Lipid Disorders

Mohamad Alkhouli, MD
Harish Jarrett, MBChB
Sara Sirna, MD

ESSENTIALS OF DIAGNOSIS

- Elevated plasma levels of low-density lipoprotein cholesterol, non–high-density lipoprotein cholesterol, lipoprotein(a), and apolipoprotein (apo) B-100.
- Reduced plasma levels of high-density lipoprotein and apo A-I.
- Elevated plasma levels of triglycerides.
- Skin xanthomas.

General Considerations

Multiple epidemiologic studies have demonstrated the relationship between cardiovascular mortality and elevated plasma cholesterol levels. Lipid-lowering therapy, particularly with hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins), has demonstrated survival benefit in both primary prevention (patients without evidence of atherosclerotic cardiovascular disease [ASCVD]) and secondary prevention (patients with evidence of ASCVD). As a result, screening, risk stratifying, and treating dyslipidemia have become integral parts of preventive cardiovascular medicine.

A. Lipoproteins and Apolipoproteins

Cholesterol, cholesteryl esters, and triglycerides are the major lipids found in plasma. Cholesterol is an integral component of the cell membrane. It also serves a role in steroid hormone and bile acid synthesis. Triglycerides consist of fatty acid chains and phospholipids. Fatty acid chains are a primary source of energy in humans; phospholipids are key elements of all cell membranes. Cholesterol and triglycerides are insoluble in water and are transported in plasma by lipoproteins, classified as high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, very-low-density lipoprotein (VLDL) cholesterol, intermediate-density lipoprotein (IDL) cholesterol, and chylomicrons. Lipoproteins consist of a lipid core and a water-soluble phospholipid outer layer that carry apolipoproteins, which are specific proteins that serve as coenzymes or receptor ligands or act as regulators of lipoprotein metabolism. Apolipoprotein (apo) A-I is present in HDL and promotes cholesterol efflux from tissues. Apo B, present as either apo B-100 (VLDL, IDL, LDL) or apo B-48 (chylomicron), serves as the LDL receptor ligand. Apo C-I, apo C-II, and apo C-III participate in triglyceride metabolism, and apo E is present on chylomicrons.

Lipoprotein(a) [Lp(a)] highly correlates with cardiovascular disease (CVD) and consists of an LDL particle and a specific apolipoprotein A. The structure of Lp(a) is similar to plasminogen and is thought to increase thrombogenesis. It is known to predict early atherosclerotic risk independent of other risk factors. Figure 1–1 illustrates the classes of lipoproteins and their characteristics.

B. Metabolism

Transportation of dietary lipids to peripheral tissues and the liver is known as the exogenous metabolic pathway. Here, triglycerides are hydrolyzed by pancreatic lipases and are emulsified by bile acids, leading to micelle formation. Micelle uptake occurs in the intestinal brush border where fatty acids are re-esterified and packaged together with apo B-48, phospholipids, and cholesterol to form chylomicrons. Chylomicrons then reach the portal circulation where they are hydrolyzed to release fatty acids by lipoprotein lipase (LPL). LPL activity is regulated through apo C-II, which activates LPL, and apo C-III, which inhibits LPL. The free fatty acids are used by muscle or stored as fat in an insulin-regulated process. As the particles get smaller, the cholesterol and apolipoproteins are transferred to HDL, creating a chylomicron remnant that is then taken up by the liver for degradation in an apo E-mediated process.

