hypertriglyceridemia often benefit from a formal dietary consultation with a dietician intimately familiar with counseling patients on the dietary management of high TGs. Dietary fat intake should be restricted to reduce the formation of chylomicrons in the intestine. The excessive intake of simple carbohydrates should be discouraged because insulin drives TG production in the liver. Aerobic exercise and even increase in regular physical activity can have a positive effect in reducing TG levels and should be strongly encouraged. For patients who are overweight, weight loss can help to reduce TG levels. In extreme cases, bariatric surgery has been shown to not only produce effective weight loss but also substantially reduce plasma TG levels.

**Pharmacologic Therapy for Severe Hypertriglyceridemia** Despite the above interventions, however, many patients with severe hypertriglyceridemia require pharmacologic therapy (Table 421-5). Patients who persist in having fasting TG >500 mg/dL despite active lifestyle management are candidates for pharmacologic therapy. There are three classes of drugs that are used for management of these patients: fibrates, omega-3 fatty acids (fish oils), and niacin. In addition, statins can reduce plasma TG levels and also reduce ASCVD risk.

***FIBRATES*** Fibric acid derivatives, or fibrates, are agonists of PPARα, a nuclear receptor involved in the regulation of lipid metabolism. Fibrates stimulate LPL activity (enhancing TG hydrolysis), reduce apoC-III synthesis (enhancing lipoprotein remnant clearance), promote β-oxidation of fatty acids, and may reduce VLDL TG production. Fibrates are a first-line therapy for severe hypertriglyceridemia (>500 mg/dL). This class of therapeutic agents sometimes lowers but more often raises the plasma level of LDL-C in individuals with severe hypertriglyceridemia. Fibrates are generally well tolerated, but are associated with an increase in the incidence of gallstones. Fibrates can cause myopathy, especially when combined with other lipid-lowering therapy (statins, niacin), and can raise creatinine. Fibrates should be used with caution in patients with CKD. Importantly, fibrates can potentiate the effect of warfarin and certain oral hypoglycemic agents, so the anticoagulation status and plasma glucose levels should be closely monitored in patients on these agents.

***OMEGA 3 FATTY ACIDS (FISH OILS)*** Omega-3 fatty acids, or omega-3 polyunsaturated fatty acids (n-3 PUFAs), commonly known as fish oils, are present in high concentration in fish and in flaxseed. The most widely used n-3 PUFAs for the treatment of hyperlipidemias are the two active molecules in fish oil: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). n-3 PUFAs have been concentrated into tablets and in doses of 3–4 g/d are effective at lowering fasting TG levels. Fish oils are a reasonable consideration for first-line therapy in patients with severe hypertriglyceridemia (>500 mg/dL) to prevent pancreatitis. Fish oils can cause an increase in plasma LDL-C levels in some patients. In general, fish oils are well tolerated, with the major side effect being dyspepsia. They appear to be safe, at least at doses up to 3–4 g, but can be associated with a prolongation in the bleeding time.

***NICOTINIC ACID*** Nicotinic acid, or niacin, is a B-complex vitamin that has been used as a lipid-modifying agent for more than five decades. Niacin suppresses lipolysis in the adipocyte through its effect on the niacin receptor GPR109A and has other effects on hepatic lipid metabolism that are poorly understood. Niacin reduces plasma TG and LDL-C levels and also raises the plasma concentration of HDL-C. Because it has a number of side effects and can be difficult to use, it is at best a third-line agent for the management of severe hypertriglyceridemia. Niacin therapy is generally started at lower doses and gradually titrated up to higher doses. The most frequent side effect of niacin is cutaneous flushing, which is mediated by activating GPR109A in the skin. Niacin can cause dyspepsia and can exacerbate esophageal reflux and peptic ulcer disease. Mild elevations in transaminases occur in up to 15% of patients treated with any form of niacin. Niacin can raise plasma levels of uric acid and precipitate gouty attacks in susceptible patients. Acanthosis nigricans, a dark-colored coarse skin lesion, and maculopathy are infrequent side effects of niacin.

## MANAGEMENT OF CHOLESTEROL TO PREVENT CARDIOVASCULAR DISEASE

In contrast to hypertriglyceridemia and pancreatitis, there are abundant and compelling data that intervention to reduce LDL-C substantially reduces the risk of CVD, including myocardial infarction and stroke, as well as total mortality. Thus, it is imperative that patients with hypercholesterolemia be assessed for cardiovascular risk and for the need for intervention. It is also worth noting that patients at high risk for CVD who have plasma LDL-C levels in the "normal" or average range also benefit from intervention to reduce LDL-C levels.

**Lifestyle** The first approach to a patient with hypercholesterolemia and high cardiovascular risk is to make any necessary lifestyle changes. In obese patients, efforts should be made to reduce body weight to the ideal level. Patients should receive dietary counseling to reduce the content of saturated fats, *trans* fats, and cholesterol in the diet. Regular aerobic exercise has relatively little impact on reducing plasma LDL-C levels, although it has cardiovascular benefits independent of LDL lowering.

**Pharmacologic Therapy for Hypercholesterolemia** The decision to use LDL-lowering drug therapy (Table 421-5)—with a statin being first-line therapy—depends on the level of LDL-C as well as the level of cardiovascular risk. In general, patients with a Mendelian disorder of elevated LDL-C such as FH must be treated to reduce the very high lifetime risk of CVD, and treatment should be initiated as early as possible in adulthood or, in some cases, during childhood.

Otherwise, the decision to initiate LDL-lowering drug therapy is generally determined by the level of cardiovascular risk. In patients with established CVD, statin therapy is well supported by clinical trial data and should be used regardless of the LDL-C level. For patients >40 years old without clinical CVD, the AHA/ACC risk calculator *(http://my.americanheart.org/professional/StatementsGuidelines/PreventionGuidelines/Prevention-Guidelines_UCM_457698_SubHomePage.jsp)* can be used to determine the 10-year absolute risk for CVD, and current guidelines suggest that a 10-year risk >7.5% merits consideration of statin therapy regardless of plasma LDL-C level. For younger patients, the assessment of lifetime risk of CVD may help inform the decision to start a statin.

***HMG-CoA REDUCTASE INHIBITORS (STATINS)*** Statins inhibit HMG-CoA reductase, a key enzyme in cholesterol biosynthesis. By inhibiting cholesterol biosynthesis, statins lead to increased hepatic LDL receptor activity and accelerated clearance of circulating LDL, resulting in a dose-dependent reduction in plasma levels of LDL-C. The magnitude of LDL lowering associated with statin treatment varies widely among individuals, but once a patient is on a statin, the doubling of the statin dose produces an ~6% further reduction in the level of plasma LDL-C. The statins currently available differ in their LDL-C–reducing potency (Table 421-5). Currently, there is no convincing evidence that any of the different statins confer an advantage that is independent of the effect on LDL-C. Statins also reduce plasma TGs in a dose-dependent fashion, which is roughly proportional to their LDL-C–lowering effects (if the TGs are <400 mg/dL). Statins have a modest HDL-raising effect (5–10%) that is not generally dose-dependent.

Statins are well tolerated and can be taken in tablet form once a day. Potential side effects include dyspepsia, headaches, fatigue, and muscle or joint pains. Severe myopathy and even rhabdomyolysis occur rarely with statin treatment. The risk of statin-associated myopathy is increased by the presence of older age, frailty, renal insufficiency, and coadministration of drugs that interfere with the metabolism of statins, such as erythromycin and related antibiotics, antifungal agents, immunosuppressive drugs, and fibric acid deriva-