TLC include reduced intake of saturated fats and cholesterol, dietary options to reduce LDL, such as consumption of plant stanols and sterols and soluble fiber, weight reduction, and increased physical activity. In general, physical activity of moderate intensity 30 minutes per day for most days of the week should be encouraged.^{39,40} Patients with known CAD or who are at high risk should be evaluated before they undertake vigorous exercise. Weight and BMI should be determined at each visit, and lifestyle patterns to induce a weight loss of 10% should be discussed with persons who are overweight. All patients should be counseled to stop smoking and to meet the Joint National Committee VII guidelines for control of hypertension.

■ NONPHARMACOLOGIC THERAPY

Individualized dietary counseling that provides acceptable substitutions for unhealthy foods and ongoing reinforcement by a registered dietitian are necessary for maximal effect. The objectives of dietary therapy are to progressively decrease the intake of total fat, saturated fatty acids (i.e., saturated fat), and cholesterol and to achieve a desirable body weight. Typical American diets now include 13% to 20% of total calories from saturated fat and cholesterol intake of 350

to 450 mg/day, both in excess of a “heart healthy” diet for normal Americans, let alone patients with a lipid disorder. Excessive dietary intake of cholesterol and saturated fatty acids leads to decreased hepatic clearance of LDL and deposition of LDL and oxidized LDL in peripheral tissues. The targeted saturated fatty acids have carbon chain lengths of 12 (lauric acid), 14 (myristic acid), and 16 (palmitic acid). The rationale for using a nutritionally balanced, low-fat, low-cholesterol diet for treatment of hypercholesterolemia is based on the following principles: (a) it represents a reasonable extension of the diet recommended for the general public; (b) it progressively decreases the major cholesterol-raising constituent of the diet; (c) it precludes large intakes of polyunsaturated fats; and (d) it facilitates weight reduction by removing foods of high caloric density.^{41–44}

Dietary expertise in providing a wide range of options and suggestions in food preparation can make the difference between a good and an inadequate response to diet. Information on eating out in a healthy fashion and advice for shopping are important factors for success in diet therapy. An example is awareness of products with misleading labels, such as coffee creamers that state they contain “no cholesterol” when they may contain hydrogenated (saturated) fats or oils (e.g., palmitic acid, palm kernel oil, or coconut oil), which makes them undesirable because of their saturated fat content. Variations in polyunsaturated and saturated fat and cholesterol intake influence the LDL concentration, but the amount of cholesterol has been found to have a greater effect than the proportion of polyunsaturated or saturated fat. There were racial differences in elevation of LDL, with diets high in saturated fat consumed more by whites than by other racial groups. The isomeric form of fatty acids is important.⁴¹ Fatty acids with the *cis* configuration are the preferred substrate for the ACAT reaction and significantly increase hepatic LDL receptor clearance while reducing LDL-C production rate. The *trans* isomeric form cannot be used by ACAT and is biologically inactive, with no effect on LDL concentration.

Ideally, therapeutic TLC, including reduced intake of saturated fats and cholesterol, increased stanol/sterol and fiber intake, weight reduction, and increased physical activity, should be used to attain lower LDL-C and to achieve reductions in CHD risk (Table 23–10). TLC may obviate the need for drug therapy, augment LDL-lowering drug therapy, and allow for lower doses. Weight control plus increased physical activity reduce risk beyond LDL-C lowering, are the primary management approach for the metabolic syndrome, raise HDL, and reduce non-HDL-C.^{45,46} Many persons should be given a 3-month trial (two visits 6 weeks apart) of dietary therapy and TLC before advancing to drug therapy unless patients are at very high risk (severe hypercholesterolemia, known CHD, CHD risk equivalents, multiple risk factors, strong family history). Although changes in blood lipid levels may change before 3 months, adoption

TABLE 23-9 Classification of Lipid Levels in Children and Adolescents (Age <20 Years)

| | Desirable (mg/dL) | Borderline (mg/dL) | Undesirable (mg/dL) |
|-------------------|----------------------|-----------------------|------------------------|
| Total cholesterol | <170 | 170–199 | ≥200 |
| LDL cholesterol | <110 | 110–129 | ≥130 |
| HDL cholesterol | >45 | 25–45 | <35 |
| Triglycerides | <125 | NA | ≥125 |

HDL, high-density lipoprotein; LDL, low-density lipoprotein; NA, not applicable.
From Davis et al.³³

TABLE 23-10 Macronutrient Recommendations for the Therapeutic Lifestyle Changes Diet

| Component ^a | Recommended Intake |
|----------------------------|---|
| Total fat | 25%–35% of total calories |
| Saturated fat | Less than 7% of total calories |
| Polyunsaturated fat | Up to 10% of total calories |
| Monounsaturated fat | Up to 20% of total calories |
| Carbohydrates ^b | 50%–60% of total calories |
| Cholesterol | <200 mg/day |
| Dietary fiber | 20–30 g/day |
| Plant sterols | 2 g/day |
| Protein | Approximately 15% of total calories |
| Total calories | To achieve and maintain desirable body weight |

^aCalories from alcohol not included.

^bCarbohydrates should derive from foods rich in complex carbohydrates, such as whole grains, fruits, and vegetables.

of a different eating pattern may require a longer period of time. It is important to involve all family members, especially if the patient is not the primary person preparing food. The NCEP and AHA both have excellent Internet-based resources to aid patients in altering their diet in a culturally sensitive manner (<http://www.americanheart.org/presenter.jhtml?identifier=1200009>; <http://www.nhlbi.nih.gov/health/index.htm>). If all of the recommended dietary changes from NCEP were made, the estimated reduction, on average, in LDL would range from 20% to 30%.¹ Adherence to diet and interindividual variability in macronutrient intake influence the eventual LDL level achieved. Based on the NHANES data, less than half of patients who should be instructed on heart healthy diet receive any dietary instructions.

Other dietary interventions or diet supplements may be useful in certain patients with lipid disorders. Increased intake of soluble fiber in the form of oat bran, pectins, certain gums, and psyllium products can result in useful adjunctive reductions in total cholesterol and LDL-C, but these dietary alterations or supplements should not be substituted for more active forms of treatment. Total daily fiber intake should be about 20–30 g/day, with about 25% or 6 g/day, being soluble fiber.¹ Studies with psyllium seed in doses of 10 to 15 g/day show reductions in total cholesterol and LDL-C ranging from approximately 5% to 20%.^{47,48} They have little or no effect on HDL-C or triglyceride concentrations. These products also may be useful in managing constipation associated with the bile acid sequestrants. Psyllium binds cholesterol in the gut but also reduces hepatic production and clearance. Fish oil supplementation provides an increased amount of the omega-3 polyunsaturated fatty acids, such as eicosapentaenoic acid and docosahexaenoic acid. In epidemiologic studies, ingestion of large amounts of cold-water oily fish was associated with a reduction in CHD risk, but whether the same advantage is conferred with commercially prepared fish oil products is unclear. Each 20 g/day ingestion of fish lowers CHD risk by 7%, and eating fish at least once weekly should reduce CHD mortality.⁴⁹ Fish oil supplementation has a fairly large effect in reducing triglycerides and VLDL-C, but it either has no effect on total cholesterol and LDL-C or may cause elevations in these fractions. Other actions of fish oil may account for their protective effects. These effects include quantitative and qualitative alterations in the synthesis of prostanoid substances, changes in immune function and cellular proliferation, and potential antioxidative actions.⁵⁰ Responses noted with fish oil are discussed in Pharmacologic Therapy below.⁵¹

Fat substitutes such as olestra (sucrose polyester, Olean, Procter and Gamble), a mixture of hexa-esters, hepta-esters, and octa-esters formed from the reaction of sucrose with long-chain fatty acids, are approved by the Food and Drug Administration (FDA) as a nondigestible, nonabsorbable, noncaloric fat substitute for snack foods. Olestra is heat stable, so it can be used in the preparation of fried and baked foods, an advantage over several other fat substitutes. It is similar in composition to triglycerides, but olestra is not hydrolyzed in the gastrointestinal tract by pancreatic lipase and, consequently, is not taken up by the intestinal mucosa. The principal adverse effects associated with olestra use are bloating, flatulence, diarrhea, and “anal leakage.” Because of the ability of olestra to solubilize lipophilic substances, there has been concern over potential drug interactions in which lipophilic drugs (e.g., digitoxin, cyclosporine, or colchicine) or vitamins (A, D, E, and K) are solubilized in olestra and excreted in the feces.

Studies have demonstrated the LDL-lowering effect of plant sterols, which are isolated from soybean and tall pine-tree oils. Ingestion of 2 to 3 g/day will reduce LDL by 6% to 15%.¹ Plant sterols can be esterified to unsaturated fatty acids (creating sterol esters) to increase lipid solubility. Hydrogenating sterols produces plant stanols and, with esterification, stanol esters. The efficacies of plant sterols and stanols are considered comparable. Because lipids are needed to

solubilize stanol/sterol esters, they usually are available in commercial margarines. The presence of plant stanols/sterols is listed on the food label. When margarine products are used, persons must be advised to adjust caloric intake to account for the calories contained in the products. For example, Benecol (McNeil) is a butter-like spread that contains a plant stanol ester, an ingredient that can lower cholesterol, which is derived from plant stanols found naturally in small amounts in foods such as wheat, rye, and corn.⁵² In August 2007, the FDA issued a warning about the consumption of red yeast rice and products containing red yeast rice/policosonal. These products contained lovastatin, which could interact with other drugs and would have the same toxicity of statins but would not be recognized by the consumer. The reduction in LDL with their use is minimal.⁵³

Drug therapy is indicated after an adequate trial of TLC changes as outlined in Tables 23–8 and 23–9.