The endogenous metabolic pathway refers to transport of hepatic lipoproteins to peripheral tissues via LDL. It
ensures a steady supply of substrate given that food supply varies. Here VLDL, a triglyceride-rich lipoprotein, serves a similar role to the chylomicron in the exogenous pathway. VLDL is derived from esterified long-chain fatty acids in the liver. Its triglyceride component is also hydrolyzed by LPL. VLDL acquires apolipoproteins (B-100, C-I, C-II, C-III, and E) from HDL and also exchanges triglycerides for cholesteryl esters in a process mediated by cholesteryl ester transfer protein (CETP). This mechanism allows cholesterol transfer from HDL to VLDL, allowing reverse cholesterol transport. Following hydrolysis, up to 40% of the resulting VLDL remnant, known as IDL, is taken up by the liver in an apo E-mediated transfer, and the remainder is converted to LDL by hepatic lipase. LDL particles mostly contain cholesteryl esters together with apo B-100 and are the main carriers of cholesterol. LDL is internalized through apo B-100, which binds to LDL receptors present on the cell surface. Cells are also capable of synthesizing cholesterol through an enzymatic process that involves HMG-CoA reductase. Figure 1–2 illustrates the endogenous and exogenous lipid metabolism pathways.
There is an inverse relationship between HDL levels and atherosclerotic coronary artery disease (CAD). HDL is responsible for reverse cholesterol transport. It inhibits lipoprotein oxidation and maintains endothelial integrity. Synthesized mostly in the liver but also in the intestine, the nascent HDL molecule consists of apo A-I, phospholipids, and cholesterol. HDL acquires cholesterol in an apo A-I–mediated process, which is then esterified by lecithin-cholesterol acyltransferase (LCAT) within the HDL particle forming mature HDL-containing cholesteryl esters, which can be taken up by the liver. Cholesterol and triglycerides can also be transferred from HDL to VLDL and chylomicrons via CETP, a process that allows HDL to transport cholesterol between cells, VLDL and chylomicrons, and the liver.

C. Atherosclerosis

Dyslipidemia is a major predisposing factor in the development of atherosclerosis and ASCVD. Elevated plasma LDL concentrations can directly and indirectly contribute to atherosclerosis. Oxidized LDL accumulates in subintimal macrophages through active scavenger receptor–mediated uptake that leads to cellular dysfunction, apoptosis, and necrosis. Unlike the LDL receptor–mediated endocytosis, this process is not regulated by cholesterol content. These macrophages are termed foam cells and form subintimal fatty streaks. This culminates in the release of proinflammatory and prothrombotic molecules, which causes endothelial injury. Oxidized LDL can also directly cause endothelial injury through interaction with the cell surface. Endothelial injury results in platelet aggregation and smooth muscle proliferation, which initiates atherosclerotic plaque formation. HDL serves a protective role in atherogenesis. Its antiatherogenic effects are exerted through maintenance of endothelial function, apo A-I–mediated reverse transport of macrophage cholesterol, antioxidant effects, and antithrombotic effects.

Clinical Findings

Patients with dyslipidemia are asymptomatic with the exception of those who present with acute pancreatitis in the setting of severe hypertriglyceridemia. The clinical findings depend on the cause of dyslipidemia.

The most severe forms of hyperlipidemia are caused by genetic disorders of lipoprotein metabolism such as familial hypercholesterolemia (FH). FH is an autosomal dominant disease with defects in the gene for the LDL receptor. The mutant gene prevents the LDL receptor from removing LDLs from the blood. LDL cholesterol levels are typically in excess of 300 mg/dL. Common manifestations include fatty skin deposits called xanthomas over parts of the hands, elbows, knees, and ankles and around the corner of the eye (xanthelasmas). It frequently presents as premature CAD with chest pain (angina) or acute myocardial infarction. Other common primary causes of dyslipidemia are familial combined hyperlipidemia (both high LDL and triglyceride levels) and pure hypertriglyceridemia (very high triglyceride levels).

Table 1–1 summarizes the most common causes of dyslipidemia.

A. Secondary Causes of Dyslipidemia

Dyslipidemia develops in many patients as a result of an underlying metabolic abnormality rather than a primary dyslipidemia. Metabolic syndrome is characterized by abdominal obesity, hypertension, insulin resistance (± glucose intolerance), prothrombotic state, elevated triglycerides, small LDL particles, and low HDL levels.

Obesity affects over one-third of adults in the United States and represents a significant secondary cause of dyslipidemia due to caloric excess mostly derived from saturated fat and sugar. Decreased insulin sensitivity and increased carbohydrate intake cause an increase in triglyceride formation, which then enters the circulation in the form of VLDL. HDL levels are decreased in obesity. Similarly, patients with type 2 diabetes mellitus are dyslipidemic due to insulin resistance and subsequent insulin excess. This causes an increase in free fatty acid formation in the periphery and in the liver that translates to an increase in VLDL production and hypertriglyceridemia. Lipoprotein catabolism is down-regulated due to decreased LPL activity, resulting in further increases in plasma VLDL.

