Triglycerides: Do They Matter?

The growing consensus is that they do, and a variety of lifestyle and pharmacologic treatments are available.

ABSTRACT: Since the introduction of HMG-CoA reductase inhibitors, also known as statins, as an adjunct to diet in the treatment of hyperlipidemia and the greater emphasis placed on reducing low-density lipoprotein (LDL) cholesterol levels in the prevention of atherosclerosis and cardiovascular disease (CVD), there has been less focus on the value of lowering serum triglyceride levels. Many patients are aware of their "good" and "bad" cholesterol levels, but they may not be aware of their triglyceride level or of the association between high triglycerides and the development of CVD. In recent years, however, in light of the increasing incidences of obesity, insulin resistance, and type 2 diabetes, lowering triglyceride levels has gained renewed interest. In addition to the focus on lowering LDL cholesterol levels in CVD prevention, clinicians need to be aware of the role of triglycerides—their contribution to CVD, and the causes and treatment of hypertriglyceridemia.

Keywords: cardiovascular disease, coronary heart disease, hypertriglyceridemia, lifestyle moderation, therapeutic lifestyle changes, treatment, triglycerides

Several factors have led clinicians to place less emphasis on controlling serum triglyceride levels in the past few decades: a lack of strong evidence on their contribution to cardiovascular disease (CVD); the introduction of HMG-CoA reductase inhibitors, also known as statins, in the treatment of hyperlipidemia; and an increased emphasis on reducing low-density lipoprotein (LDL) cholesterol levels—together with the beneficial effects of raising high-density lipoprotein (HDL) cholesterol levels—in preventing CVD. There has also been an effort to stop focusing on specific target goals of therapy, as evidenced in the recently issued American Heart Association/American College of Cardiology (AHA/ACC) guidelines that shifts the focus toward percent LDL reductions and away from achieving specific LDL goals.[1]

Targeting triglyceride levels in the prevention of CVD has been controversial because strong evidence for the effect of high triglyceride levels on coronary artery disease (CAD) was lacking. This lack of evidence was due, in part, to the association of triglycerides with other known metabolic risk factors, such as age, hypertension, smoking, type 2 diabetes, obesity, and low HDL and high LDL cholesterol levels.[2,3] However, recent studies have indicated that fasting and nonfasting serum triglyceride levels may be independent risk factors for CAD; this has led to a growing interest among clinicians in lowering triglyceride levels.[4] In fact, in patients who undergo treatments for CAD, such as percutaneous coronary intervention or coronary artery bypass surgery, hypertriglyceridemia is associated with worse outcomes.[5] Several trials have also demonstrated that severe hypertriglyceridemia is associated with an increased risk of acute pancreatitis.[5,6]

Clinicians often encounter patients who are aware of their "good" and "bad" cholesterol levels; however,

even well-informed patients may be unaware of their triglyceride level and of the association between high triglycerides and the development of CVD. Controlling patients' triglyceride levels is especially important in light of the increasing incidence of concomitant diseases such as obesity, insulin resistance, and type 2 diabetes.[7] The purpose of this article is to discuss the importance of lowering triglyceride levels and the lifestyle changes and medications that can help to achieve this goal.

OVERVIEW OF PLASMA LIPIDS AND LIPID TRANSPORT

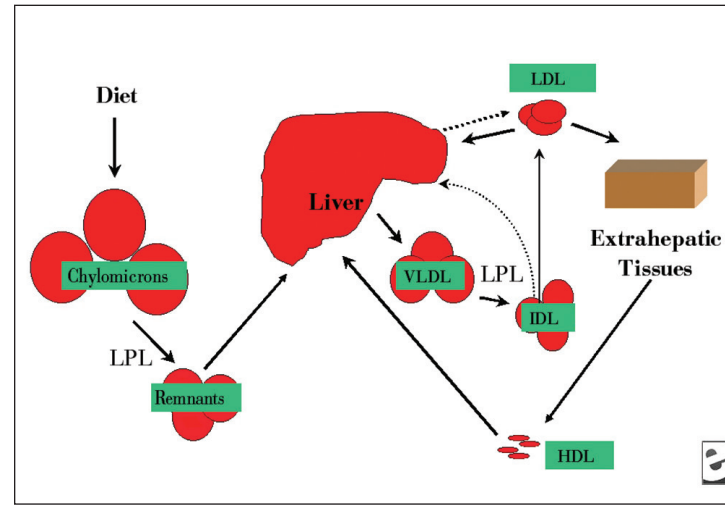
Lipids are a large group of organic molecules that, along with proteins and carbohydrates, make up the main structural components of living cells. While lipids are commonly thought of as "fats," they comprise a variety of usually water-insoluble substances that are essential in human physiology and metabolism, including triglycerides—our focus in this article—as well as fats, waxes, sterols, fat-soluble vitamins, mono- and diglycerides, and phospholipids. Lipids are important in storing and converting energy and signaling between cells, among other functions. Because of their relative insolubility in water, lipids do not circulate freely in the blood; they are transported inside larger molecular complexes, the lipoproteins. Two of these are familiar to clinicians and patients alike: HDL and LDL cholesterol. Less well known are the triglyceride-rich lipoproteins: very-low-density lipoproteins (VLDLs), chylomicrons, and their remnants.