■ PHARMACOLOGIC THERAPY

Numerous randomized, double-blinded clinical trials have demonstrated that reduction of LDL reduces CHD event rates in primary prevention, secondary intervention, and angiographic trials.⁵⁴ Generally speaking, for every 1% reduction in LDL, there is a 1% reduction in CHD event rates.¹ However, if treatment extends beyond the typical duration of a clinical trial (2–5 years), the accumulated benefit could be greater. A 1% elevation of HDL results in an approximately 2% reduction in CHD events.^{12,55} Of interest, angiographic trials, which typically cause small changes in luminal diameter (i.e., approximately 0.04-mm difference in change between placebo and active treatment), result in fewer clinical events, such as MI, and a decreased need for revascularization. These unexpected findings suggest that plaque size and luminal encroachment by plaque may be less important than the effects of cholesterol lowering on activity in the plaque and endothelial dysfunction. These studies provide a strong rationale for attempting to lower plasma cholesterol and LDL in patients with hypercholesterolemia.

④ Although many efficacious lipid-lowering drugs exist, none is effective for all lipoprotein disorders, and all such agents are associated with some adverse effects.⁵⁶ Lipid-lowering drugs can be broadly divided into agents that decrease the synthesis of VLDL and LDL, agents that enhance VLDL clearance, agents that enhance LDL catabolism, agents that decrease cholesterol absorption, agents that elevate HDL, or some combination of these characteristics (Table 23–11). Table 23–12 lists recommended drugs of choice for each lipoprotein phenotype and alternate agents. Table 23–13 lists available products and their doses.

Treatment of type I hyperlipoproteinemia is directed toward reducing the levels of chylomicrons derived from dietary fat, with subsequent reduction in plasma triglycerides. Total daily fat intake should be no more than 10–25 g/day, or approximately 15% of total calories. Secondary causes of hypertriglyceridemia (see Table 23–5) should be excluded. Any underlying disorder should be treated appropriately. Type V hyperlipoproteinemia also requires stringent restriction of the fat component of dietary intake; in addition, drug therapy is indicated (as outlined in Table 23–12) if the response to diet alone is inadequate. Medium-chain triglycerides, which are absorbed without chylomicron formation, can be used as a dietary supplement for caloric intake if needed for types I and V. Hepatic fibrosis has been reported with medium-chain triglycerides. Omega-3 fatty acids may be useful for patients with LPL deficiency. In patients with apolipoprotein C-II deficiency, infusion of plasma may normalize plasma triglyceride levels.

Primary hypercholesterolemia (familial hypercholesterolemia, familial combined hyperlipidemia, type IIa hyperlipoproteinemia) is treated with bile acid resins (BARs) or sequestrants (colestipol, cholestyramine, and colestevlam), HMG-CoA reductase inhibitors

TABLE 23-11 Effects of Drug Therapy on Lipids and Lipoproteins

| Drug | Mechanism of Action | Effects on Lipids | Effects on Lipoproteins | Comment |
|---|--|---------------------------------|--------------------------|---|
| Cholestyramine, colestipol, colesevelam | ↑ LDL catabolism ↓ Cholesterol absorption | ↓ Cholesterol | ↓ LDL ↑ VLDL | Problem with compliance; binds many coadministered acidic drugs |
| Niacin | ↓ LDL and VLDL synthesis | ↓ Triglyceride ↓ Cholesterol | ↓ VLDL ↓ LDL ↑ HDL | Problems with patient acceptance; good in combination with bile acid resins; extended-release niacin causes less flushing and is less hepatotoxic than sustained-release form |
| Gemfibrozil, fenofibrate, clofibrate | ↑ VLDL clearance ↓ VLDL synthesis | ↓ Triglyceride ↓ Cholesterol | ↓ VLDL ↓ LDL ↑ HDL | Clofibrate causes cholesterol gallstones; modest LDL lowering; raises HDL; gemfibrozil inhibits glucuronidation of simvastatin, lovastatin, atorvastatin |
| Lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin | ↑ LDL catabolism; inhibit LDL synthesis | ↓ Cholesterol | ↓ LDL | Highly effective in heterozygous familial hypercholesterolemia and in combination with other agents |
| Ezetimibe | Blocks cholesterol absorption across the intestinal border | ↓ Cholesterol | ↓ LDL | Few adverse effects; effects additive to other drugs |

HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein.

(statins), niacin, or ezetimibe. ⁵ Of these choices, statins are first choice because they are the most potent LDL-lowering agents. Statins interrupt the conversion of HMG-CoA to mevalonate, the rate-limiting step in de novo cholesterol biosynthesis, by inhibiting HMG-CoA reductase (see Fig. 23-3). Currently available products include lovastatin, pravastatin, simvastatin, fluvastatin, and atorvastatin. Rosuvastatin is the most potent statin currently on the market. Table 23-14 lists the pharmacokinetic properties of the statins.⁵⁷ The plasma half-lives of all the statins are reported to be short, except for atorvastatin and rosuvastatin, which may account for their potency. In the Comparative Dose Efficacy Study of Atorvastatin Versus Simvastatin, Pravastatin, Lovastatin, and Fluvastatin in Patients with Hypercholesterolemia (CURVES), the largest head-to-head comparison of statins, atorvastatin was found to be the most potent drug for lowering total cholesterol and LDL-C, with reductions in LDL-C of 38%, 46%, 51%, and 54% for the 10-, 20-, 40-, and 80-mg doses, respectively.⁵⁸ Metabolic studies of statin use in normal volunteers and patients with hypercholesterolemia suggest reduced synthesis of LDL-C as well as enhanced catabolism of LDL mediated through LDL receptors as the principal mechanisms for lipid-lowering effects. Total cholesterol and LDL-C are reduced in a dose-related fashion by at least 30% on average when added to dietary therapy, with the

effects more pronounced in nonfamilial than in familial hypercholesterolemia. ⁶ Combination therapy with bile acid sequestrants and lovastatin is rational: LDL receptor numbers are increased, leading to greater degradation of LDL-C; intracellular synthesis of cholesterol is inhibited; and enterohepatic recycling of bile acids is interrupted. Combination therapy with a statin pulse ezetimibe also is rational because ezetimibe inhibits cholesterol absorption across the gut border and adds 12% to 20% further reduction when combined with a statin or other drugs.⁵⁹ Elevation of serum transaminase levels (primarily alanine aminotransferase) to more than three times the upper limit of normal occurs in approximately 1.3% of patients taking moderate to high doses of statins; serious muscle toxicity occurs in <0.6% of patients.⁶⁰ Meta-analysis of placebo-controlled studies with statins demonstrated a low risk of abnormal alanine aminotransferase or creatine kinase (CK) and a low risk of myopathy without or with rhabdomyolysis.⁶¹ Lens opacities have been reported with lovastatin. However, in the age groups studied, these abnormalities are common and tend to wax and wane with time irrespective of drug therapy, and no statistical association is known to exist. As a category of monotherapy, the HMG-CoA reductase inhibitors are the most potent total cholesterol and LDL-C-lowering agents and are among the best tolerated.^{60,61} In an analysis of more than 75,000 patients allocated to statins in clinical trials, Alsheikh-Ali et al.⁶² found that risk of statin-associated elevated liver enzymes or rhabdomyolysis was not related to the magnitude of LDL-C lowering. A highly significant inverse relationship between achieved LDL-C levels and rates of newly diagnosed cancer was observed ($R^2 = 0.43$, $P = 0.009$).⁶² The WHO Foundation Collaborating Centre for International Drug Monitoring has issued a report suggesting that a rare relationship may exist between statin use and the onset of upper motor neuron diseases such as amyotrophic lateral sclerosis, but this association remains uncertain.⁶³ Numerous pharmacokinetic and pharmacodynamic differences among statins and patients give rise to variable responses to therapy.⁶⁴

The primary action of BAR is binding bile acids in the intestinal lumen, with concurrent interruption of enterohepatic circulation of bile acids and markedly increased excretion of acidic steroids in the feces. This action decreases the bile acid pool size and stimulates hepatic synthesis of bile acids from cholesterol. Depletion of the hepatic pool of cholesterol results in increased cholesterol biosynthesis and increased number of LDL receptors on the hepatocyte membrane. The increased number of receptors stimulates catabolism from plasma and lowers LDL levels. BAR also reduces CETP, which correlates with total cholesterol and LDL-C concentrations, perhaps by interfering with hepatic microsomal cholesterol content; however,

TABLE 23-12 Lipoprotein Phenotype and Recommended Drug Treatment

| Lipoprotein Type | Drug of Choice | Combination Therapy |
|------------------|------------------------------|---------------------------------------|
| I | Not indicated | — |
| IIa | Statins | Niacin or BAR |
| | Cholestyramine or colestipol | Statins or niacin |
| | Niacin | Statins or BAR |
| IIb | Statins | Ezetimibe |
| | Fibrates | BAR, fibrates, ^b or niacin |
| | Niacin | Statins, niacin, BAR ^a |
| III | Fibrates | Statins or fibrates |
| | Niacin | Ezetimibe |
| IV | Fibrates | Statins or niacin |
| | Niacin | Statins or fibrates |
| V | Fibrates | Ezetimibe |
| | Niacin | Niacin |
| | | Fish oils |

^aBile acid resins (BARs) are not used as first-line therapy if triglycerides are elevated at baseline because hypertriglyceridemia may worsen with BAR alone.

^bFibrates includes gemfibrozil or fenofibrate.