Hypothyroidism commonly results in dyslipidemia due to a decrease in hepatic LDL receptor activity and consequent delayed clearance of LDL. The severity of the dyslipidemia directly correlates with the degree of hypothyroidism, and correction reverses the dyslipidemia.

Liver disease can affect plasma lipid concentrations. Hepatitis is associated with increased VLDL production, and not surprisingly, severe disease and liver failure result in low plasma lipoprotein levels as synthetic function progressively decreases. Cholestatic liver disease results in significant hypercholesterolemia through the accumulation of lipoprotein-X, the deposition of which leads to the appearance of xanthomata in the skin.

Chronic kidney disease is associated with elevation in VLDL as a result of decreased lipolysis and clearance. Nephrotic syndrome results in marked hypercholesterolemia as a result of increased hepatic production of LDL and decreased clearance of VLDL, induced due to low plasma oncotic pressure.

Other secondary causes to consider include cigarette smoking, which decreases plasma HDL concentration. Commonly used drugs such as thiazide diuretics, β-blockers, and estrogen compounds can affect plasma lipid concentrations. Antiretroviral agents, particularly protease inhibitors, are associated with a lipodystrophy syndrome. Antipsychotics are also potential causative agents that are associated with weight gain and insulin resistance.
Table 1-1. Primary Gene Defects

<table>
<thead>
<tr>
<th>Genetic Disorder</th>
<th>Protein (gene) Defect</th>
<th>Lipoproteins Elevated</th>
<th>Clinical Findings</th>
<th>Genetic Transmission</th>
<th>Estimated Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipoprotein lipase deficiency</td>
<td>LPL</td>
<td>Chylomicrons</td>
<td>Eruptive xanthomas, hepato-splenomegaly, pancreatitis</td>
<td>AR</td>
<td>1 in 1,000,000</td>
</tr>
<tr>
<td>Familial apolipoprotein C-II</td>
<td>Apo-CII</td>
<td>Chylomicrons</td>
<td>Eruptive xanthomas, hepato-splenomegaly, pancreatitis</td>
<td>AR</td>
<td>&lt; 1 in 1,000,000</td>
</tr>
<tr>
<td>Apo A-V deficiency</td>
<td>ApoA-V</td>
<td>Chylomicrons, VLDL</td>
<td>Eruptive xanthomas, hepato-splenomegaly, pancreatitis</td>
<td>AD</td>
<td>&lt; 1 in 1,000,000</td>
</tr>
<tr>
<td>GP1HBP1 deficiency</td>
<td>GP1HBP1</td>
<td>Chylomicrons</td>
<td>Eruptive xanthomas, pancreatitis</td>
<td>AD</td>
<td>&lt; 1 in 1,000,000</td>
</tr>
<tr>
<td>Familial hepatic lipase deficiency</td>
<td>Hepatic lipase</td>
<td>VLDL remnants</td>
<td>Pancreatitis, CHD</td>
<td>AR</td>
<td>&lt; 1 in 1,000,000</td>
</tr>
<tr>
<td>Familial dysbetalipoproteinemia</td>
<td>ApoE</td>
<td>Chylomicrons, VLDL</td>
<td>Palmar and tuboeruptive xanthomas, CHD, PVD</td>
<td>AR, AD</td>
<td>1 in 10,000</td>
</tr>
<tr>
<td>Familial hypercholesterolemia</td>
<td>LDL receptor</td>
<td>LDL</td>
<td>Tendon xanthomas, CHD</td>
<td>AD</td>
<td>1 in 500</td>
</tr>
<tr>
<td>Familial defective apo B-100</td>
<td>ApoB-100</td>
<td>LDL</td>
<td>Tendon xanthomas, CHD</td>
<td>AD</td>
<td>&lt; 1 in 1000</td>
</tr>
<tr>
<td>Autosomal dominant hypercholesterolemia</td>
<td>PCSK9</td>
<td>LDL</td>
<td>Tendon xanthomas, CHD</td>
<td>AD</td>
<td>&lt; 1 in 1,000,000</td>
</tr>
<tr>
<td>Autosomal recessive hypercholesterolemia</td>
<td>LDLRAP</td>
<td>LDL</td>
<td>Tendon xanthomas, CHD</td>
<td>AR</td>
<td>&lt; 1 in 1,000,000</td>
</tr>
<tr>
<td>Silosterolemia</td>
<td>ABCG5 or ABCG8</td>
<td>LDL</td>
<td>Tendon xanthomas, CHD</td>
<td>AR</td>
<td>&lt; 1 in 1,000,000</td>
</tr>
</tbody>
</table>

AD, autosomal dominant; AR, autosomal recessive; ARH, autosomal recessive hypercholesterolemia; CHD, coronary heart disease; LDL, low-density lipoprotein; LPL, lipoprotein lipase; PVD, peripheral vascular disease; VLDL, very-low-density lipoprotein.


