CLINICAL PRACTICE

Hypertriglyceridemia

John D. Brunzell, M.D.

This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A healthy 45-year-old man is found on routine screening to have hypertriglyceridemia. He is a nonsmoker, has a reasonable diet, consumes one alcoholic drink per week, and exercises regularly. He takes no medications. His father died at the age of 55 years in an automobile accident; his mother is healthy at 67 years of age, and he has two healthy older brothers. His blood pressure is normal, his body-mass index (the weight in kilograms divided by the square of the height in meters) is 28, and his waist circumference is 96 cm. His fasting triglyceride level is 400 mg per deciliter, total cholesterol 230 mg deciliter, low-density lipoprotein (LDL) cholesterol 120 mg per deciliter, and high-density lipoprotein (HDL) cholesterol 30 mg per deciliter. His fasting blood glucose level is 90 mg per deciliter. Thyroid and renal function are normal. How should his case be assessed and managed?

THE CLINICAL PROBLEM

Hypertriglyceridemia is a common form of dyslipidemia[1] that is frequently associated with premature coronary artery disease,[2-5] which is generally defined by the occurrence of a myocardial infarction or the need for a coronary-artery procedure before 55 years of age for men and 65 years of age for women. These upper age limits might increase by 5 to 10 years in nonsmoking men and women. Whether hypertriglyceridemia causes coronary artery disease or is a marker for other lipoprotein abnormalities that cause premature coronary artery disease remains controversial.[6] Specifically, hypertriglyceridemia correlates strongly with the presence of small, dense particles of LDL cholesterol and reductions in the HDL_2 component of HDL cholesterol, both of which are known to be associated with premature coronary artery disease. Hypertriglyceridemia has been shown to predict coronary artery disease after adjustment for many traditional risk factors,[6] but not after adjustment for LDL or HDL cholesterol subfractions.

Several common genetic disorders of hypertriglyceridemia cause premature coronary artery disease. These disorders include familial combined hyperlipidemia, the residual dyslipidemia in patients with well-controlled type 2 diabetes mellitus, and familial hypoalphalipoproteinemia. Each of these disorders shares features of the metabolic syndrome.[7] Disorders associated with premature coronary artery disease are common: familial combined hyperlipidemia[2,4,5] and familial hypoalphalipoproteinemia[4,8] each affect about 1% of the general population, and type 2 diabetes affects more than 5%. Together, these three disorders have been purported to account for up to 50% of premature coronary artery disease events.[9] These diagnoses therefore warrant aggressive interventions to reduce the cardiovascular risk. In contrast, one other inherited form of hypertriglyceridemia — monogenic familial hypertriglyceridemia — is not associated with premature coronary artery disease; this

From the Department of Medicine, Division of Metabolism, Endocrinology, and Nutrition, and the Northwest Lipid Metabolism and Diabetes Research Laboratories, University of Washington, Seattle. Address reprint requests to Dr. Brunzell at brunzell@u.washington.edu.