TABLE 23-13 Comparison of Drugs Used in the Treatment of Hyperlipidemia

| Drug | Manufacturer | Dosage Forms | Usual Daily Dose | Maximum Daily Dose |
|---|-------------------------------|--|--|--|
| Cholestyramine (Questran) | BMS | Bulk powder/4-g packets | 8 g tid | 32 g |
| Cholestyramine (Questran Light) | BMS | Bulk powder/4-g packets | | |
| Cholestyramine (Cholybar) | Parke-Davis | 4-g resin per bar | | |
| Colestipol hydrochloride (Colestid) | Upjohn | Bulk powder/5-g packets | 10 g bid | 30 g |
| Colesevelam (WelChol) | Sankyo | 625-mg tablets | 1,875 mg bid | 4,375 mg |
| Niacin | Various | 50-, 100-, 250-, 500-mg tablets; 125-, 250-, 500-mg capsules | 2 g tid | 9 g |
| Extended-release niacin (Niaspan) | Kos | 500, 750, 1,000 mg tablets | 500 mg | 2,000 mg |
| Extended-release niacin + lovastatin (Advicor) ^a | Kos | Niacin/lovastatin 500-mg/20-mg tablets Niacin/lovastatin 750-mg/20-mg tablets Niacin/lovastatin 1,000-mg/20-mg | Niacin/lovastatin 500 mg/20 mg | Niacin/lovastatin 1,000 mg/20 mg tablets |
| Clofibrate | Banner Pharmacaps, USL Pharma | 500-mg capsules | 1 g bid | 2 g |
| Fenofibrate (TriCor and others) | Abbott, various | 67-, 134-, 200-mg capsules (micronized); 54-, 160-mg tablets; 40-, 120-mg tablets; 50-, 160-mg tablets | 54 mg or 67 mg | 201 mg |
| Gemfibrozil (Lopid) | Parke-Davis | 300-mg capsules | 600 mg bid | 1.5 g |
| Lovastatin (Mevacor) | MSD | 20-, 40-mg tablets | 20–40 mg | 80 mg |
| Pravastatin (Pravachol) | Bristol-Myers Squibb | 10-, 20-mg tablets | 10–20 mg | 40 mg |
| Simvastatin (Zocor) | MSD | 5-, 10-, 20-, 40- and 80-mg tablets | 10–20 mg | 80 mg |
| Atorvastatin (Lipitor) | Pfizer | 10-mg tablets | 10 mg | 80 mg |
| Rosuvastatin (Crestor) | Astra-Zeneca | 5- and 10-mg tablets | 5 mg | 40 mg |
| Ezetimibe (Zetia) | MSD | 10-mg tablets | 10 mg | 10 mg |
| Atorvastatin/amlodipine (Caduet) | Pfizer | Atorvastatin/amlodipine 10 mg/5 mg Atorvastatin/amlodipine 20 mg/5 mg Atorvastatin/amlodipine 40 mg/5 mg Atorvastatin/amlodipine 80 mg/5 mg Atorvastatin/amlodipine 10 mg/10 mg Atorvastatin/amlodipine 20 mg/10 mg Atorvastatin/amlodipine 40 mg/10 mg Atorvastatin/amlodipine 80 mg/10 mg | Atorvastatin/amlodipine 10 mg/5 mg | Atorvastatin/amlodipine 80 mg/10 mg |
| Pravastatin/aspirin (Pravigard PAC) | BMS | Pravastatin/aspirin 20 mg/81 mg Pravastatin/aspirin 20 mg/325 mg Pravastatin/aspirin 40 mg/81 mg Pravastatin/aspirin 40 mg/325 mg Pravastatin/aspirin 80 mg/81 mg Pravastatin/aspirin 80 mg/325 mg | | |
| Simvastatin/ezetimibe (Vytorin) | Merck/Schering-Plough | Simvastatin/ezetimibe 10 mg/10 mg Simvastatin/ezetimibe 20 mg/10 mg Simvastatin/ezetimibe 40 mg/10 mg | Simvastatin/ezetimibe 20 mg/10 mg | Simvastatin/ezetimibe 40 mg/10 mg |
| ω-3 Acid ethyl esters (Lovaza) | Reliant | Eicosapentaenoic acid (EPA) 465 mg, docosahexaenoic acid (DHA) 375 mg | Four 1-g capsules QD or two 1-g capsules bid | Four 1-g capsules QD or two 1-g capsules bid |

BMS, Bristol-Myers Squibb; MSD, Merck Sharp & Dohme.

Probuco is no longer on the market in the United States. Gemfibrozil, fenofibrate, and lovastatin are available as generic products.

^aManufacturer does not recommend use of the fixed combination as initial therapy for primary hypercholesterolemia or mixed dyslipidemia. It is specifically indicated for patients receiving lovastatin alone plus diet who require an additional reduction in triglyceride levels or increase in HDL-cholesterol levels; it also is indicated for those treated with niacin alone who require additional decreases in LDL cholesterol.

this effect is not as great as with statins.⁶⁵ BARs are generally ineffective in patients with homozygous familial hypercholesterolemia because these individuals genetically lack the ability to increase synthesis of LDL receptors. The increase in hepatic cholesterol biosynthesis may be paralleled by increased hepatic VLDL production; consequently, BARs may aggravate hypertriglyceridemia in patients with combined hyperlipidemia. Gastrointestinal complaints of con-

stipation, bloating, epigastric fullness, nausea, and flatulence are most commonly reported.¹ With intensive education, patients can learn to tolerate resins on a long-term basis, as evidenced in clinical trials by adherence to active drug regimens. In routine clinical practice, at least 40% of patients discontinue therapy within 1 year, but adherence rates can be improved with pharmacist interventions.^{66,67} Adverse effects can be managed by increasing fluid intake, modifying the diet

TABLE 23-14 Pharmacokinetics of the Statins

| Parameter | Lovastatin | Simvastatin | Pravastatin | Fluvastatin | Atorvastatin | Rosuvastatin |
|---------------------------|------------|-------------|-------------|-------------|--------------|--------------|
| Isoenzyme | 3A4 | 3A4 | None | 2C9 | 3A4 | 2C9/2C19 |
| Lipophilic | Yes | Yes | No | Yes | Yes | No |
| Protein binding (%) | >95 | 95–98 | ~50 | >90 | 96 | 88 |
| Active metabolites | Yes | Yes | No | No | Yes | Yes |
| Elimination half-life (h) | 3 | 2 | 1.8 | 1.2 | 7–14 | 13–20 |

Isoenzyme refers to the specific isoenzyme in the cytochrome P450 system, which is responsible for the metabolism of each drug. Pharmacokinetic parameters in this table are based on studies and reviews presented in the literature.

to increase bulk, and using stool softeners. The other major limiting complaint with BARs is their gritty texture and bulk. This problem can be minimized by mixing the powder with orange drink or juice. Tablet forms of bile acid sequestrants should help to improve compliance with this form of therapy, whereas the bar does not improve compliance.⁶⁸ Other potential adverse effects include impaired absorption of fat-soluble vitamins A, D, E, and K; hypernatremia and hyperchloremia; gastrointestinal obstruction; and reduced bioavailability of acidic drugs such as coumarin anticoagulants, digitoxin, nicotinic acid, thyroxine, acetaminophen, hydrocortisone, hydrochlorothiazide, loperamide, and possibly iron. Hyperchloremic metabolic acidosis, hypernatremia, and gastrointestinal obstruction have been reported to occur almost exclusively in children, and malabsorption of fat-soluble vitamins probably is most common with high doses (e.g., 30 g/day of cholestyramine) of the BARs. Drug interactions can be avoided by alternating administration times, with an interval of at least 6 hours between the BAR and other drugs. Colestipol and cholestyramine have comparable side effects; however, colestipol may have better palatability because it is odorless and tasteless. Colesevelam is the newest BAR, and total and LDL-C reduction are dose related. Adverse effects are qualitatively similar to those occurring with the older BARs but may occur less often. Because of adverse effects that occur commonly with BARs at higher doses, BARs are increasingly used in combination with other drugs because low doses are tolerated well, and the BARs work in complementary fashion with other agents.

Niacin (nicotinic acid) can be used for treatment of primary hypercholesterolemia in combination with bile acid sequestrants or as monotherapy for this and other disorders (Table 23–12). Niacin reduces hepatic synthesis of VLDL, which in turn leads to reduced synthesis of LDL. Factors responsible for decreased VLDL production include inhibition of lipolysis with decreased free fatty acids in plasma, decreased hepatic esterification of triglycerides, and a possible direct effect on hepatic production of apolipoprotein B.⁶⁹ The complementary action of niacin and bile acid sequestrants in increasing catabolism and decreasing LDL synthesis may account for the additive effects of this combination in patients with hyperlipidemia. Niacin also increases HDL by reducing its catabolism. Niacin selectively decreases hepatic removal of HDL apolipoprotein A-I but not removal of cholesterol esters, thereby increasing the capacity of retained apolipoprotein A-I to augment reverse cholesterol transport in isolated hepatic cells. Niacin is used principally for treatment of mixed hyperlipidemia or as a second-line agent in combination therapy for hypercholesterolemia. It is considered the first-line agent or an alternative for treatment of hypertriglyceridemia and diabetic dyslipidemia.^{70,71} Numerous smaller trials suggest that lower doses of niacin can be combined with statins or gemfibrozil to minimize adverse effects and maximize response. These combinations require careful monitoring because interactions occur.