Triglycerides are stored in adipose cells, which are constantly undergoing breakdown and resynthesis in order to produce energy.[8] Composed of three fatty acids bound to glycerol, triglycerides are either manufactured in the body or consumed in food. After glucose, triglycerides are an important source of energy in human physiology. Hypertriglyceridemia can result from either increased production or decreased breakdown of triglyceride-rich lipoproteins, leading to the increased presence of atherogenic remnant particles in the circulation.[3]

Following ingestion of a meal, dietary fat and cholesterol are absorbed from the small intestine, where they are processed by dietary enzymes and incorporated into chylomicrons. The chylomicrons are then secreted from the intestine into the lymphatic system and from there enter the systemic circulation through the thoracic duct.[3] Chylomicrons undergo various metabolic processes that result in free fatty acids, which can be used as a source of energy in the muscle or heart or stored in adipose tissue (see Figure 1).

Although LDL is one of the primary lipoproteins involved in atherosclerosis, other lipoproteins are also able to penetrate the arterial wall and contribute to plaque formation.[3] Plasma triglyceride levels reflect the presence of VLDLs, chylomicrons, and remnant lipoprotein particles. Although chylomicrons (and most likely VLDLs) are too large to penetrate the arterial wall, the remnants are small enough and have been shown to promote atherosclerosis.[3]

Figure 1. Diagram of Cholesterol Metabolism



Dietary fat and cholesterol are absorbed from the intestine and incorporated into chylomicrons, which interact with lipoprotein lipase (LPL) to release free fatty acids for energy. The liver also produces cholesterol in the form of very-low-density lipoprotein (VLDL), which is hydrolyzed by LPL, generating smaller, denser intermediate-density lipoprotein (IDL). About half of IDL particles are removed by the liver and half undergo further catabolism to become low-density lipoproteins (LDLs), which are transported either to the liver or to extrahepatic tissues for use. Cholesterol is transported from the tissues to the liver by high-density lipoprotein (HDL). Image reprinted with permission from Medscape Drugs and Diseases (http://emedicine.medscape.com), 2016, available at: http://emedicine.medscape.com/article/121424-overview.

HYPERTRIGLYCERIDEMIA

The AHA defines high triglyceride levels as those between 200 and 499 mg/dL and very high triglycerides as those greater than or equal to 500 mg/dL.[7] (See Table 1.[7]) Approximately one-third of the U.S. adult population have triglyceride levels greater than or equal to 150 mg/dL, with Mexican American men having the highest rates of both high and very high triglyceride levels.[7] The prevalence of hypertriglyceridemia increases with age and is greater in men than in women.[9]

Causes of hypertriglyceridemia. Hypertriglyceridemia can be classified as primary or secondary.[6]

Table 1. Classification of Triglyceride Levels[7]

Triglyceride Level	Classification
< 150 mg/dL	Normal
150 to 199 mg/dL	Borderline High
200 to 499 mg/dL	High
≥ 500 mg/dL	Very High

Primary hypertriglyceridemia is the result of various genetic disorders that affect lipoprotein metabolism.[10] Secondary hypertriglyceridemia is associated with a number of metabolic conditions. Obesity and uncontrolled or poorly controlled diabetes are the metabolic stressors most frequently associated with secondary hypertriglyceridemia. Alcohol consumption, which increases VLDL in the plasma, can also elevate triglyceride levels.[10] Nephrotic syndrome and uremia, both of which increase VLDL, are also associated with hypertriglyceridemia.[6] Other conditions associated with elevated triglyceride levels include type 2 diabetes, insulin resistance, metabolic syndrome, Cushing's syndrome, HIV infection, hypothyroidism, hypopituitarism, acromegaly, and certain autoimmune disorders, such as systemic lupus erythematosus.[10,11] Although elevated triglycerides are seen in the third trimester of pregnancy, their presence usually does not affect endothelial function and, therefore, doesn't carry the same risk of CAD.[12] Furthermore, certain drugs such as corticosteroids, thiazide and loop diuretics, bile acid sequestrants, protease inhibitors, β-blockers, and estrogens can also lead to elevated triglyceride levels.[13]