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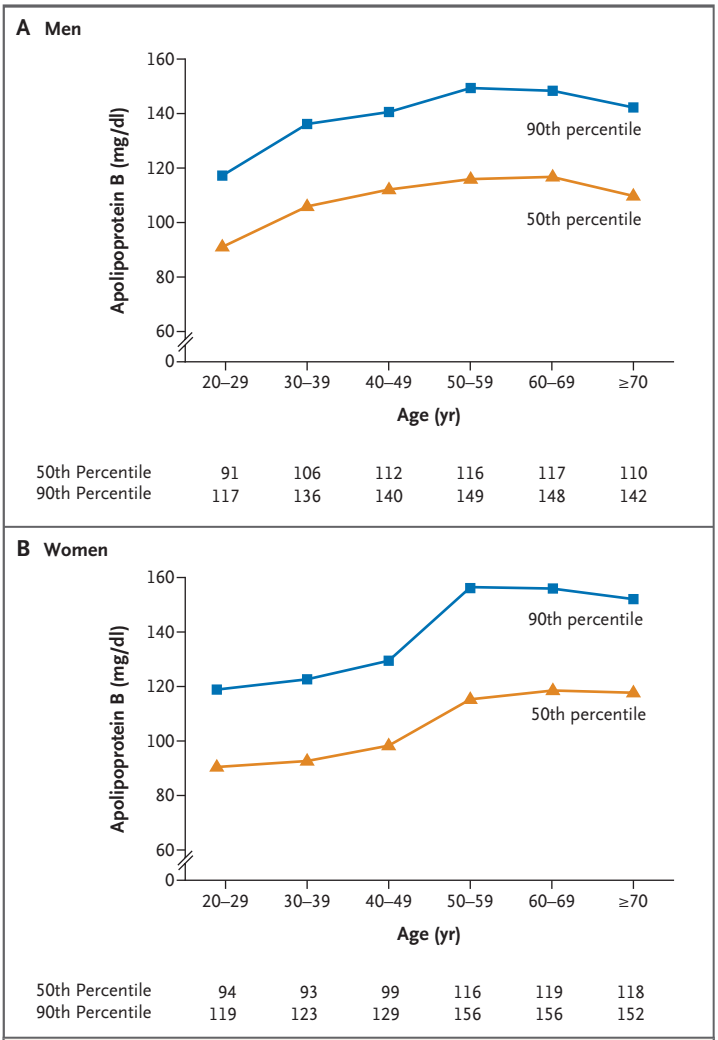

Figure 1. Apolipoprotein B Levels According to Age and Sex.

Patients with the metabolic syndrome who have elevated levels of apolipoprotein B (>90th percentile for age) have familial combined hyperlipidemia and should receive aggressive lipid-lowering therapy. The data, which are based on a total of 11,483 participants in the third National Health and Nutrition Examination Survey (1988–1991), are from Carr and Brunzell.[7]

disorder also affects up to 1% of the population[3,9,10] and must be distinguished from the other disorders in making treatment decisions.

Obesity (in particular, central obesity) is associated with increased triglyceride levels and decreased HDL cholesterol levels. Central obesity paired with insulin resistance is probably a major factor contributing to the dyslipidemia[11] associated with type 2 diabetes, familial combined hyperlipidemia, and familial hypoalphalipoproteinemia. The metabolic syndrome is associated with an increased risk of coronary artery disease even among people who do not have diabetes,[12] but it is unclear whether this is the case when familial combined hyperlipidemia and familial hypoalphalipoproteinemia are absent.[7]

Other abnormalities leading to secondary hypertriglyceridemia include untreated or uncontrolled diabetes, treatment with several medications (Table 1), and alcohol consumption. More complex forms of secondary hypertriglyceridemia develop with hypothyroidism, end-stage renal disease, the nephrotic syndrome, and human immunodeficiency virus infection; these disorders are not covered in this article. Patients with triglyceride levels above 2000 mg per deciliter (22.6 mmol per liter) almost always have both a secondary and a genetic form of hypertriglyceridemia.[13]

STRATEGIES AND EVIDENCE

EVALUATION

The evaluation of patients with hypertriglyceridemia should initially focus on whether there is a family history of the condition or a personal or family history of premature coronary artery disease; in addition, potential secondary causes (e.g., medications or untreated diabetes) should be identified. The presence of premature coronary artery disease in a first-degree relative (parent or sibling) or in a sibling of a parent suggests familial combined hyperlipidemia or familial hypoalphalipoproteinemia and indicates the need to consider drug therapy.

Xanthomas are usually not present in mild-to-moderate hypertriglyceridemia; when present, they do not help distinguish the various hypertriglyceridemic disorders. The body-mass index should be calculated, and waist circumference measured. The combination of an elevated triglyceride level and a large waist circumference[14] may be a better marker of insulin resistance and the risk of coronary disease than hypertriglyceridemia alone; the presence of a large waist circumference (defined in European Americans as a value greater than 40 in. [101.6 cm] for men and 35 in. [88.9 cm] for women) may help to distinguish familial hypertriglyceridemia (which is not associated with central adiposity or an increased cardiovascular risk) from familial combined hyperlipidemia or familial hypoalphalipoproteinemia.