Many adverse drug reactions occur commonly with niacin use, but most of the symptoms and biochemical abnormalities do not require discontinuation of therapy. Cutaneous flushing and itching appear to be prostaglandin mediated and can be reduced by aspirin 325 mg given shortly before niacin ingestion.^{1,72} Flushing seems to be related to rising plasma concentrations of niacin; taking the dose with meals and slowly titrating the dose upward may minimize these effects. Laropiprant is a selective antagonist of the prostaglandin D₂ receptor subtype 1 (DP1), which may mediate niacin-induced vasodilation. Coadministration of laropiprant 30, 100, and 300 mg with extended-release (ER) niacin significantly lowered flushing symptom scores (by at least 50%) and significantly reduced malar skin blood flow measured by laser Doppler perfusion imaging.⁷³ Gastrointestinal intolerance and flushing are common problems. Acanthosis nigricans, a darkening of the skin in skinfold areas and an external marker of insulin resistance, may be seen with high doses of niacin. Sustained-

release products may minimize these complaints in some patients, but controlled trials with regular-release products do not demonstrate much difference between sustained- and regular-release products. The only legend form of niacin, Niaspan (Kos), is an extended-release form of niacin with pharmacokinetics intermediate between instant and sustained-release products, which are sold as food supplements rather than legend products. In controlled trials, Niaspan is reported to have fewer dermatologic reactions and a low risk for hepatotoxicity. Niaspan in combination with statins produces large reductions in LDL and increases in HDL.⁷⁴ Potentially important laboratory abnormalities occurring with niacin therapy include elevated liver function tests, hyperuricemia, and hyperglycemia. Experience with niacin in diabetes suggests that some diabetic patients do not have worsened glycemic control with dose-titration and sustained-release products.⁷⁵ With doses less than 3 g/day, the degree of liver function test elevation generally is not marked and often is transient, and a temporary reduction in dosage frequently corrects the problem. Niacin-associated hepatitis is more common with sustained-release preparations, and their use should be restricted to patients intolerant of regular-release products.^{75,76} Sustained-release products often are more expensive and, given the lack of data on reduced adverse effects and increased incidence of hepatitis, regular-release products should always be used first. Preexisting gout and diabetes may be exacerbated by niacin; patients with these conditions should be monitored more closely and their medication titrated appropriately. Patients with well-controlled diabetes mellitus type 2 do not have significant changes in glycemic control with niacin doses up to 2 g/day.⁷⁶ Niacin is contraindicated in patients with active liver disease. Dry eyes and other ophthalmologic complaints are occasionally noted. Concomitant alcohol and hot drinks may magnify flushing and pruritus with niacin and should be avoided at the time of ingestion. Nicotinamide should not be used for treatment of hyperlipidemia because it does not effectively lower cholesterol or triglyceride levels.

Combined hyperlipoproteinemia (type IIb) can be treated with statins, niacin, or gemfibrozil to lower LDL-C without elevating VLDL and triglycerides. Niacin is the most effective agent and can be combined with a bile acid sequestrant. BARs alone for treatment of this disorder may elevate VLDL and triglycerides, and their use as single agents for treatment of combined hyperlipoproteinemia should be avoided. Fibric acid (gemfibrozil, fenofibrate) monotherapy is effective in reducing VLDL, but a reciprocal rise in LDL may occur, and total cholesterol values may remain relatively unchanged. Gemfibrozil reduces synthesis of VLDL and, to a lesser extent, apolipoprotein B, with a concurrent increase in the rate of removal of triglyceride-rich lipoproteins from plasma. Plasma HDL concentrations may rise 10% to 15% or more with fibrates. Ezetimibe also can be used in combination therapy for type IIb disease. Gastrointestinal complaints with fibric acid derivatives occur in 3% to 5% of patients, rash in 2%, dizziness in 2.4%, and transient elevations in transaminase levels and alkaline phosphatase in 4.5% and 1.3%, respectively.⁷⁷ Gemfibrozil and fenofibrate may enhance the formation of gallstones associated with an increase in the lithogenic index; however, the rate is low (0.5%–7%) and similar to that seen with placebo in the Helsinki Heart Study.⁷⁷ Fibric acid derivatives may potentiate the effects of oral anticoagulants, so prothrombin time and international normalized ratio should be monitored very closely when this combination is used.

Type III hyperlipoproteinemia can be treated with fibric acid derivatives or niacin. Although fibric acid derivatives have been suggested as the drugs of choice for treatment of this disorder, the lack of data from major studies on hypercholesterolemia supporting their efficacy in altering cardiovascular mortality and the numerous, well-documented serious adverse effects occurring with their use make niacin a reasonable consideration. Gemfibrozil increases the

activity of LPL and reduces the synthesis or secretion of VLDL from the liver into the plasma. A myositis syndrome of myalgia, weakness, stiffness, malaise, and elevations in creatinine phosphokinase and aspartate aminotransaminase is seen with the fibric acid derivatives and seems to be more common in patients with renal insufficiency.⁷⁷ Enhanced hypoglycemic effects are reported to occur when fibric acid derivative are given to patients taking sulfonylurea compounds, but the mechanisms for these interactions are not well understood.

Three fibric acid derivatives (clofibrate, gemfibrozil, and fenofibrate) are approved for use in the United States. Gemfibrozil and fenofibrate are used much more commonly than clofibrate. All reduce LDL-C by 20% to 25% in patients with heterozygous familial hypercholesterolemia. The response of LDL-C, HDL-C, and triglycerides to this category of drug is highly dependent on the specific lipoprotein type (e.g., type IIa vs IIb) and the baseline triglyceride concentration.⁷⁸

As a potential alternative therapy for this phenotype, numerous epidemiologic and normal volunteer studies have found that diets high in omega-3 polyunsaturated fatty acids (from fish oil), mostly commonly eicosapentaenoic acid, reduce cholesterol, triglycerides, LDL-C, and very-low-density lipoprotein cholesterol (VLDLC) and may elevate HDL-C.⁵¹ The effects of fish oil on lipoprotein metabolism are mediated by a reduction in VLDL production and suppression of VLDL apolipoprotein B. In patients with hypertriglyceridemia (either phenotype type IIb or V), a diet high in omega-3 fatty acids given for 4 weeks reduced cholesterol 27% and 45% and triglyceride 64% and 79% in the type IIb and type V patients, respectively.⁴⁹ A diet high in eicosapentaenoic acid given to hyperlipidemic hemodialysis patients resulted in significant decreases in cholesterol and triglycerides for as long as 13 weeks. Fish oil supplementation may be most useful in patients with hypertriglyceridemia; however, its role in treatment is not well defined. Potential complications of fish oil supplementation, such as thrombocytopenia and bleeding disorders, have been noted, especially with high doses (eicosapentaenoic acid 15–30 g/day). Well-controlled trials are needed to determine if fish oils are safe and effective before their use can be broadly recommended. Based a meta-analysis, fish consumption lowers the risk of CHD, but nutraceuticals have not been adequately tested.⁴⁹ A prescription form of concentrated fish oil, Lovaza, has become available.⁵¹ This product lowers triglycerides by 14% to 30% and raises HDL by approximately 10%, depending on baseline values.

Combination drug therapy may be considered after adequate trials of monotherapy and for patients who are documented as compliant to the prescribed regimen. Two or three lipoprotein profiles at 6-week intervals should confirm lack of response prior to initiation of combination therapy. Cholestyramine can be added for patients with fasting hypertriglyceridemia but should not be used as the initial drug because triglycerides are likely to increase. Contraindications to, and drug interactions with, combined therapy should be carefully screened. Consideration should be given to the extra cost of drug product and monitoring that may be required. In general, a statin and a BAR or niacin with a BAR provide the greatest reduction in total cholesterol and LDL-C. Regimens intended to increase HDL levels should include either gemfibrozil or niacin, bearing in mind that statins combined with either of these drugs may result in a greater incidence of hepatotoxicity or myositis. This is particularly important for statins that are eliminated via cytochrome 3A4 or through glucuronidation.⁵⁷ Familial combined hyperlipidemia may respond better to a fibric acid and a statin than to a fibric acid and a BAR.⁷⁹

Severe forms of hypercholesterolemia, such as familial hypercholesterolemia, familial defective apolipoprotein B-100, severe polygenic hypercholesterolemia, familial combined hyperlipidemia, and familial dysbetalipoproteinemia (type III), may require more intensive therapy. In particular, patients with familial hypercholesterol-

emia often require combination therapy (two or three drugs) and are managed with surgical therapy (partial ileal bypass), plasmapheresis (LDL apheresis), and liver transplantation (to replace LDL receptors).

■ HYPERTRIGLYCERIDEMIA

It is important to remember that lipoprotein pattern types I, III, IV, and V are associated with hypertriglyceridemia, and that these primary lipoprotein disorders and underlying diseases should be excluded prior to implementing therapy (see Table 23–5). A family history positive for CHD is important in identifying patients at risk for premature atherosclerosis.^{80,81} If a patient with CHD has elevated triglycerides, the associated abnormality probably is a contributing factor to CHD and should be treated.²⁹

High serum triglycerides (see Tables 21–6 and 21–12) should be treated by achieving desirable body weight, consumption of a diet low in saturated fat and cholesterol, regular exercise, smoking cessation, and restriction of alcohol (in selected patients). ATP III identifies the sum of LDL and VLDL (termed *non-HDL* [total cholesterol – HDL]) as a secondary target of therapy in persons with high triglycerides (≥ 200 mg/dL).^{1,29} This approach is used when triglycerides are >200 mg/dL and accounts for atherogenic particles carried in VLDL and remnant particles. The goal for non-HDL in persons with high serum triglycerides can be set 30 mg/dL higher than that for LDL on the premise that VLDL ≤ 30 mg/dL is normal. **7** In patients with borderline-high triglycerides but accompanying risk factors for established CHD disease, family history of premature CHD, concomitant LDL elevation or low HDL, and genetic forms of hypertriglyceridemia associated with CHD (familial dysbetalipoproteinemia, familial combined hyperlipidemia), drug therapy with niacin should be considered. Niacin can be used cautiously in diabetics based on the results of the Arterial Disease Multiple Intervention Trial (ADMIT), which found triglycerides were reduced by 23%, HDL-C increased by 29%, glucose increased only slightly (mean 8.7 mg/dL), and hemoglobin A_{1c} did not change.⁸² Alternative therapies include gemfibrozil, statins, and fish oil.^{81,83,84} Fibrates may increase LDL, and their use in borderline-high triglyceridemia requires careful monitoring to detect this deleterious change in lipid profile. Statins also can be used because they provide modest reductions in triglycerides and modest elevations in HDL. Higher doses of statins may reduce HDL as well as LDL and triglycerides, with the amount of reduction related to the baseline concentration and dose.^{81,84} In this situation, the goal of therapy is to lower triglycerides and VLDL particles that may be atherogenic, increase HDL, and reduce LDL.