#### Diagnosis

The National Cholesterol Education Program, Adult Treatment Panel (NCEP-ATP) III recommends screening for lipid disorders with a fasting lipid profile every 5 years for adults over 20 years old. The US Preventive Services Task Force (USPSTF) advocates for routine screening of men and women above 35 and 45 years old, respectively. The USPSTF also recommends screening at earlier age if risk factors for coronary heart disease (CHD) are present. When lipid abnormalities are discovered, a thorough history should be performed, assessing for symptomatic CVD, as well as attempts to identify potential secondary causes of dyslipidemia. A thorough family history should be obtained, and risk factors such as sedentary lifestyle, obesity, poor diet, and cigarette smoking should be addressed. Physical examination may reveal xanthomas and xanthelasmas, which may aid in the diagnosis of a primary dyslipidemia. Basic metabolic panel, creatinine, and thyroid and liver function tests should be obtained to exclude any secondary causes of hyperlipidemia.


#### Treatment

##### A. LDL Goals

The degree of cardiovascular risk is the major determinant in the decision to commence drug therapy. Current NCEP-ATP-III guidelines incorporate the Framingham 10-year absolute cardiovascular risk rates in identifying target LDL goals for patients with hyperlipidemia. The major risk factors (exclusive of LDL cholesterol) that modify LDL goals are cigarette smoking, hypertension (blood pressure > 140/90 mm Hg...
or on antihypertensive medication), low HDL cholesterol (< 40 mg/dL), family history of premature CHD (CHD in male first-degree relative < 55 years; CHD in female first-degree relative < 65 years), and age (men > 45 years; women > 55 years). HDL cholesterol > 60 mg/dL counts as a “negative” risk factor; its presence removes one risk factor from the total count. The presence of peripheral arterial disease, abdominal aortic aneurysm, symptomatic carotid artery disease, or diabetes is considered CHD equivalents. Patients are classified as low, intermediate, and high risk based on the number of their risk factors. The treatment goal and the threshold to initiate drug therapy differ between the three risk groups as illustrated in Table 1–2. Some authorities recommend an LDL goal of ≤ 70 mg/dL for very-high-risk patients (eg, a diabetic patient with recent myocardial infarction), a strategy that has been adapted by most cardiologists.

The major limitation of the Framingham model is that this approach only measures a 10-year and not a lifetime risk of developing CAD. In addition, two major risk factors, diabetes and family history, are not included in the Framingham risk calculation. Therefore, it should be noted that the Framingham risk score may underestimate one’s actual risk.

It should be emphasized that treating LDL to optimal target reduces the risk of coronary events but does not eliminate it completely. Patients with LDL at goal who are at very high risk may benefit from further testing to define their “residual risk” of coronary events. Levels of HDL, high-sensitivity C-reactive protein, and Lp(a); particle sizes/numbers; calcium scoring; and vascular intima imaging are useful tools in assessing this residual risk.

It may be reasonable to test serum Lp(a) in those with premature CAD, with a strong family history of premature CAD, or with recurrent disease despite statin treatment. Treatment consists of niacin, 1–3 g mostly in the long-acting form, and aspirin.

### B. HDL Goals

Low HDL is an independent risk factor for increased CVD and mortality, although a causal relationship has not been established. High HDL levels convey reduced coronary risk and are associated with a longevity syndrome. Low HDL levels can be caused by genetic mutations, as is the case with familial hypoalphalipoproteinemia, familial HDL deficiency, and Tangier disease. Acquired and often reversible causes include obesity, sedentary lifestyle, cigarette smoking, metabolic syndrome, hypertriglyceridemia, and certain drugs (β-blockers and steroids). These risk factors should be aggressively targeted. As of today, the studies have been inconclusive regarding increasing HDL with pharmacologic intervention and reducing the risk of CHD. In addition, NCEP-ATP-III guidelines highlight that LDL and non-HDL goals should be reached first before HDL goals are addressed.