Measurement of triglycerides. Triglyceride levels increase after eating, and they may be elevated for up to six hours after a high-fat meal.[14] Although fasting for nine to 12 hours is generally recommended before triglyceride levels are measured, triglycerides may increase transiently after periods of prolonged fasting.[15] In addition to fasting, other factors that affect triglyceride measurement include the effects of posture and length of tourniquet time (that is, the amount of time the veins are occluded) during venipuncture.[15] Postural changes can result in temporary changes in triglyceride levels because of shifts in plasma volume; therefore, a standardized venipuncture procedure, in which the patient is asked to sit for a minimum of five minutes, should be implemented.[16] Longer venous occlusion times can raise triglyceride levels; therefore, venipuncture should occur within one minute of tourniquet application.

Although the current standard of care is to measure fasting triglyceride levels, recent studies indicate that measuring nonfasting triglycerides may be adequate for the diagnosis of hypertriglyceridemia and may even be a more accurate indicator of cardiovascular risk.[17] Moreover, it may not be feasible to obtain fasting triglyceride levels at afternoon appointments. Therefore, it would be reasonable to obtain nonfasting levels, if necessary, and recheck the levels in two to four weeks if they exceed 200 mg/dL.[7]

LIFESTYLE MANAGEMENT

The treatment of elevated triglycerides emphasizes targeted therapeutic lifestyle changes; however, secondary causes of hypertriglyceridemia need to be either ruled out or diagnosed and treated.[18] For example, reducing serum glucose in individuals with diabetes helps decrease triglyceride levels.[10] Furthermore, medications that have the potential to cause elevated triglycerides need to be evaluated; drug substitution within the same class of drugs may be helpful. For example, oral contraceptives that contain a high concentration of estrogen can greatly influence triglyceride levels; therefore, in patients with hypertriglyceridemia preparations that contain less estrogen or other forms of contraception should be considered.[7]

Clinicians should counsel patients with hypertriglyceridemia that lifestyle modification is the cornerstone of treatment. An interdisciplinary approach that includes consultation with a registered dietician may be beneficial.[19] For patients who are overweight, the aim is to lose weight by consuming fewer calories and increasing daily exercise; reducing carbohydrate consumption can also help to reduce weight and lower triglycerides.[20] In patients with triglyceride levels greater than or equal to 150 mg/dL, physical activity has been shown to decrease triglycerides by up to 20%.[21] To promote increased physical activity, it's important that clinicians negotiate measurable, achievable goals with the patient; therefore, they should encourage patients to choose an activity they enjoy, such as brisk walking, bike riding, hiking, dancing, or golf.[19] The American College of Sports Medicine (ACSM) recommends a minimum of 150 minutes per week of moderate-intensity endurance exercise (the equivalent of an expenditure of 1,000 kilocalories per week).[22] Clinicians should strongly encourage patients to exercise consistently for 30 minutes a day, five days per week, or for 50 minutes a day, three days per week.[23] Pedometers are also popular and may provide a more accurate assessment of activity as compared with an individual's subjective recall.[24] Walking 10,000 steps per day is often recommended as a general guideline.[25] However, an important point for clinicians and patients to remember is that steps taken in the incidental activities of daily living should not be counted toward the 10,000-step goal.[25] Recent data demonstrate that individuals who reported exercising strenuously three days per week accumulated a mean 5,486 (SD, 231) steps per day; those who exercised four to five days

per week accumulated a mean 6,200 (SD, 220) steps per day. Overweight participants reported taking fewer steps, and the number of steps taken per day also decreased with age.[24] The ACSM recommends that clinicians encourage patients to set goals for steps per minute as well as duration of exercise—for example, 100 steps per minute for 30 minutes per session.[22]

Dietary recommendations aimed at lowering triglyceride levels include reducing caloric intake as well as consumption of refined carbohydrates, fructose, and saturated fat and increasing the intake of dietary fiber to more than 30 g per day.[7]

asymptomatic hypertriglyceridemia prevents or decreases the risk of pancreatitis.[29] Pharmacologic treatment, in addition to intensive lifestyle modification that includes abstinence from alcohol, is considered reasonable in preventing pancreatitis in patients with triglyceride levels greater than or equal to 500 mg/dL and in those with a history of triglyceride-induced pancreatitis.[7] Medications commonly used to treat hypertriglyceridemia include fibrates, niacin, omega-3 fatty acids, statins, and ezetimibe.