Very high triglycerides are associated with pancreatitis and other consequences of the chylomicron syndrome. At this level of triglycerides elevation, a genetic form of hypertriglyceridemia often coexists with other causes of elevated triglycerides, such as diabetes. Dietary fat restriction (10%–20% of calories as fat), weight loss, alcohol restriction, and treatment of the coexisting disorder are the basic elements of management. Drugs useful for treatment of hypertriglyceridemia include gemfibrozil, niacin, and higher-potency statins (atorvastatin, rosuvastatin, and simvastatin). Gemfibrozil is the preferred drug in diabetics because of the effect of niacin on glycemic control unless the newer extended-release forms are used. Fenofibrate may be preferred in combination with statin therapy because it does not impair glucuronidation and minimizes potential drug interactions. Successful treatment is defined as a reduction in triglycerides <500 mg/dL.¹

■ LOW HDL-C

Low HDL is a strong independent risk predictor of CHD. ATP III redefined low HDL-C as <40 mg/dL but specified no goal for HDL-C

raising.¹ Low HDL may be a consequence of insulin resistance, physical inactivity, type 2 diabetes mellitus, cigarette smoking, very high carbohydrate intake, and certain drugs (see Table 23–5).⁸ In low HDL, the primary target remains LDL according to ATP III, but emphasis shifts to weight reduction, increased physical activity, smoking cessation, and, if drug therapy is required, fibric acid derivatives and niacin. Niacin has the potential for the greatest increase in HDL, and the effect is more pronounced with regular or immediate-release forms than with sustained-release forms.⁸⁵

■ DIABETIC DYSLIPIDEMIA

Diabetic dyslipidemia is characterized by hypertriglyceridemia, low HDL, and LDL that is minimally elevated. Small, dense LDL (pattern B) in diabetes is more atherogenic than larger, more buoyant forms of LDL (pattern A). Routine lipoprotein profiles do not differentiate between pattern A and pattern B.^{86–88} Diabetes in ATP III is a CHD risk equivalent. The primary target is LDL, and the goal of treatment is to lower LDL-C to <100 mg/dL.¹ When LDL is >130 mg/dL, most patients require simultaneous therapeutic lifestyle changes and drug therapy. When LDL-C is between 100 and 129 mg/dL, intensifying glycemic control, options include adding drugs for the atherogenic dyslipidemia (fibrates, niacin), and intensifying LDL-C-lowering therapy. Because the primary target is LDL-C in patients with diabetic dyslipidemia, statins are considered by many to be the initial drugs of choice.^{1,29} The relative risk reduction for CHD in diabetics versus nondiabetics was greater in several trials, including the West of Scotland Coronary Prevention Study (37% vs 20%),⁸⁹ Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS; 43% vs 36%),⁹⁰ Cholesterol and Recurrent Events (CARE) trial (25% vs 23%),⁹¹ and Scandinavian Simvastatin Survival Study (4S; 55% vs 32%).⁹² All statins are fairly comparable in triglyceride lowering, and because statins differ in potency for LDL reduction, a ratio of LDL reduction to triglyceride reduction can be applied. Statin therapy may protect against the development of diabetes.²⁶ The most recent trial of LDL lowering in type 2 diabetes mellitus is the Collaborative Atorvastatin Diabetes Study (CARDS).⁹³ This was a randomized, double-blinded placebo comparison of atorvastatin 10 mg/day versus placebo in 2,838 diabetes to reduce first CHD events. Baseline LDL was 118 mg/dL, and with atorvastatin LDL fell by 46 mg/dL. The primary end point, a composite of acute CHD death, nonfatal MI, hospitalized unstable angina, resuscitated cardiac arrest, coronary revascularization, or stroke, was reduced by 37%. This study suggests that all diabetics should have LDL much lower than 100 mg/dL, and these results are consistent with the Heart Protection Study analysis of diabetic patients.⁹⁴

According to the Diabetes Atherosclerosis Intervention Study (DAIS), fenofibrate reduced angiographic progression of CAD in type 2 diabetics.⁹⁵ Fewer CHD events were seen with fenofibrate compared with placebo, but the difference was not significant. Fibrates principally lower VLDL and triglycerides while increasing HDL, with only modest lowering of total cholesterol and LDL-C. Fibrates may increase LDL levels. In contrast to niacin, fibrates tend to improve glucose tolerance, with the greatest effect seen with bezafibrate. The Helsinki Heart Study found gemfibrozil was most effective for diabetic dyslipidemia.⁹⁶ Although the effect of statins on triglycerides and HDL abnormalities commonly seen in patients with diabetes is less than with fibrates, the subgroup analyses cited earlier suggest that these drugs significantly reduce CHD risk. Cholestyramine in diabetic patients may result in lower LDL levels but may increase VLDL and triglyceride levels, which already are commonly elevated in diabetes. Resins may aggravate constipation, which is common in diabetics. As demonstrated in ADMIT and in the Assessment of Diabetes Control and Evaluation of the Efficacy of Niaspan Trial (ADVENT), immediate-release and extended-release niacin are highly effective in raising HDL and lowering triglycerides and LDL.^{82,97}

■ SPECIAL CONSIDERATIONS

Elderly

Hypercholesterolemia is an independent risk factor for CHD in the elderly (>65 years old) as it is in younger patients. The attributable risk, which is the difference in absolute rates of CHD between segments of the population with higher or lower serum cholesterol levels, increases with age. Older patients potentially benefit to a greater extent from cholesterol lowering than do younger patients. Data from studies of elderly men in a variety of settings are consistent with a relative risk of at least 1.5 in the highest compared to the lowest quartile of cholesterol levels.^{98,99} Treatment of hypercholesterolemia in the elderly may result in reduction of absolute risk comparable to that obtained in younger persons.¹ Subgroup analyses of the West of Scotland (primary) and 4S (secondary) intervention studies show that elderly patients had lower CHD risk reduction (relative risk reduction 27% and 29%, respectively) compared to younger patients (relative risk reduction 40% and 39%, respectively).^{89,100} The Framingham study suggests that elderly women are at higher risk because of high blood cholesterol levels, but no other large studies included women, and the risks or benefits from cholesterol reduction are not well defined. Primary prevention in younger patients requires approximately 2 years before reduction in CHD risk is apparent, and this lag time should be taken into consideration during patient selection for therapy. Relative risk of nonlipid CHD risk factors does not decline with aging, and aggressive management of modifiable nonlipid risk factors is important in older patients. High-risk elderly patients are less likely to be prescribed statins, and their potent benefits are not realized.¹⁰¹ Because most women with CHD are elderly and at risk for osteoporosis, they are logical candidates for diet therapy with consideration of calcium intake consistent with osteoporosis prevention, exercise, and perhaps estrogen replacement therapy. Evidence suggests that statins reduce the risk of osteoporosis; however, data from various studies are conflicting.¹⁰²

Drug therapy in principle differs little between older and younger patients, and older patients respond as well as younger patients to lipid-lowering drugs.^{103,104} Based on the Heart Protection Study, which comprised more elderly patients than any other trial, simvastatin 40 mg/day reduced the CHD event rate in patients older than 70 years the same as in younger patients.¹⁰⁵ The gain in life expectancy may be small, depending on the patient's age at the start of treatment and the magnitude of cholesterol reduction.⁸² Changes in body composition, renal function, and other physiologic changes of aging may make older patients more susceptible to adverse effects of lipid-lowering drug therapy. In particular, older patients are more likely to have constipation (BARs), skin and eye changes (niacin), gout (niacin), gallstones (fibrates), and bone/joint disorders (fibrates, statins). Therapy should be started with lower doses and titrated up slowly to minimize adverse effects.

Women

Cholesterol is an important determinant of CHD in women, but the relationship is not as strong as that seen in men. HDL may be a more important predictor of disease in women.⁴ LDL and HDL genetic regulation in women and men does not appear to be different. Based on the Nurses' Health Study, obesity is an important determinant of CHD in women, with a relative risk of 3.3 in the highest Quetelet index (weight in kilograms divided by the square of the height in meters) compared to the lowest category (i.e., <21 vs ≥29); low HDL levels usually accompany obesity.¹⁰⁶ No major differences exist in the influence of exercise, alcohol ingestion, and smoking on lipid levels between men and women. Women in the highest tertile of cholesterol appear to be more responsive to dietary therapy than women in the lower tertiles and more responsive than predicted using formulas based on men.

Based on the Heart and Estrogen/Progestin Replacement Study (HERS)¹⁰⁷ and the Women's Health Initiative (WHI) trial,^{108–110} published national guidelines recommended similar types of lifestyle and risk factor goals and interventions as recommended by NCEP for the entire population.⁴ Hormone therapy may continue to have a role for treatment of postmenopausal symptoms; however, a notable exception is hormone replacement therapy and heart protection. Combined estrogen plus progestin hormone therapy for prevention of cardiovascular disease should not be initiated in postmenopausal women. Combined estrogen plus progestin hormone therapy for prevention of cardiovascular disease should not be continued in postmenopausal women. Other forms of menopausal hormone therapy (e.g., unopposed estrogen) for prevention of cardiovascular disease should not be initiated or continued in postmenopausal women pending the results of ongoing trials. Results of the Women's International Study of Long Duration Oestrogen after Menopause (WISDOM) confirm the lack of benefit seen in HERS and WHI.¹¹¹ In a post hoc analysis of the WHI, women who initiated hormone therapy closer to menopause tended to have a reduced CHD risk compared with the increased CHD risk in women more distant from menopause, but this trend did not meet statistical significance.¹⁰⁸

Cholesterol and triglyceride levels rise progressively throughout pregnancy, with an average increment in cholesterol of 30 to 40 mg/dL occurring around weeks 36 to 39. Triglyceride levels may increase by as much as 150 mg/dL. Drug therapy is not instituted, nor is it usually continued during pregnancy. If the patient is very high risk, a bile acid resin may be considered because no systemic drug exposure occurs.¹ Statins are category X and are contraindicated. Ezetimibe might be an alternative because it is a category C drug (animal studies have shown that the drug exerts teratogenic and embryocidal effects, no adequate and well-controlled studies in pregnant women are available, or no studies are available in either animals or pregnant women). Dietary therapy is the mainstay of treatment, with emphasis on maintaining a nutritionally balanced diet per the needs of pregnancy.

