combination with another lipid-lowering agent such as an HMG-CoA reductase inhibitor. Abnormal liver function and gastrointestinal symptoms (e.g., nausea, bloating, cramping) are common side effects that limit the use of bile acid sequestrants. They can also interfere with the absorption of other drugs such as warfarin and thyroxine.

Fibric acid derivatives such as gemfibrozil and fenofibrate increase FFA oxidation in muscle and liver. The reduced lipogenesis in the liver decreases VLDL and subsequent LDL production. Fibric acid derivatives also enhance LPL activity and HDL synthesis. As a result, treatment is usually associated with not only lower triglyceride and LDL levels, but also higher HDL levels. Reduced cardiovascular events have been demonstrated in a subset of individuals with high triglyceride (>200 mg/dL) and low HDL (<40 mg/dL) levels, but improvements in cardiovascular or all-cause mortality otherwise have not been confirmed with these agents. Liver toxicity and myositis are potential side effects of fibric acid derivatives, and they also interfere with the metabolism of warfarin, leading to a need for its dose adjustment.

Nicotinic acid has an antilipolytic effect and therefore decreases the influx of FFA to the liver. As a result, hepatic VLDL synthesis and LDL production are reduced. Nicotinic acid also decreases HDL catabolism. Lower triglyceride and LDL levels and higher HDL levels are observed with treatment. In addition, nicotinic acid stimulates tissue plasminogen activator and prevents thrombosis. It is the preferred agent for the reduction of lipoprotein(a) or Lp(a) (discussed later). The cardioprotective effect of nicotinic acid may be linked to its effect on Lp(a) and HDL. Side effects include hepatotoxicity, hyperuricemia, hyperglycemia, and flushing.

Omega-3 fatty acids reduce VLDL production and subsequently lower triglyceride levels (by 35%). They also modestly increase HDL (3%) and LDL (5%). The impact on lipids can occur over months to years and requires treatment doses as high as 3 to 4 g of fish oil per day. However, reductions in death due to sudden cardiac events and CHD are observed within weeks of treatment initiation. This benefit can be seen with lower treatment doses (fish oil <2 g/day) and is most likely related to the impact of omega-3 fatty acid on cardiac electrophysiology. Omega-3 fatty acids constitute 30% to 50% of fish oil supplements and 85% of prescribed pharmacologic preparations (i.e., Lovaza and Vascepa). In clinical trials, both Lovaza and Vascepa 4 g/day lowered triglyceride levels by 45%. Fish oil supplements seem to be a reasonable, cost-effective means to reduce triglyceride levels; side effects include eructation, taste perversion, and dyspepsia.

Other agents to consider are neomycin, lomitapide, and mipomersen. These agents can be considered in the management of patients with refractory LDL elevations. Neomycin complexes with bile acid and lowers LDL levels. It also inhibits production of apolipoprotein(a) in the liver and lowers Lp(a). It is recommended as adjuvant therapy for patients with familial hypercholesterolemia and Lp(a) excess. Important side effects include nephrotoxicity and ototoxicity. Lomitapide inhibits microsomal triglyceride transfer protein in the liver and decreases apo B. Significant reductions in LDL (up to 50%) are seen with treatment. Liver toxicity is a serious adverse event associated with this agent. Mipomersen is another agent approved for use in homozygous familial hypercholesterolemia. It binds apo B messenger RNA and inhibits apo B production. Apo B is a structural component of VLDL, IDL, and LDL. Treatment reduces LDL by up to 50%. Side effects include flu-like symptoms, injection site reactions, elevations in liver enzymes, and liver toxicity. The side effect profile and expense associated with both lomitapide and mipomersen limit the use of these agents to individuals with homozygous familial hypercholesterolemia.

LIPID DISORDERS

A number of specific disorders of overproduction or impaired removal of lipoproteins result in dyslipidemia (see Tables 69-2 and 69-3). These disorders are often familial, but secondary causes also need to be considered. Comorbid conditions (diabetes, hypothyroidism), medications (estrogen, glucocorticoids, β-blockers), and lifestyle factors (diet, alcohol) can increase the production and clearance of lipoproteins. Addressing these factors can often normalize lipid levels. If abnormalities persist, evaluation of genetic factors and treatment with pharmacologic therapy may need to be considered.

Familial Hypercholesterolemia

Mutations in the gene that encodes the LDL (apo B/E) receptor result in familial hypercholesterolemia. Impairment in LDL receptor synthesis or function decreases the clearance of LDL and increases circulating LDL levels, resulting in cholesterol plaque formation. These plaques deposit in the arteries (atheroma), skin or tendons (xanthoma), eyelids (xanthelasma), and iris (corneal arcus). The homozygous form of this autosomal dominant disorder is rare. Affected individuals present early in life with elevated levels of total cholesterol (600 to 1000 mg/dL) and LDL-cholesterol (550 to 950 mg/dL). Triglyceride and HDL-cholesterol levels are normal. These patients develop CHD, aortic stenosis due to atherosclerosis of the aortic root, and tendon xanthomas (often in the Achilles tendon). If the condition remains untreated, patients with homozygous familial hypercholesterolemia typically die of myocardial infarction before 20 years of age. The heterozygous form of familial hypercholesterolemia affects 1 in every 500 individuals, with the partial receptor defect resulting in cells that display half the normal number of fully functional LDL receptors. These individuals have less strongly elevated concentrations of total cholesterol (>300 to 600 mg/dL) and LDL-cholesterol (250 to 500 mg/dL) than do those with the homozygous form. Premature CHD (before 45 years of age in men and 55 years in women) and tendon xanthomas are characteristic clinical findings.

Although familial hypercholesterolemia can be established by identifying one of the many gene mutations in the LDL receptor or by demonstrating diminished LDL receptor function, the diagnosis of familial hypercholesterolemia usually is made on the basis of clinical features. Elevated total cholesterol (>300 mg/dL) and LDL-cholesterol (>250 mg/dL) in an individual with a personal or family history of premature CHD and tendon xanthomas identifies patients at risk for familial hypercholesterolemia. Treatment requires a low-fat (<20% of total calories), low cholesterol (<100 mg/day) diet in combination with drug