Fibrates. Although fibrates typically decrease triglyceride levels by approximately 36%, the

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Although the literature suggests that low-to-moderate alcohol consumption may lower triglyceride levels, excess alcohol consumption is known to increase the secretion of VLDLs and lead to hypertriglyceridemia. The type of alcohol and other factors, such as a high-fat diet, can intensify hypertriglyceridemia; therefore, clinicians should encourage patients with high triglyceride levels to limit or cease consumption of alcoholic beverages.[26] Clinicians should also encourage patients to consume fresh fruits and vegetables; whole grains; fish containing omega-3 fatty acids, such as salmon, trout, and halibut; and plants and plant-based foods containing omega-3 fatty acids, such as flaxseed, walnuts, soybeans, and canola oil.[19, 27, 28] Diets that contain moderate levels of unsaturated fat and plant-based proteins may also lower triglyceride levels.[7]

PHARMACOLOGIC THERAPY

Recommendations regarding pharmacologic treatment are limited by the lack of clinical trials designed specifically to examine the effect of triglyceride reduction on the incidence of CVD, and the fact that most trials restricted participants to those with triglyceride levels lower than 400 mg/dL.[7] However, some trials have suggested that pharmacologic treatment may be of value.[7] Also of note, while it's clear that patients with very high triglyceride levels are at increased risk for pancreatitis, it's uncertain whether treatment of cardiovascular outcomes have been inconsistent.[18] The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, which evaluated the effect of fibrate therapy on cardiovascular events in 9,795 participants with type 2 diabetes, did not demonstrate a benefit of fenofibrate on the primary outcome of myocardial infarction, sudden death, and coronary events.[30] This may be due, in part, to the treatment effect of statins: the placebo group reported greater use of statins than the fibrate group. In a 2010 systematic review and meta-analysis, however, fibrate therapy was shown to reduce the incidence of major cardiovascular events, although there was no beneficial effect on stroke and all-cause mortality.[31] Current guidelines recommend fenofibrate as the fibrate of choice in fibrate–statin combination therapy.[32] However, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid study did not find that the combination of fenofibrate and simvastatin lowered the rate of the primary outcome of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke in patients with type 2 diabetes, when compared with simvastatin monotherapy.[33] Subgroup analysis suggested that in patients whose triglyceride levels were high (greater than or equal to 204 mg/dL) and whose HDL cholesterol levels were low (less than or equal to 34 mg/dL), the fenofibrate-statin combination did lower the rate of the primary outcome compared with the statin alone.

Fibrates available in the United States include fenofibrate (Tricor and others) and gemfibrozil (Lopid and others). Although myopathy and rhabdomyolysis occur infrequently, they have been reported when fibrates are coadministered with a statin, particularly in the case of gemfibrozil.[34] Elderly patients and patients with diabetes, renal failure, or hypothyroidism are at a higher risk for complications of myopathy and rhabdomyolysis.[35] Clinicians should monitor patients and instruct them to report any complaints of muscle discomfort or weakness. Fibrates can elevate serum transaminase; therefore, clinicians should also monitor liver function tests when a patient is on a fibrate.[36] Because fibrates may reversibly increase serum creatinine levels in patients with renal insufficiency, it's important to obtain baseline renal function studies before administering a fibrate.[36]

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Furthermore, administration of fibrates and warfarin (Coumadin and others) may cause adverse interactions; therefore, to prevent bleeding, clinicians should monitor the international normalized ratio in patients taking a fibrate with this oral anticoagulant.[37] Finally, fibrates increase cholesterol excretion into the bile; therefore, patients may be at increased risk for gallstones and the development of cholelithiasis.[34] Therefore, clinicians should instruct patients to report abdominal discomfort immediately.