Children

Drug therapy in children is not recommended until they are 10 years and older, and the guidelines for institution of therapy and the goals of therapy are different from those in adults (see Table 23–9).³³ Younger children are generally managed with therapeutic lifestyle changes until after age 2 years.^{1,44} In the past bile acid sequestrants were recommended as first-line therapy, but evidence now shows that statins are safe and effective in children and provide greater lipid lowering than BAR.^{38,112,113} Severe forms of hypercholesterolemia (e.g., familial hypercholesterolemia) may require more aggressive treatment.

■ CONCURRENT DISEASE STATES

Nephrotic syndrome, end-stage renal disease and nephrotic syndrome, and hypertension compound the risk of dyslipidemia and may present difficult-to-treat lipid abnormalities. Abnormalities of lipoprotein metabolism in the nephrotic syndrome include elevated total and LDL-C, lipoprotein(a), VLDL, and triglycerides. The ratio of apolipoprotein C-III to apolipoprotein C-II is elevated, consistent with greater LPL inhibitor activity, and the extent of hypoalbuminemia is correlated with dyslipidemia. The basic abnormality appears to be overproduction of LDL apolipoprotein B from VLDL rather than reduced clearance of LDL-C and related proteins. Protein restriction and a “vegan” diet corrects lipid abnormalities to some extent. Statins have been shown to be effective in reducing elevated total cholesterol and LDL-C in the nephrotic syndrome, although the levels do not usually return to normal.¹¹⁴ Fibric acid derivatives and statins reduce small, dense LDL-C by different

mechanisms, suggesting a potential role for combination therapy in optimizing the lowering of small, dense LDL-C and remnant lipoproteins. Statins appear to be safe and effective in renal insufficiency and may alter the natural course of declining renal function.^{115–119}

Renal insufficiency without proteinuria leads to hypertriglyceridemia, slightly elevated total cholesterol and LDL-C (particularly with chronic ambulatory peritoneal dialysis), and low HDL levels (especially during hemodialysis). These abnormalities are thought to be caused by a deficiency in apolipoprotein C-II, perhaps as a result of sustained use of heparin during hemodialysis and depletion of LPL, carbohydrate-induced obesity and hypertriglyceridemia, loss of carnitine during hemodialysis, use of acetate buffer (acetate is a precursor to fatty acid synthesis) during hemodialysis, and decreased LCAT activity during hemodialysis. Dialysis does not correct the lipid abnormalities. Renal transplantation may correct lipid abnormalities in some patients; however, use of transplantation-related medications, such as corticosteroids, cyclosporine, and certain antihypertensive agents (see Chaps. 15 and 92), may aggravate the lipid abnormalities in other patients. Cyclosporine interferes with the metabolism of statins metabolized by cytochrome P450 3A4 (Table 23–14), and patients must be observed closely for myositis and worsening renal function. Of interest, correction of lipid abnormalities may improve renal hemodynamics. Pravastatin and fluvastatin may be safer than other statins, but this must be validated in larger, long-term trials. Diet will modify lipoprotein levels, and polyunsaturated fatty acids may have a role in impeding the progression of renal disease as well as the cardiovascular complications. Bile acid sequestrants do not correct the lipid abnormalities seen in renal insufficiency. Lovastatin or its active metabolite may accumulate in renal insufficiency, and lower doses of reductase inhibitors should be used to avoid adverse effects. Gemfibrozil can be used with caution; its pharmacokinetics are unchanged and it lowers triglycerides and increases HDL.¹²⁰ Statins (simvastatin, lovastatin and atorvastatin) and fibric acid derivatives may increase the risk of severe myopathy, and attention to symptoms of myositis is needed. Niacin may be useful in nondiabetic patients with renal insufficiency.

Hypertensive patients have a greater-than-expected prevalence of high blood cholesterol levels; conversely, patients with hypercholesterolemia have a higher than expected prevalence of hypertension caused by the metabolic syndrome. Recommendations for management of hypertension in patients with hypercholesterolemia include avoiding use of drugs that elevate cholesterol, such as diuretics and β -blockers, and using agents that either are lipid neutral or may reduce cholesterol slightly (see Chap. 15).¹ Bile acid sequestrants may bind to thiazide diuretics and some β -blockers and may interfere with their absorption. Reactions may be avoided by giving the antihypertensive 1 hour before or 4 hours after the resin. Niacin may magnify the hypotensive effects of vasodilators.

■ PHARMACOECONOMIC CONSIDERATIONS

The clinical benefits of lipid-lowering therapy for primary and secondary intervention are well established based on the results of studies showing a reduction in CHD morbidity and mortality.^{121,122} The balance of benefits and costs has been examined in a few studies.^{82,95} The cost per year of life saved has been estimated to range from less than \$10,000 to more than \$1 million dollars, depending on the presence or absence of CHD, patient's age, baseline total or LDL-C level, reduction in cholesterol, and number of risk factors present. **9** Intervention with statin therapy in general is cost effective in patients with known CHD, with CHD risk equivalents, or with a 10-year risk of 10% to 20%. Other types of therapy may be cost effective if certain assumptions concerning compliance and efficacy are met. Based on 4S, the range for secondary intervention is \$3,800 for a 70-year-old man with a high cholesterol level to \$27,400 per year of life gained for a middle-aged woman with an average

cholesterol level.¹²³ In contrast, primary prevention in men based on the West of Scotland trial averages about \$35,000 per year of life gained.¹²⁴ These studies demonstrate that primary and secondary intervention are well within the accepted boundary of less than \$50,000 for a medical intervention to be considered cost effective. Based on the specific lipoprotein phenotype, fibric acid derivatives, niacin, or combination therapy of statins plus BAR may be cost effective. Cost effectiveness is maximized by treating high-risk patients and those with established CHD.

Specialty lipid clinics have become increasingly popular, and many use pharmacists to provide direct patient care in this setting. An interesting analysis showed that a specialty clinic may be more expensive (\$659 ± \$43 vs \$477 ± \$42 per patient, $P < 0.001$) than usual care. However, the overall cost effectiveness is improved when expressed as program costs per unit (mmol/L) reduction in the LDL-C, a measure of cost effectiveness that was significantly lower for specialized care (\$758 ± \$58 vs \$1,058 ± \$70, $P = 0.002$) because more patients achieve their targeted goal.¹²⁵ Project IMPACT (Improve Persistence and Compliance with Therapy) demonstrated that pharmacists, working collaboratively with patients and physicians, can improve persistence and compliance, and that nearly two thirds of patients achieved their NCEP lipid goal.¹²⁶ Other programs showed similar trends.^{67,127,128}

■ OTHER THERAPIES

Partial ileal bypass has been used for treatment of severe heterozygous and homozygous familial hypercholesterolemia; however, it is ineffective in the latter case. Ileal bypass removes the site of bile acid reabsorption, depleting the bile acid pool and increasing the catabolism of cholesterol. The Program on the Surgical Control of the Hyperlipidemias (POSCH), a randomized trial of diet versus surgery, reported that total cholesterol and LDL-C were decreased (23.3% and 37.7%, respectively) and HDL increased (4.3%) in patients who had undergone ileal bypass for hypercholesterolemia.⁹⁷ Surgery delayed overall death by nearly 3 years ($P = 0.032$) and delayed CHD mortality by nearly 4 years ($P = 0.046$) compared to the control group. Revascularization procedures were delayed by an average of 7 years ($P < 0.001$). Postsurgery diarrhea was more common in the surgical group, as were the rates of kidney stones (4% vs 0.4%), gallstones (10% vs 2%), and bowel obstruction (13.5% vs 3.6%).

Portacaval shunts have been used to decrease the formation of LDL-C, with reported reductions of 10% to 20%. Plasma exchange

combined with niacin was found to reduce plasma cholesterol levels by approximately 50% over 5 years in patients with homozygous familial hypercholesterolemia, and coronary atherosclerosis did not progress as documented by angiography. LDL apheresis (i.e., selective removal of LDL-C via a filtering system) plus statin therapy is effective in lowering LDL-C and appears to affect the progression of vascular disease. Combined liver and heart transplantation in patients with homozygous familial hypercholesterolemia reduced total cholesterol and LDL-C concentrations from approximately 1,100 and 900 mg/dL before surgery to approximately 300 and 185 mg/dL after surgery, respectively. Liver transplantation replaced the missing LDL receptors, enhanced catabolism, and reduced lipoprotein synthesis in this patient population.