### C. Hypertriglyceridemia and Non-HDL Goals

Hypertriglyceridemia is common and is often associated with obesity, physical inactivity, high-carbohydrate diet, alcohol consumption, and cigarette smoking. Other conditions such as diabetes, metabolic syndrome, and renal disease, as well as drugs (particularly estrogens and protease inhibitors), are also contributory. Patients with hypertriglyceridermia are at increased risk of developing ASCVD. As with low HDL levels, it is unclear whether a causal relationship exists. Current NCEP-ATP-III treatment guidelines recommend reducing serum triglyceride levels in addition to lowering LDL values. Therapeutic lifestyle change should be the major treatment goal given the constellation of risk factors that contribute to the hypertriglyceridermic state.

In addition to aerobic exercise, dietary management should focus on carbohydrate reduction as well as restricting foods that have a high glycemic index. No dietary fat restriction is required, but the correct type of fat consumption should always be emphasized. Patients with extremely high triglyceride levels (> 1000 mg/dL) are at risk of developing acute pancreatitis due to high levels of circulating chylomicrons. In this subgroup of patients, all types of dietary fat should be restricted to reduce this risk. Fibrates, nicotinic

### Table 1-2. LDL Treatment Goals

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL Goal (mg/dL)</th>
<th>LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)</th>
<th>LDL Level at Which to Consider Drug Therapy (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD or CHD risk equivalent (10-year risk &gt; 20%)</td>
<td>&lt; 100 &lt; 70 (optional)</td>
<td>&gt; 100</td>
<td>&gt; 130</td>
</tr>
<tr>
<td>2 risk factors (10-year risk &lt; 20%)</td>
<td>&lt; 130</td>
<td>&gt; 130</td>
<td>10-year risk 10-20% &gt; 130 10-year risk &lt; 10% &gt; 160</td>
</tr>
<tr>
<td>0-1 risk factor</td>
<td>&lt; 160</td>
<td>&gt; 160</td>
<td>&gt; 190</td>
</tr>
</tbody>
</table>

acid, and fish oils are pharmacologic agents that can reduce triglyceride levels and are discussed separately. Table 1–3 categorizes triglyceride levels and summarizes NCEP-ATP-III guidelines for treating hypertriglyceridemia.

Non-HDL cholesterol is calculated by subtracting HDL cholesterol from total cholesterol (TC – HDL). This fraction includes all apo B–containing (and therefore atherogenic) lipoprotein particles: LDL, Lp(a), IDL, and VLDL. This measure is useful in the setting of a raised triglyceride level (200–499 mg/dL). The goal non-HDL level is 30 mg/dL higher than the goal LDL level.

Non-HDL cholesterol is calculated by subtracting HDL cholesterol from total cholesterol (TC – HDL). This fraction includes all apo B–containing (and therefore atherogenic) lipoprotein particles: LDL, Lp(a), IDL, and VLDL. This measure is useful in the setting of a raised triglyceride level (200–499 mg/dL). The goal non-HDL level is 30 mg/dL higher than the goal LDL level.

Table 1–3. Triglyceride Treatment Goals

<table>
<thead>
<tr>
<th>Category</th>
<th>Triglyceride Levels (mg/dL)</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal</td>
<td>&lt; 150</td>
<td>None</td>
</tr>
<tr>
<td>Borderline</td>
<td>150–199</td>
<td>Therapeutic lifestyle change (including weight reduction and aerobic exercise)</td>
</tr>
<tr>
<td>High</td>
<td>200–499</td>
<td>Therapeutic lifestyle change Achieve primary LDL goal Achieve secondary non-HDL goal Consider pharmacologic therapy</td>
</tr>
<tr>
<td>Very high</td>
<td>&gt; 500</td>
<td>Pharmacologic therapy to decrease triglyceride levels Once &lt; 500 mg/dL, address LDL goal</td>
</tr>
</tbody>
</table>

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

E. Pharmacologic Treatment

Most patients with dyslipidemia will require targeted pharmacologic therapy to address their dyslipidemia. Statins are considered the cornerstone in treating dyslipidemia. Other drugs, however, are beneficial as an adjunctive or sole therapy in certain populations.