Niacin (nicotinic acid, vitamin B_3), a water-soluble vitamin, decreases triglyceride levels by approximately 25% to 40% when used in pharmacologic doses[38] and reduces the incidence of major coronary heart disease (CHD) events, but not stroke.[39] However, clinical trials have failed to show an additional cardiovascular benefit from therapy with a combination of niacin and a statin as compared with statin therapy alone.[40,41] In fact, in the Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE), compared with those who received statin and a placebo, participants who received a statin and a combination of extended-release niacin and laropiprant experienced higher rates of serious adverse events, including new-onset diabetes or decline in glycemic control in existing diabetes, gastrointestinal adverse effects, myopathy, gout, and increased incidences of infections and bleeding. Consequently, because of these severe adverse effects, laropiprant (a selective prostaglandin D2 receptor 1 antagonist) is no longer sold.[40] Despite these results, niacin use has been increasing steadily.[42] Increased niacin use may be related to recommendations in earlier national guidelines as well as product availability and marketing.[43] Interestingly, niacin has a favorable impact on the decline of the glomerular filtration rate in chronic kidney disease.[44] Studies, however, are needed to assess the effect of niacin on reducing cardiovascular events in patients with chronic kidney disease.

There are primarily three different formulations of niacin: immediate release, extended release, and sustained release. Many of these niacin preparations are available as over-the-counter (OTC) dietary supplements, but they aren't subject to oversight by the U.S. Food and Drug Administration (FDA); therefore, OTC formulations are not recommended as a substitute for prescription niacin.[45] (Despite the lack of FDA regulation, clinicians are likely to encounter patients who take or intend to take OTC medications and dietary supplements. Clinicians should teach these patients to look for the verification seal of the U.S. Pharmacopeial Convention [USP] before purchasing such products.)

Prescription extended-release niacin formulations include Niaspan and Niacor.[45] Niacin is associated with mild adverse effects such as cutaneous dilatation with flushing, as well as the more serious adverse effect of hepatotoxicity. Before initiating niacin, obtain liver function studies, a fasting blood glucose or glycated hemoglobin level, and a uric acid level. Clinicians should avoid prescribing niacin in patients with hyperglycemia, elevated liver enzymes, acute gout, new-onset atrial fibrillation, and unexplained abdominal pain or gastrointestinal symptoms.[1] To avoid the cutaneous symptoms associated with niacin (flushing), start with a low dose and titrate upward over a period of eight to 12 weeks.[46] Clinicians should educate patients on the adverse effects of niacin, including flushing, which is uncomfortable but usually transient and harmless.[46] Niacin should be taken with food or after premedicating with aspirin or another

nonsteroidal antiinflammatory drug at least 30 minutes prior to the niacin dose in order to lessen flushing symptoms.[46] Clinicians should also tell patients to avoid alcohol, spicy foods, hot beverages, and hot showers prior to taking niacin.[46]

Omega-3 fatty acids. Long-chain omega-3 fatty acids are known to decrease triglyceride levels by 20% to 50%.[7,47] However, cardiovascular outcomes have been inconsistent in clinical trials.[18] Some studies found an important reduction in major cardiovascular events, but others have not; differences in outcomes may be related to variations in dosage, medication, or the populations studied.[18,48] Currently, two major trials are being conducted to evaluate the safety and efficacy of omega-3 fatty acids when used with statins in patients with hypertriglyceridemia—the Reduction of Cardiovascular Events with EPA—Intervention Trial (REDUCE-IT) and the Long-Term Outcomes Study to Assess Statin Residual Risk Reduction with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia (STRENGTH).[18]

Both clinicians and consumers should note that nonmarine-derived omega-3 fatty acids may not reduce triglyceride levels.[7] The AHA has recommended since 2002 that, to obtain necessary dietary omega-3 fatty acids, patients without CHD should consume "a variety of (preferably oily) fish at least twice a week," as well as "oils and foods rich in α-linolenic acid (flaxseed, canola, and soybean oils; flaxseed and walnuts)."[49] The same guidelines recommended that patients with documented CHD should consume approximately 1 g of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) daily, preferably from oily fish.[49] (For EPA and DHA content in a variety of fish, see http://health.gov/dietaryguidelines/dga2005/report/HTML/table_g2_adda2.htm.) Supplements that combine EPA and DHA may be considered in consultation with a clinician. However, clinicians should remind patients that certain types of fish can to varying degrees be a source of heavy metal pollutants, including mercury, cadmium, lead, tin, and arsenic.[50] Clinicians should advise patients that consumption of fish high in mercury is a serious threat to pregnant women and fetuses, and may actually worsen CVD in adults.[51] Although fish consumption is believed to be safe, tuna, halibut, swordfish, blue shark, and cat shark may contain high levels of mercury, while common sole may contain high levels of lead. Seafood that contain lower levels of mercury and higher levels of omega-3 fatty acids include salmon, trout, and shrimp. In 2014 the U.S. Environmental Protection Agency and the FDA jointly issued an updated advisory on fish consumption, cautioning pregnant women, women who might get pregnant, breastfeeding mothers, and adults who feed young children to avoid four kinds of fish that are high in mercury: tilefish from the Gulf of Mexico, shark, swordfish, and king mackerel.[52] Patients should discuss with their health care provider the risks, adverse effects, and benefits of dietary and supplemental EPA.