■ SUMMARY OF MAJOR STUDIES

10 Primary and secondary prevention diet and drug trials have been performed to determine whether lowering cholesterol levels will prevent CHD. These trials are summarized in Tables 23–15 and 23–16. A number of earlier angiographic studies demonstrated that cholesterol reduction led to regression of atherosclerosis and plaque stabilization. Most of the primary and secondary studies were double blinded, randomized, and placebo controlled, lasted for at least 5 years, and had sufficient patient numbers to be meaningful. Exceptions to these qualifications were seen in the early studies, such as the Newcastle and Edinburgh trials, which were small and generally did not show much benefit; and the Coronary Drug Project (CDP), using dextrothyroxine, which was terminated early because of observed adverse effects on CHD mortality. The Helsinki Heart Study, using gemfibrozil, resulted in a reduction in nonfatal MI, which was the primary contributor to reduced CHD incidence (Table 23–15).¹⁴

Total cholesterol and LDL-C were reduced an average of 13.4% and 20.3%, respectively, by cholestyramine in the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT). The reduction of lipid levels was related to the amount of drug ingested (5.4% reduction in total cholesterol with 1–2 packets vs 19.0% reduction with ≥5 packets).¹²⁹ The prescribed dose of cholestyramine was 24 g (or 6 packets) per day. The cholestyramine group experienced a 19% reduction in risk ($P < 0.05$) of the primary end point of definite CHD death and/or definite nonfatal MI, reflecting a 24% reduction in definite CHD death and a 19% reduction in nonfatal MI. Other end points of new positive exercise tests, angina, and coronary bypass surgery were reduced by 25%, 20%, and 21%, respectively. Death from all causes was

TABLE 23-15 Primary Prevention Trials with Lipid-Lowering Drugs

| Trial | Followup (y) | N | Treatment | Control Events | Treatment Events | P Value | RRR | ARR | NNT |
|----------------|--------------|--------|---|----------------|------------------|---------|-------------------|------|------------------|
| AFCAPS/TexCAPS | 5 | 6,605 | Lovastatin 20–40 mg | 5.5% | 3.5% | <0.001 | 36.4% | 2.0% | 50 |
| Helsinki | 5 | 4,081 | Gemfibrozil 1,200 mg | 4.1% | 2.7% | <0.02 | 34.0% | 1.4% | 71 |
| LRC-CPPT | 7.4 | 3,806 | Cholestyramine 24 g | 9.8% | 8.1% | <0.05 | 17.3% | 1.7% | 59 |
| Oslo | 5 | 1,232 | Diet + smoking cessation | 4.2% | 2.5% | 0.03 | 40.5% | 1.7% | 59 |
| WOSCOPS | 4.9 | 6,595 | Pravastatin 40 mg | 7.8% | 5.5% | <0.001 | 29.5% | 2.3% | 43 |
| ALLHAT | 4.8 | 10,355 | Usual care Pravastatin 40 mg | 10.4% | 9.3% | 0.16 | 9.0% | 1.1% | 91 |
| WHI | 5.2 | 16,608 | Usual care Diet, CEE 0.625 mg + MPA 2.5 mg | 1.5% | 1.9% | 0.05 | 1.29 ^a | 0.4% | 200 ^b |
| WHI | 5.2 | 16,608 | Usual care Diet, CEE 0.625 mg | 3.7% | 3.3% | NS | 9.0% | 0.4% | 250 |
| CARDS | 4 | 2,838 | Atorvastatin 10 mg | 9.0% | 5.8% | 0.001 | 37.0% | 3.2% | 32 |

AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study (Downs et al., 1998); ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; approximately 13%–15% of patients had a history of coronary heart disease (CHD); events are CHD events only; ARR, absolute risk reduction; CARDS, Collaborative Atorvastatin Diabetes Study (presented at the 2004 American Diabetes Association meeting); CEE, conjugated equine estrogen; Helsinki, Helsinki Heart Study (Frick et al., 1987); LRC-CPPT, Lipid Research Clinics Coronary Primary Prevention Trial (Insull et al., 1984); MPA, medroxyprogesterone acetate; NA, not available; NNT, number needed to treat; Oslo, Oslo Study (Hjermann et al., 1988); RRR, relative risk reduction; WHI, Women's Health Initiative; WOSCOPS, West of Scotland Coronary Prevention Study (Shepherd et al., 1995).

^aHazard ratio. Risk of coronary heart disease was increased by 29%.

^bNumber needed to harm as CEE + MPA was worse than placebo.

TABLE 23-16 Secondary Prevention Trials with Lipid Lowering Drugs

| Trial | Followup (y) | N | Treatment | Control Events | Treatment Events | P Value | RRR | ARR | NNT |
|---------|--------------|--------|--------------------------------------|----------------|------------------|---------|-------|------|-----|
| VA-HIT | 5.1 | 2,531 | Gemfibrozil 1,200 mg | 23.7% | 17.3% | 0.006 | 22% | 4.4% | 23 |
| AVERT | 1.5 | 341 | Atorvastatin 80 mg | 21% | 13.0% | 0.048 | 38% | 8% | 12 |
| CARE | 5 | 4,159 | Pravastatin 40 mg | 13.2% | 10.2% | 0.003 | 22.7% | 3.0% | 33 |
| CDP | 5 | 8,341 | Niacin 3 g + clofibrate 1.8 g | 20.9% | 20.6% | NS | 1.4% | 0.3% | 333 |
| HERS | 4.1 | 2,673 | Estrogen 0.625 mg + progestin 2.5 mg | 12.7% | 12.5% | 0.91 | 1.6% | 0.2% | 500 |
| LIPID | 7.4 | 3,806 | Pravastatin 40 mg | 9.8% | 8.1% | <0.05 | 17.3% | 1.7% | 59 |
| 4S | 5 | 4,444 | Simvastatin 20 mg | 11.5% | 8.2% | 0.0003 | 28.7% | 3.3% | 30 |
| WHO | 5.3 | 15,745 | Clofibrate 1.6 g | 3.9% | 3.1% | <0.005 | 20.5% | 0.8% | 125 |
| BIP | 6.2 | 3,090 | Placebo | 15.0% | 13.6% | 0.26 | 9.3% | 1.4% | 72 |
| | | | Bezafibrate 400 mg | | | | | | |
| TIMI-22 | 2 | 4,162 | Pravastatin 40 mg | 26.3% (P) | 22.4% (A) | 0.005 | 16% | 3.9% | 26 |
| | | | Atorvastatin 80 mg | | | | | | |
| HPS | 5 | 20,536 | Simvastatin 40 mg | 14.7% | 12.9% | 0.003 | 13% | 1.8% | 56 |
| MIRACL | | 3,086 | Atorvastatin 80 mg | 17.4% | 14.8% | 0.048 | 16% | 2.6% | 39 |
| PROSPER | 3 | 5,804 | Pravastatin 40 mg | 16.2% | 14.1% | 0.014 | 24% | 2.1% | 48 |
| SPARCL | 4.0 | 4,731 | Atorvastatin 80 mg | 13.1% | 11.2% | 0.03 | 16% | 2.2% | 46 |
| TNT | 4.9 | 10,001 | Atorvastatin 10 mg vs 80 mg | 10.9% | 8.7% | <0.001 | 22% | 2.2% | 46 |

4S, Scandinavian Simvastatin Survival Study (Pederson et al., 1994); ARR, absolute risk reduction; AVERT, Atorvastatin Versus Revascularization Treatments; BIP, Bezafibrate Infarction Prevention; CARE, Cholesterol and Recurrent Events (Melendez et al., 1996); CDP, Coronary Drug Project (Berge et al., 1975); HERS, Heart and Estrogen Replacement Study (Hulley et al., 1998); HPS, Heart Protection Study; results expressed as all-cause mortality (HPS Collaborative Group, 2002); LIPID, Long-Term Intervention with Pravastatin in Ischaemic Disease Study (MacMahon et al., 1995); MIRACL, Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (Schwartz et al., 2001); NNT, number needed to treat; PROSPER, prospective study of pravastatin in the elderly at risk; RRR, relative risk reduction; SPARCL, Stroke Prevention by Aggressive Reduction in Cholesterol Levels; TIMI-22, Thrombolysis in Myocardial Infarction study 22; also known as the PROVE-IT trial (Cannon et al., 2004); TNT, treatment to new targets; VA-HIT, Veterans Administration-High-Density Lipoprotein Cholesterol (HDL-C) Intervention Trial; WHO, World Health Organization (Committee of Principal Investigators, 1978).

not significantly reduced by cholestyramine secondary to more accidents and violence in this group. The mean falls in total cholesterol and LDL-C in the cholestyramine group were 8% and 12% relative to levels in placebo-treated men, providing evidence that for every 1% reduction in cholesterol, a 2% decline in CHD mortality can be realized.

AFCAPS/TexCAPS was a primary prevention trial conducted in 6,605 men and women aged 57 to 63 years with average total cholesterol (<221 mg/dL) and LDL (<150 mg/dL) who were treated with lovastatin 20 to 40 mg/day for 5.2 years. The study showed a 37% reduction ($P < 0.001$) in the risk for first acute major coronary event (fatal or nonfatal MI, unstable angina, or sudden cardiac death).⁹⁰ The need for revascularization procedures was reduced by 33% ($P < 0.001$). The implications of this trial are enormous; based on these results, millions of “normal” people potentially could benefit from lipid lowering with statins. The number of patients who need to be treated (Table 23-15) for primary prevention ranged from 43 in the West of Scotland trial to 71 in the Helsinki Heart Study. This range is within the typical boundary used for treatment decisions and described previously; cost effectiveness is achieved routinely in patients with moderate to high risk. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial—Lipid Lowering Trial (ALLHAT-LLT) tested pravastatin 40 mg/day versus placebo in hypertensive patients with at least one CHD risk factor. Pravastatin did not reduce either all-cause mortality or CHD significantly compared with usual care in older participants with well-controlled hypertension and moderately elevated LDL-C. The results may be due to the modest differential in total cholesterol (9.6%) and LDL-C (16.7%) between pravastatin and usual care compared with prior statin trials supporting cardiovascular disease prevention.¹³⁰ The long-awaited WHI trial proved to be disappointing, showing no beneficial effects on CHD event reduction in the hormone replacement arm (conjugated equine estrogens + medroxyprogesterone) or the conjugated equine estrogens alone arm compared to placebo.^{107,109} Women did experience greater risk for thromboembolism, a slight increase in breast cancer, and a reduced risk of hip fracture. Consequently, hormone replacement therapy can no longer be recommended for cardiovascular protection.⁴ In the WISDOM trial, comparison of hormone therapy ($n = 2,196$) versus placebo ($n = 2,189$) revealed a significant increase in the number of major cardiovascular events (7 vs 0, $P = 0.016$) and venous thromboembolism (22 vs 3,

hazard ratio 7.36, 95% confidence interval 2.20–24.60), confirming the findings of HERS and WHI. There were no statistically significant differences in the numbers of breast or other cancers, cerebrovascular events, fractures, and overall death.¹¹¹