1. HMG-CoA reductase inhibitors (statins)—Statins (simvastatin, atorvastatin, pravastatin, rosuvastatin, fluvastatin, and lovastatin) are the most commonly used drugs in treating dyslipidemia. They are competitive inhibitors of HMG-CoA reductase, which is required for cholesterol biosynthesis. The decrease in intrahepatic cholesterol levels through this mechanism leads to an increase in LDL receptor expression and increased clearance of plasma LDL and decreased hepatic synthesis of VLDL and LDL. In addition, there is a modest increase in HDL levels. There is a synergistic effect when used in combination with either a cholesterol absorption inhibitor or a bile acid sequestrant, which can be helpful in optimizing LDL levels. They also appear to exert LDL independent anti-inflammatory effects on the endothelium and atherosclerotic plaques. For the most part, statins are well tolerated. Commonly reported side effects include myalgia, myositis, reversible transaminitis, and rarely rhabdomyolysis.
2. Cholesterol absorption inhibitors—Ezetimibe binds to and inhibits the protein Niemann-Pick C1-like 1 (NPC1L1) and inhibits the intestinal absorption of cholesterol. The net effect is a decrease in cholesterol reaching the liver and a subsequent increase in hepatocyte LDL receptor expression, thereby decreasing plasma LDL with no effect on HDL or triglyceride levels. Ezetimibe, the first drug in this class, decreases plasma cholesterol by 15–20% and has a synergistic effect when used in combination with a statin. Major side effects are rare, even when used together with a statin, but liver function should be monitored.

3. Fibrac acid derivatives (fibrates)—The major effects of the fibrate class of drugs (gemfibrozil and fenofibrate) are to reduce serum triglyceride levels and raise HDL levels. This effect is mediated by activation of nuclear peroxisome proliferator-activated receptor alpha (PPARα), which results in increased LPL activity and increased VLDL clearance. The elevation of HDL levels is mediated through PPARα-mediated synthesis of apo A-I and apo A-II. Gemfibrozil is indicated in secondary prevention of ASCVD in the setting of hypertriglycerideremia, low HDL, and normal LDL based on the Veterans Administration HDL Intervention Trial (VA-HIT). Common side effects include cholelithiasis, myalgias, and elevated transaminase levels. Combination therapy with statins is effective in treating elevated LDL as well as hypertriglycerideremia; however, fibrates, especially gemfibrozil, can decrease statin elimination and increase the risk of significant myositis and rhabdomyolysis.

4. Bile acid sequestrants (resins)—Bile acid sequestrants interrupt the enterohepatic circulation through binding bile acids and preventing reuptake in the ileum. This results in a decrease in total body and intrahepatic cholesterol, leading to subsequent increase in LDL (apo B and apo E) receptor expression. The LDL receptors (apo B and apo E) then bind LDL cholesterol from the plasma, leading to further decrease in LDL levels. Resins are more effective when used together with a statin. Resins can increase VLDL levels and are therefore restricted to patients with relatively normal triglyceride levels.

Bile acid sequestrants are not absorbed from the gastrointestinal tract, and this reflects their side-effect profile. Bloating and constipation are common and dose dependent, which affects compliance. Bile acid sequestrants can also bind to and impair the absorption of other drugs such as digoxin, warfarin, β-blockers, thiazide diuretics, and fatsoluble vitamins. This effect can be minimized by administering other drugs 1 hour before or 4 hours after the bile acid sequestant, but this can also affect compliance.

The available bile acid sequestrants, cholestyramine, colestipol, and colesevelam, are not systemically absorbed and thus can be used safely in pregnant patients, patients who are lactating, and children.

5. Nicotinic acid (niacin)—The predominant effect of niacin is to substantially increase HDL levels and decrease triglyceride levels. The mechanism by which niacin increases HDL levels remains unclear. Its effects on plasma triglyceride levels are mediated through enhanced LPL activity as well as inhibition of free fatty acid release from peripheral fat. The main obstacle with niacin therapy has been its tolerability. Common side effects include elevated transaminases, hyperglycemia, gastritis, and flushing. Taking aspirin 30 minutes prior to each dose may reduce flushing. Close monitoring of liver function is warranted due to the risk of niacin-induced hepatitis, which warrants discontinuation of therapy. An escalating dosing schedule can improve tolerability and compliance. Niacin has been shown to be effective in combination with a statin.