Usually, a fasting lipid profile is the only laboratory work needed to evaluate lipids in a patient

with elevated triglyceride levels and premature coronary artery disease. Although nonfasting triglyceride levels have recently been associated with coronary heart disease,[15] the measurement of nonfasting triglyceride levels is not currently recommended because no standard values have been developed and because most of the variation in postprandial triglyceride levels is determined by the fasting level. Patients with familial combined hyperlipidemia may have elevated or normal LDL cholesterol levels. HDL cholesterol levels are reduced in both familial combined hyperlipidemia and familial hypoalphalipoproteinemia.

Small, dense LDL particles are also present in both familial combined hyperlipidemia and familial hypoalphalipoproteinemia and, as noted above, have been associated with premature coronary artery disease.[16] In patients with elevated triglyceride levels in the absence of a personal or family history of clinical atherosclerosis, the measurement of apolipoprotein B levels may help to distinguish familial combined hyperlipidemia from familial hypertriglyceridemia. In both disorders, the level of apolipoprotein B can be used to estimate the total number of LDL particles (large and small). Apolipoprotein B levels are higher in familial combined hyperlipidemia and lower in familial hypertriglycieridemia.[17] The nomograms for apolipoprotein B (Fig. 1), developed from the third National Health and Nutrition Examination Survey, can be used to define elevated apolipoprotein B as an age- and sex-adjusted value above the 90th percentile.[7] The current National Cholesterol Education Program recommends the measurement of non-HDL cholesterol (which consists of total cholesterol minus HDL cholesterol and includes triglyceride-rich lipoprotein cholesterol) instead of apolipoprotein B. Even though non-HDL cholesterol is a better predictor of cardiovascular risk than LDL cholesterol,[18] several studies have suggested that apolipoprotein B may be an even better predictor than non-HDL cholesterol.[9,19] Although data from an international study indicate that the ratio of apolipoprotein B to apolipoprotein A-I is highly predictive of early coronary artery disease,[20] the added value of apolipoprotein A-I measurements in refining risk estimates is unclear; consequently, apolipoprotein A-I levels are not routinely measured in clinical practice.

Likewise, measurement of the size or density of LDL particles is currently considered a research tool and is not recommended in routine care. Measurement of Lp(a) lipoprotein levels does not help to distinguish forms of hypertriglyceridemia, but it may be useful in assessing the relative risk of atherosclerosis among patients who have hypertriglyceridemia in combination with other lipid or nonlipid cardiovascular risk factors.[21] However, data that support the routine measurement of Lp(a) lipoprotein levels in patients with normal lipid levels are lacking. Similarly, there are no data to support routine assessment for subclinical vascular disease (by means of coronary calcium scanning or other types of imaging) in patients with asymptomatic hypertriglyceridemia.

Table 1. Effects of Selected Drugs on Triglyceride and Cholesterol Levels.*

Drug	Triglycerides	LDL Cholesterol	HDL Cholesterol
Alcohol	Increased	No effect	Increased
Estrogens, estradiol	Increased	Decreased	Increased
Androgens, testosterone	Increased	Increased	Decreased
Progestins	Decreased	Increased	Decreased
Glucocorticoids	Increased	No effect	Increased
Cyclosporines	Increased	Increased	Increased
Tacrolimus	Increased	Increased	Increased
Thiazide diuretics	Increased	Increased	Decreased
Beta-blockers	Increased	No effect	Decreased
Sertraline	Possible increase	Increased	No effect
Protease inhibitors	Increased	No effect	No effect
Valproate and related drugs	Increased	No effect	Decreased
Isotretinoin	Increased	No effect	Decreased

* Alcohol, estrogens, estradiol, glucocorticoids, thiazide diuretics, beta-blockers, sertraline, protease inhibitors, valproate and related drugs, and isotretinoin can cause severe hypertriglyceridemia and the chylomicronemia syndrome in patients with a familial form of hypertriglyceridemia. LDL denotes low-density lipoprotein, and HDL high-density lipoprotein.