In the CDP, niacin significantly reduced definite nonfatal MI compared to placebo (10.1% vs 13.9%), whereas clofibrate did not reduce death from any cause or nonfatal or fatal MI during the 5-year followup.¹³¹

One of the most important studies published is 4S, a secondary intervention trial with a large number of patients.¹³² Simvastatin 20–40 mg/day reduced LDL-C by 35% and reduced the risk of death from any cause by 30%. Coronary deaths were reduced with simvastatin (relative risk 0.58, confidence interval 0.46–0.73). Therapy was shown to be effective in women (18%–19% of patients enrolled) and in the elderly (≥ 60 years). The relative risk of death or major coronary event was reduced to a greater extent in the elderly than in younger patients. Death from noncardiovascular causes was similar for simvastatin and placebo (2.1% and 2.2%, respectively). The survival curves for simvastatin and placebo began to separate at 1 year and became more divergent with additional followup. 4S clearly demonstrates the benefit of cholesterol lowering and placates long-held fears of death from non-CHD causes. The Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) study ($N = 7,498$ men and 1,516 women) investigated the effect of pravastatin therapy over 6 years on CHD mortality in patients with prior MI or unstable angina and mean cholesterol level of 219 mg/dL.¹³³ Pravastatin reduced the risk of CHD mortality by 24% (8.3% vs 6.4%, $P = 0.0004$) and total mortality by 23% (14.1% vs 11.0%, $P = 0.00002$), reduced stroke by 20% (4.3% vs 3.5%, $P = 0.22$), and reduced the need for coronary artery bypass graft surgery (11.3% vs 8.9%, $P = 0.0001$) and percutaneous transluminal coronary angioplasty (5.3% vs 4.4%, $P = 0.04$).

The Veterans Administration High-Density Lipoprotein Intervention trial (VA-HIT) was a double-blinded trial that compared gemfibrozil (1,200 mg/day) with placebo in 2,531 men with CHD, HDL-C level ≤ 40 mg/dL, and LDL-C level ≤ 140 mg/dL.¹³⁴ The primary study outcome was nonfatal MI or death from coronary causes. Median followup was 5.1 years. At 1 year, mean HDL-C level was 6% higher, mean triglyceride level was 31% lower, and mean total cholesterol level was 4% lower in the gemfibrozil group than in the placebo group. LDL-C levels did

not differ significantly between groups. A primary event occurred in 21.7% of the patients assigned to placebo and in 17.3% of the patients assigned to gemfibrozil. The overall reduction in the risk of an event was 4.4 percentage points, and the reduction in relative risk was 22% ($P = 0.006$). This trial presents the strongest evidence to date that raising HDL-C and lowering triglycerides levels reduce risk for CHD.

The Atorvastatin Versus Revascularization Treatment (AVERT) trial compared atorvastatin 80 mg/day with percutaneous transluminal coronary angioplasty.¹³⁵ The followup period was 18 months. Of the patients who received aggressive lipid-lowering treatment with atorvastatin, 13% had ischemic events compared to 21% of patients who underwent angioplasty. Thus, the incidence of ischemic events was 36% lower in the atorvastatin group over an 18-month period ($P = 0.048$, which was not statistically significant after adjustment for interim analyses). This reduction in events was the result of a smaller number of angioplasty procedures, coronary artery bypass operations, and hospitalizations for worsening angina (the most common end point). Compared to the patients who were treated with angioplasty and usual care, the patients who received atorvastatin had a significantly longer time to the first ischemic event ($P = 0.03$). In low-risk patients with stable CAD, aggressive lipid-lowering therapy is at least as effective as angioplasty and usual care in reducing the incidence of ischemic events.

The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) investigates men and women in the age range from 70 to 82 years at risk for cardiovascular disease and found that pravastatin 40 mg/day reduced CHD events by 24%, with no effect on cognitive function.¹³⁶ The more recent Thrombolysis in Myocardial Infarction 22 (TIMI-22) study (also known as PROVE-IT [Pravastatin or Atorvastatin Evaluation and Infection Therapy]), enrolled 4,162 patients who had been hospitalized for an acute coronary syndrome within the preceding 10 days and compared pravastatin 40 mg/day (standard therapy) with atorvastatin 80 mg/day (intensive therapy).¹³⁷ An intensive lipid-lowering statin regimen with atorvastatin 80 mg/day provided greater protection against death or major cardiovascular events than did a standard regimen. This study clearly points to “lower is better” for LDL concentration and likely will lead to revision in guideline goals to lower LDL levels. The Treating to New Targets (TNT) study assessed the efficacy and safety of lowering LDL-C levels to <100 mg/dL (2.6 mmol/L) in patients with stable CHD.^{138,139} Intensive lipid-lowering therapy with atorvastatin 80 mg/day in patients with stable CHD provided significant clinical benefit beyond than treatment with atorvastatin 10 mg/day, providing additional evidence that intensive lipid lowering brings greater benefits.

Statins reduce the incidence of strokes among patients at increased risk for cardiovascular disease. Whether statins reduce the risk of stroke after a recent stroke or transient ischemic attack (TIA) was addressed by Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL). During a median followup of 4.9 years, 265 patients (11.2%) who received atorvastatin 80 mg/day and 311 patients (13.1%) who received placebo had a fatal or nonfatal stroke (5-year absolute reduction in risk 2.2%, adjusted hazard ratio 0.84, 95% confidence interval 0.71–0.99, $P = 0.03$; unadjusted $P = 0.05$).¹⁴⁰

The enzyme ACAT esterifies cholesterol in a variety of tissues. In some animal models, ACAT inhibitors have antiatherosclerotic effects. However, when tested in clinical trials, ACAT inhibition was not an effective strategy for limiting atherosclerosis and may promote atherogenesis.¹⁴¹

Statins differ in their pharmacokinetic properties and in pleiotropic effects (i.e., nonlipid lowering). The contribution of lipid lowering alone (a class effect) versus other effects (antiinflammatory, antithrombotic) is controversial.

Proteinuria has been associated with high-dose rosuvastatin therapy (40 mg/day), but a review of a clinical trial database revealed an increase in the estimated glomerular filtration rate for rosuvastatin-treated patients that was consistent across all major demographic and clinical subgroups of interest, including patients with baseline proteinuria, patients with baseline estimated glomerular filtration rate <60 mL/min/1.73 m², and patients with hypertension and/or diabetes.¹⁴²

The role of nontraditional risk factors (high-sensitivity C-reactive protein, homocysteine) is being studied and may lead to recommendations for the use of these tests in patient evaluation.

EVALUATION OF THERAPEUTIC OUTCOMES

Short-term evaluation of therapy for hyperlipidemia is based on response to diet and drug treatment as measured in the clinical laboratory by total cholesterol, LDL-C, HDL-C, and triglycerides for patients being treated for primary intervention, as well as on response to secondary intervention. The followup interval is dependent on the severity of illness, and patients with known CAD or multiple risk factors should be monitored more closely. Less commonly used laboratory measurements include C-reactive protein, homocysteine, apolipoprotein B, and lipoprotein(a) levels. Because many patients being treated for primary hyperlipidemia have no symptoms and may not have any clinical manifestations of a genetic lipid disorder such as xanthomas or eruptions, monitoring and outcome are solely laboratory based. In patients treated for secondary intervention, symptoms of atherosclerotic cardiovascular disease (e.g., angina or intermittent claudication) may improve over months to years. In patients have xanthomas or other external manifestations of hyperlipidemia, the lesions should regress with therapy. Lipid measurements should be obtained in the fasted state to minimize interference from chylomicrons. Once the patient is stable, monitoring is needed at intervals of 6 months to 1 year. The goals for LDL-C and HDL-C are listed in Tables 23–8 and 23–9.

Patients with multiple risk factors and established CHD should be monitored and evaluated for progress in managing their other risk factors, such as hypertension, smoking cessation, exercise and weight control, and glycemic control if diabetic. The goals are to maintain blood pressure $<130/80$ mm Hg, especially for patients with diabetes or renal insufficiency, stop smoking, maintain an ideal body weight, exercise for at least 20 minutes per day at least three times per week, and keep plasma glucose concentration <100 mg/dL (threshold for glucose intolerance). Invasive evaluation, such as cardiac catheterization, is useful in patients with established CHD and typically is used for planning revascularization rather than monitoring of lipid-lowering therapy.

Evaluation of dietary therapy is part of the outcome evaluation for treating hyperlipidemia, and the assistance of a dietitian is recommended. Use of diet diaries and recall survey instruments enables systematic collection of information about diet and may improve patient adherence to dietary recommendations. Patients undergoing resin therapy should have a fasting lipoprotein profile checked every 4 to 8 weeks until a stable dose is achieved; triglycerides should be checked at stable dose to ensure levels have not increased. Niacin requires baseline liver function tests, and uric acid

CLINICAL CONTROVERSIES

The CETP inhibitor torcetrapib was associated with a substantial increase in HDL-C and decrease in LDL-C. It also was associated with an increase in blood pressure and no significant decrease in the progression of coronary atherosclerosis. The lack of efficacy may be related to the mechanism of action of this drug class or to molecule-specific adverse effects. Other means of raising HDL-C (HDL mimetics, which include apolipoprotein A-I mutants and peptide mimetics of apolipoprotein A-I and HDL Milano A, a synthetic form of HDL) still hold hope of HDL modification leading to a reduction in clinical events.

and glucose concentrations; repeat tests are appropriate at doses of 1,000–1,500 mg/day. Myopathy or diabetes-like symptoms should be investigated and may require CK or glucose determinations; more frequent monitoring in diabetics may be necessary. A fasting lipoprotein profile 4 to 8 weeks after the initial dose or after dose changes with statins is appropriate. Liver function tests should be obtained at baseline and periodically thereafter based on package insert information; recognized experts believe that monitoring for hepatotoxicity and myopathy should be symptom triggered.^{56,61} Ezetimibe requires little specific monitoring.

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