6. Omega-3 fatty acids (fish oils)—Omega-3 polyunsaturated fatty acids are used in the treatment of hypertriglyceridermia. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are the active compounds and are available over the counter and by prescription. They act through an uncertain mechanism to lower triglyceride levels at doses of 3–4 g/day. Fish oils are well tolerated at these doses but can prolong the bleeding time. Studies have shown morbidity and mortality benefit in secondary prevention with ingestion of 1 g of fish oil daily. Future studies are addressing the effects of fish oil on primary prevention. Consuming one to two servings of oily fish per week has been shown to reduce the risk of CVD in adult patients.

F. Treatment in Specific Patient Populations

1. Familial hyperlipidemia—Those who inherit only one copy of the defective gene (familial heterozygous hyperlipidemia) may respond well to high-dose statin therapy and diet and lifestyle modification. Those with severe forms of the disease may require apheresis, an extracorporeal therapy that removes LDL and returns the remainder of the blood to the patient.
2. **Diabetics**—The insulin-resistant state observed in type 2 diabetes mellitus is associated with hypertriglyceridemia as a result of increased circulating free fatty acids and decreased lipolysis. An increase in VLDL, IDL, and LDL is observed in addition to a decrease in HDL levels. Aggressive LDL reduction confers significant improvements in all-cause mortality in patients with type 2 diabetes mellitus as evidenced by the results from the CARE trial, the Heart Protection Study, and the CARDS study. Thus, type 2 diabetes mellitus is considered a CAD risk equivalent, and the NCEP-ATP-III treatment guidelines reflect these findings with an LDL target of less than 100 mg/dL (2.6 mmol/L) and an optimal target of less than 70 mg/dL (1.8 mmol/L).

3. **Stroke**—Although an established risk factor for CVD, the link between dyslipidemia and cerebrovascular disease and stroke (cerebrovascular accident [CVA]) remains less clear. Regardless, statin therapy has been shown to be beneficial in both primary and secondary prevention. The HPS, CARE, and ASCOT-LLA trials all demonstrated CVA reduction with statin therapy, even in patients with cholesterol levels in the “normal” range. In addition, the SPARCL trial demonstrated that atorvastatin 80 mg daily reduced recurrent ischemic CVA in patients with a prior history of stroke or transient ischemic attack (TIA). It appears that the non–cholesterol-lowering benefits of statin therapy play a significant role in CVA reduction. This may explain why other lipid-lowering therapies have not shown CVA risk reduction benefits.

4. **Hypothyroidism**—Hypothyroidism is commonly associated with hyperlipidemia due to decreased LDL receptor activity and with hypertriglyceridemia due to decreased LPL activity. Patients with dyslipidemia should have their thyroid function assessed. If hypothyroidism is diagnosed, treatment with thyroid replacement therapy will result in improvement in the lipid profile.

### Prognosis

Hyperlipidemia remains a strong and treatable risk factor for atherosclerotic vascular disease. Major trials have demonstrated the enormous benefit of statin therapy in reducing LDL cholesterol and preventing cardiac events. Potential new therapies targeted toward reducing LDL levels are currently an area of active research. Monoclonal antibody targeted at proprotein convertase subtilisin/kexin 9 (PCKS9), a protease that degrades LDL receptors, has shown very promising results in early phase II trials. This new antibody, yet to be approved by the US Food and Drug Administration, resulted in a 60% additional reduction in LDL in patients already on maximum statin therapy. Another novel agent, mipomersen, achieves LDL reduction by binding to apo B RNA and inhibiting apo B synthesis.

Effective treatment for elevated triglyceride levels has improved the prognosis for patients with hypertriglyceridemia. Therapies that increase HDL levels are also being studied. Torcetrapib, anacetrapib, evacetrapib, and dalcetrapib are CETP inhibitors that raise HDL levels. Investigation with torcetrapib was halted due to an increase in adverse cardiovascular events, but the other agents are currently being studied with promising results. However, there is currently no treatment for low HDL levels, which has been demonstrated to reduce mortality.

---