MANAGEMENT

After treatment of secondary disorders and removal of offending medications, lifestyle modification and drug treatment should be considered in a patient with hypertriglyceridemia who is considered to be at risk for premature coronary artery disease (Fig. 2). A major question in management is whether therapy should be directed solely toward reduction of triglyceride levels or toward the modification of associated abnormalities of intermediate-density lipoprotein, LDL, and HDL

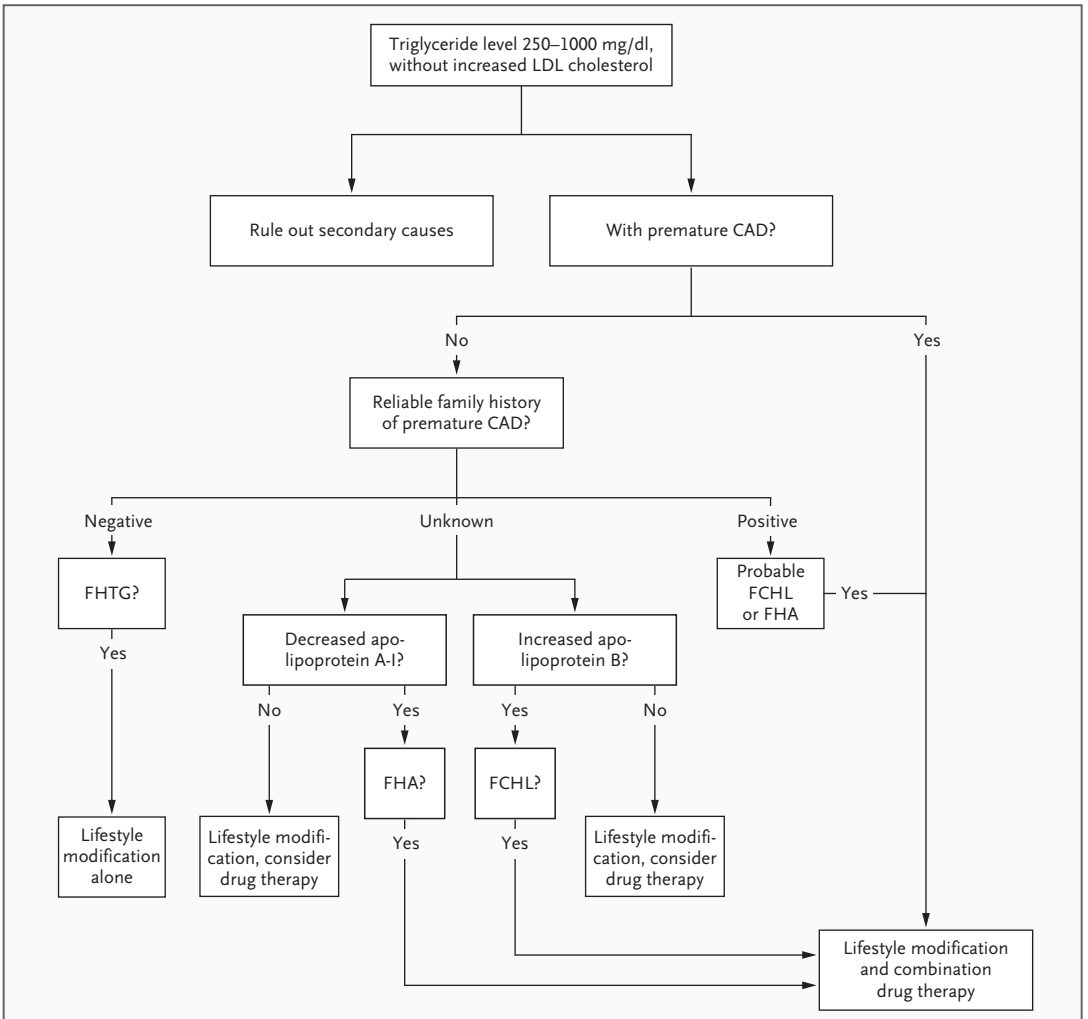

Figure 2. Algorithm for the Diagnosis and Management of Moderate Hypertriglyceridemia.