Three forms of omega-3 fatty acids are approved as prescription formulations: icosapent (Vascepa), which is pure EPA; omega-3 acid ethyl esters (Lovaza), which is a combination of EPA, DHA, and ethyl esters of omega-3 fatty acids; and Omtryg (omega-3 acid ethyl esters A), which is also a combination of EPA and DHA. Although there are many dietary fish oil and plant-based OTC supplements available, they have not undergone the rigorous testing to establish the purity and consistency required in prescription drugs.[53] Therefore, the amount of EPA and DHA per recommended serving in these products can be highly variable and may contain other fats, including cholesterols.[54] Other sources of omega-3 fatty acids include Antarctic krill (*Euphausia superba*) oil, marine algae, and foods such as flaxseed and walnuts.[55,56]

Although prescription omega-3 fatty acids are safe and usually well tolerated,[48] increases in LDL cholesterol have been linked to the DHA they contain.[47,48,57] The addition of a statin can significantly reduce this effect.[58] Typical dosages of prescription omega-3 fatty acids to treat elevated triglycerides are 1 to 2 g twice a day (2 to 4 g daily). The most common adverse effect of omega-3 is dyspepsia.[57] Omega-3 fatty acids have antithrombotic potential; however, there are no reports of significant bleeding or increases in bleeding time in patients who take omega-3 in combination with warfarin, aspirin, or other antiplatelet agents.[59] Clinicians should consider advising patients who are about to undergo surgery to discontinue omega-3 fatty acids if bleeding is a concern.

Clinicians should instruct patients on statins to report any muscle weakness.

Statins are not considered a first-line monotherapy in patients with triglyceride levels over 500 mg/dL.[32] Statins can be used in combination with niacin, fenofibrate, omega-3 fatty acids, and ezetimibe.[1] Statin-induced liver injury is rare.[60] Before starting statin therapy, baseline liver enzyme levels should be obtained because statins can elevate liver enzymes; if levels rise more than two to three times the upper limit of the normal range, clinicians should stop the statin.[61] Liver enzymes can be reassessed in three to 12 months, as clinically indicated. Clinicians should instruct patients to report any muscle weakness that may be indicative of myopathy.[1] While there are many

causes of musculoskeletal complaints, any complaints from patients treated with statins should be taken seriously and evaluated appropriately.[62, 63]

Ezetimibe (Zetia) is a selective cholesterol absorption inhibitor usually given with a statin that can enhance the lipid-lowering effect of the statin. In a meta-analysis of 5,039 patients, ezetimibe 10 mg per day in combination with statin treatment demonstrated an additional 10.7% reduction in triglyceride levels.[64] When ezetimibe was used in combination with atorvastatin in patients with combined hyperlipidemia whose triglyceride levels were between 150 and 499 mg/dL and who were given an oral fat load, postprandial triglyceride levels were significantly lower than those of patients who received atorvastatin alone.[65] Ezetimibe is fairly well tolerated and is associated with a low incidence of reversible impaired hepatic function, rare myositis, and occasional gastrointestinal upset.[13]

Hypertriglyceridemia is an important risk factor for CVD and its incidence is increasing, primarily because of the growing prevalence of metabolic syndrome in the U.S. population. Clinicians are in an excellent position to augment the mainstay of treatment, intensive lifestyle changes, with pharmacologic intervention in those patients whose triglyceride levels are greater than or equal to 500 mg/dL or who have a history of pancreatitis or both. In addition to focusing on lowering LDL cholesterol levels in patients with hyperlipidemia, clinicians must be cognizant of the contribution of elevated triglycerides and of the variety of treatment methods available. ▼

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Kristine Scordo is professor and director of the adult-gerontology acute care NP program in the College of Nursing at Wright State University in Dayton, OH. Kim Anne Pickett is a family NP at Spartanburg Regional Healthcare System in Spartanburg, SC. Contact author: Kristine Scordo, kscordo@cinci.rr.com. The authors and planners have disclosed no potential conflicts of interest, financial or otherwise.

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