disease. This syndrome is often referred to as *isolated low HDL*. A family history of low HDL-C facilitates the diagnosis of an inherited condition, which may follow an autosomal dominant pattern. The metabolic etiology of this disease appears to be primarily accelerated catabolism of HDL and its apolipoproteins. Some of these patients may have ABCA1 mutations and therefore technically have heterozygous Tangier disease. Several kindreds with primary hypoalphalipoproteinemia and an increased incidence of premature CHD have been described, although it is not clear if the low HDL-C level is the cause of the accelerated atherosclerosis in these families. Association of hypoalphalipoproteinemia with premature CHD may depend on the specific nature of the gene defect or the underlying metabolic defect that either directly or indirectly causes the low plasma HDL-C level.

INHERITED CAUSES OF VERY HIGH LEVELS OF HDL-C

CETP Deficiency Loss-of-function mutations in both alleles of the gene encoding CETP cause substantially elevated HDL-C levels (usually >150 mg/dL). As noted above, CETP transfers cholesteryl esters from HDL to apoB-containing lipoproteins (Fig. 421-3). Absence of this transfer activity results in an increase in the cholesteryl ester content of HDL and a reduction in plasma levels of LDL-C. The large, cholesterol-rich HDL particles circulating in these patients are cleared at a reduced rate. CETP deficiency was first diagnosed in Japanese persons and is rare outside of Japan. The relationship of CETP deficiency to ASCVD remains unresolved. Heterozygotes for CETP deficiency have only modestly elevated HDL-C levels. Based on the phenotype of high HDL-C in CETP deficiency, pharmacologic inhibition of CETP is under development as a new therapeutic approach to both raise HDL-C levels and lower LDL-C levels, but whether it will reduce risk of ASCVD remains to be determined.

SCREENING, DIAGNOSIS, AND MANAGEMENT OF DISORDERS OF LIPOPROTEIN METABOLISM

SCREENING

Plasma lipid and lipoprotein levels should be measured in all adults, preferably after a 12-h overnight fast. In most clinical laboratories, the total cholesterol and TGs in the plasma are measured enzymatically, and then the cholesterol in the supernatant is measured after precipitation of apoB-containing lipoproteins to determine the HDL-C. The LDL-C is then estimated using the following equation:

$$\text{LDL-C} = \text{total cholesterol} - (\text{TG}/5) - \text{HDL-C}$$

(The VLDL cholesterol content is estimated by dividing the plasma TG by 5, reflecting the ratio of TG to cholesterol in VLDL particles.) This formula (the Friedewald formula) is reasonably accurate if test results are obtained on fasting plasma and if the TG level does not exceed ~200 mg/dL; by convention it cannot be used if the TG level is >400 mg/dL. LDL-C can be directly measured by a number of methods. Further evaluation and treatment are based primarily on the clinical assessment of absolute cardiovascular risk using risk calculators such as the AHA/ACC risk calculator based on a large amount of observational data.

DIAGNOSIS

A critical first step in managing a lipoprotein disorder is to attempt to determine the class or classes of lipoproteins that are increased or decreased in the patient. Once the hyperlipidemia is accurately classified, efforts should be directed to rule out any possible secondary causes of the hyperlipidemia (Table 421-4). Although many patients with hyperlipidemia have a primary (i.e., genetic) cause of their lipid disorder, secondary factors frequently contribute to the hyperlipidemia. A careful social, medical, and family history should be obtained. A fasting glucose should be obtained in the initial workup of all subjects with an elevated TG level. Nephrotic syndrome and chronic renal insufficiency should be excluded by obtaining urine protein and serum creatinine. Liver function tests should be performed to rule out hepatitis and cholestasis. Hypothyroidism should be ruled out by measuring serum thyroid-stimulating hormone.

Once secondary causes have been ruled out, attempts should be made to diagnose the primary lipid disorder because the underlying genetic defect can provide important prognostic information regarding the risk of developing CHD, the response to drug therapy, and the management of other family members. Obtaining the correct diagnosis often requires a detailed family medical history, lipid analyses in family members, and sometimes specialized testing.

Severe Hypertriglyceridemia If the fasting plasma TG level is >1000 mg/dL, the patient has chylomicronemia. If the cholesterol-to-TG ratio is >10, familial chylomicronemia syndrome must be considered, and LPL activity measured in postheparin plasma can help with making that diagnosis. Most adults with chylomicronemia also have elevated VLDL levels. These individuals usually do not have a Mendelian disorder but instead are genetically predisposed and have secondary factors (diet, obesity, glucose intolerance, alcohol ingestion, estrogen therapy) that contribute to the hyperlipidemia. Such patients are a risk of acute pancreatitis and should be treated to reduce their TG levels and thus their risk of pancreatitis.

Severe Hypercholesterolemia If the levels of LDL-C are very high (greater than a ninety-fifth percentile for age and sex), it is likely that the patient has a genetic cause of hypercholesterolemia. At present, there is no compelling reason to perform molecular studies to further refine the molecular diagnosis because the clinical management is not affected. Recessive forms of severe hypercholesterolemia are rare, but if a patient with severe hypercholesterolemia has parents with normal cholesterol levels, ARH, sitosterolemia, and CESD should be considered. Patients with more moderate hypercholesterolemia that does not segregate in families as a monogenic trait are likely to have polygenic hypercholesterolemia.

Combined Hyperlipidemia The most common errors in the diagnosis of lipid disorders involve patients with combined hyperlipidemia. Elevations in the plasma levels of both cholesterol and TGs are seen in patients with increased plasma levels of VLDL and LDL or of remnant lipoproteins. A β-quantification to determine the VLDL cholesterol/TG ratio in plasma (see discussion of FDBL) or a direct measurement of the plasma LDL-C should be performed at least once prior to initiation of lipid-lowering therapy to determine if the hyperlipidemia is due to the accumulation of remnants or to an increase in both LDL and VLDL. Measurement of plasma apoB levels can help identify patients with FCHL who may require more aggressive treatment.

APPROACH TO THE PATIENT: Lipoprotein Disorders

The major goals in the clinical management of lipoprotein disorders are: (1) prevention of acute pancreatitis in patients with severe hypertriglyceridemia; and (2) prevention of CVD and related cardiovascular events.

MANAGEMENT OF SEVERE HYPERTRIGLYCERIDEMIA TO PREVENT PANCREATITIS

Although the observational relationship between severe hypertriglyceridemia, particularly chylomicronemia, and acute pancreatitis is well-established, there has never been a clinical trial designed or powered to prove that intervention to reduce TGs reduces the risk of pancreatitis. Nevertheless, it is generally considered appropriate medical practice to intervene in patients with TGs >500 mg/dL in order to reduce the risk of pancreatitis. It remains controversial whether individuals with severe hypertriglyceridemia are at increased risk for ASCVD.

Lifestyle Modifying the lifestyle of the patient with severe hypertriglyceridemia often is associated with a significant reduction in plasma TG level. Patients who drink alcohol should be encouraged to decrease or preferably eliminate their intake. Patients with severe