After secondary causes of hypertriglyceridemia have been ruled out, patients who do not have clinical premature coronary artery disease (CAD) should undergo evaluation, including family history, apolipoprotein B levels, and possibly apolipoprotein A-I levels, to distinguish genetic disorders associated with a risk of premature CAD (familial combined hyperlipidemia [FCHL] and familial hypoalphalipoproteinemia [FHA]) from a genetic disorder that is not associated with an increased risk of premature CAD (familial hypertriglyceridemia [FHTG]). The ultimate diagnosis dictates the form of therapy required. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129.

cholesterol.[7,14,22] Triglyceride levels greater than 1000 to 1500 mg per deciliter (11.3 to 16.9 mmol per liter)[13,23] require treatment with fibrates to reduce the risk of pancreatitis. The benefit of treating mild-to-moderate elevations in triglyceride levels is less clear.[24]

Lifestyle Modification

Weight loss results in a mild-to-moderate decrease in triglyceride levels (about 22%) and an increase in HDL cholesterol (about 9%), largely because of an increase in HDL_2 cholesterol (about 43%). The level of small, dense LDL particles may decrease by as much as 40%.[25] Although losing large amounts of weight and maintaining that weight loss are difficult,[26] even moderate weight loss may result in reductions in triglyceride levels and may be maintained with regular aerobic exercise.[26-28]

Aerobic exercise of moderate intensity with high frequency (about 4 hours per week) has been associated with maintenance of improved cardiorespiratory fitness.[29,30] It has also been associated with a decrease in intraabdominal fat, an increase in HDL cholesterol levels if those levels

were low, and a small decrease in triglyceride levels.[31,32]

Although a decrease in dietary fat can lead to weight loss (and associated reductions in triglyceride levels), diets that are low in fat but high in carbohydrates may result in reductions in both LDL and HDL cholesterol.[27] Because replacing saturated fat with monounsaturated fat leads to a smaller decrease in HDL cholesterol than replacing saturated fat with carbohydrates, a reasonable approach is to reduce foods rich in saturated fat and replace them with complex carbohydrates and monounsaturated and polyunsaturated fats.[27] It is also advisable to avoid simple sugars, particularly fructose, which has been associated with postprandial hypertriglyceridemia.[33] Fructose is present in many carbonated beverages and fruit-juice mixes, and high-fructose corn syrup is added to many prepared foods as a preservative and sweetener. For patients with exercise limitations, the combination of a diet low in saturated fat and a regimen of walking on a daily basis is a lifestyle change that can usually be maintained.

Supplementation with n–3 fatty acids may lower triglyceride levels and, according to some data, reduce cardiovascular events.[34] However, a meta-analysis of trials did not show a significant reduction in cardiovascular events or mortality with dietary or pharmacologic n–3 fatty acid supplementation.[35]

Cigarette smoking is associated with an earlier occurrence of coronary artery disease, by about 10 years. Discontinuation of smoking is associated with improvement in lipid levels despite the weight gain that often follows cessation.

Alcohol intake is associated with a reduced risk of atherosclerotic cardiovascular disease but also leads to an increase in blood pressure and in the risk of hemorrhagic stroke. Modest alcohol intake (two drinks per day for men and one drink per day for women) is considered acceptable in people who do not have a predisposition for alcohol abuse. Patients with severe hypertriglyceridemia (triglyceride levels above 2000 mg per deciliter) associated with alcohol use should abstain.[36,37] The limited effect in patients with triglyceride levels below 500 mg per deciliter (5.6 mmol per liter) should not preclude moderate alcohol intake.[38]

Medication

As noted above, no set targets for triglyceride levels are clearly warranted other than to reduce the risk of pancreatitis. Generally, medications are considered in patients with hypertriglyceridemia who have a personal or family history of premature coronary disease. When medications are used, those that specifically decrease the level of small, dense LDL particles and raise the level of HDL_2 particles are preferred (Table 2).

In patients with, or at risk for, premature coronary artery disease, statins are generally considered the first drug of choice to lower LDL cholesterol.[39] Nicotinic acid therapy, often combined with a statin, may be an alternative first choice in patients at risk for premature coronary artery disease. Nicotinic acid can reduce the level of small, dense LDL particles and raise the level of HDL_2 particles (Table 2). In the Coronary Drug Project, nicotinic acid resulted in a 15% reduction in the risk of myocardial infarction among men with hypercholesterolemia who had atherosclerosis[40] and decreased total mortality by 10% at 15 years.[41] In the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2 trial,[42] it was also shown to prevent the progression of carotid artery disease in patients with atherosclerosis who were already receiving statin therapy.

Nicotinic acid in combination with other drugs has been shown to be effective in reducing the progression of atherosclerosis in patients with hypertriglyceridemia who are at risk for premature coronary artery disease. For example, in a randomized study involving patients with atherosclerosis, low HDL cholesterol levels, and borderline-high triglyceride levels, the combination of nicotinic acid and simvastatin was associated with a slight regression of coronary stenoses, whereas placebo or antioxidant vitamins were associated with progression.[43] However, neither medication was studied alone, and there were few clinical end points. In another study, involving men with elevated apolipoprotein B levels, nicotinic acid in combination with colestipol reduced the frequency of progression of atherosclerosis as compared with placebo.[44] Nicotinic acid is available in crystalline form and extended-release form.[45] Flushing may be a bothersome side effect, but its frequency may be minimized by education about use.

Fibrates also lower triglyceride levels, but the results of randomized trials have been equivocal in terms of major outcomes, generally showing decreases in the rates of nonfatal myocardial infarction but not in the rates of fatal coronary

Table 2. Pharmacologic Treatment for Hypertriglyceridemia.

Drug Class	Decrease in Triglycerides (%)	Maintenance Regimen	Contraindications	Side Effects	Selective Decrease in Small, Dense LDL Cholesterol	Selective Increase in HDL_2 Cholesterol
Nicotinic acid	17–26	1500–2000 mg once a day	Hypersensitivity, hepatic dysfunction	Flushing, pruritus, nausea, hepatitis (at higher doses), activation of migraine (rare)	Yes	Yes
Fibrates	18–45	Gemfibrozil, 600 mg twice a day; Fenofibrate, 145 mg once a day	Hypersensitivity, hepatic dysfunction, end-stage renal disease	Myositis, cholelithiasis	Yes	No
Statins	5	Multiple agents	Hypersensitivity, pregnancy, breast-feeding	Myalgia, influenza-like syndrome, rhabdomyolysis (rare), weakness	No	No
Nicotinic acid and statin	36	Same as for individual agents	Same as for individual agents	Same as for individual agents	Yes	Yes

events or total mortality. In the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial, the use of gemfibrozil resulted in a significant decrease in the primary outcome of coronary heart disease and nonfatal myocardial infarction, but not in the secondary outcome of fatal myocardial infarction or death from any cause.[46] In a World Health Organization trial, the use of clofibrate in men with hypercholesterolemia resulted in a reduction in the rate of nonfatal myocardial infarction, but there was no decrease in the rate of fatal myocardial infarction or total mortality.[47] Such findings raise questions about the use of a fibrate as a first-line drug for mild-to-moderate hypertriglyceridemia. Gastrointestinal side effects were also common with this therapy; similar findings were reported in another randomized trial of gemfibrozil.[48]

Treatment in Patients with Diabetes

Use of statin therapy to lower LDL cholesterol levels is recommended for adults with type 2 diabetes mellitus who are considered to be at increased risk for coronary artery disease according to the criteria of the American Diabetes Association[49] and the National Cholesterol Education Program.[39] In patients with type 2 diabetes, the combination of statins and fibrates has often been used to treat hypertriglyceridemia. However, in the Fenofibrate Intervention and Event Lowering in Diabetes Trial, use of fenofibrate did not result in a significant reduction in the primary outcome — nonfatal myocardial infarction or fatal coronary heart disease — in patients with type 2 diabetes.[50] A reduction in the rate of nonfatal myocardial infarction was offset by a slight increase in the rate of fatal myocardial infarction.

It has been suggested that nicotinic acid, which may interfere with glucose control, not be used as a first-line drug for the treatment of hypertriglyceridemia in patients with diabetes. However, several trials have demonstrated that nicotinic acid therapy can be used in patients whose diabetes is well controlled, with little effect on glucose levels.[43,51,52]

AREAS OF UNCERTAINTY

Without knowledge of the family history, it may be challenging to differentiate patients who are at increased risk for premature coronary artery disease from those who are not. Apolipoprotein B levels, and often LDL cholesterol levels, tend to be higher in familial combined hyperlipidemia than in familial hypoalphalipoproteinemia or familial hypertriglyceridemia, and levels of small, dense LDL particles tend to be lower in familial hypertriglyceridemia than in the other two conditions, but there is considerable overlap among all three. Until the basic biochemical defects for each of the genetic forms of hypertriglyceridemia are defined, decisions about the use of drugs to prevent premature coronary artery disease must be based on the presence or absence of a family history of pre-

mature atherosclerosis and dyslipidemia. Once premature coronary artery disease has developed, secondary prevention with lipid-lowering therapy is indicated, and there is no need to differentiate among the types of hypertriglyceridemia. The optimal pharmacologic approach in patients with premature coronary artery disease remains uncertain, including whether it is preferable to start with a statin or to begin with nicotinic acid and add a statin as needed. The role of fibrates also remains unclear.

GUIDELINES

The National Cholesterol Education Program[39] has specific recommendations for target LDL cholesterol levels, but not for target triglyceride levels. Treatment with fibrates is recommended for patients with triglyceride levels over 1000 mg per deciliter in order to decrease the risk of triglyceride-induced pancreatitis.[13,23] After the target level for LDL cholesterol has been reached, the program recommends lowering triglyceride levels if they are above 200 mg per deciliter (2.6 mmol per liter),[39] although there are no data to support this recommendation.

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette has an elevated triglyceride level and a low HDL cholesterol level, but his LDL cholesterol is not elevated. Neither the increased triglyceride level nor the low HDL cholesterol level helps to determine whether he has familial hypertriglyceridemia, familial combined hyperlipidemia, or familial hypoalphalipoproteinemia, which makes it difficult to assess the associated risk of premature coronary artery disease. There is no apparent secondary cause of his hypertriglyceridemia, and he has no other apparent risk factors for premature coronary artery disease. A first step in evaluating patients with hypertriglyceridemia is to obtain an extensive family history, sometimes having the patient do homework to establish the presence of atherosclerosis in one or more family members, the age at onset, and, if an affected first-degree relative has died, the age at and cause of death; a family history will often identify other relatives who might need lipid-lowering therapy. A family history of premature coronary artery disease would suggest familial combined hyperlipidemia or familial hypoalphalipoproteinemia.

If a patient has many adult relatives with hypertriglyceridemia but without clinical evidence of atherosclerosis, successful treatment of the hypertriglyceridemia and low HDL cholesterol level might be accomplished with lifestyle modifications alone, including a reduced-calorie diet that is low in saturated fat and a program of regular aerobic exercise. If the patient has or is at apparent risk for premature coronary artery disease on the basis of the family history and appears to have familial combined hyperlipidemia or familial hypoalphalipoproteinemia, pharmacologic therapy should be considered in addition to lifestyle modification. Although the optimal therapy is uncertain, in such cases I would favor combined treatment with nicotinic acid and a statin.

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