Maintaining Cardiovascular Health in Patients With Mixed Dyslipidemia: Optimizing the Management of Hypertriglyceridemia and Non-HDL Cholesterol

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Target Audience
This program is designed to meet the educational needs of pharmacists, managed care professionals, and other health care professionals who are interested in learning more about the management of hypertriglyceridemia-associated mixed dyslipidemia and the reduction of cardiovascular risk.

Educational Objectives
After completing this knowledge activity, participants should be better able to:
1. Assess the impact of hypertriglyceridemia and non-HDL cholesterol on cardiovascular risk.
2. Describe the pharmacologic properties and rationale for selecting agents used in the treatment of mixed dyslipidemia.
3. Evaluate the cost-benefits of pharmacologic agents used in the management of mixed dyslipidemia.
4. Apply best-evidence when developing clinical recommendations designed to optimize the pharmacologic management of mixed dyslipidemia.

Source of Funding
Sponsored by

Developed in conjunction with

Supported by an educational grant from

Continuing Education Credit
This supplement is based on the live program titled, “Maintaining Cardiovascular Health in Patients With Mixed Dyslipidemia: Optimizing the Management of Hypertriglyceridemia and Non-HDL Cholesterol” (ACPE Universal Program Number 073-999-08-082-L01-P), held as a dinner meeting on April 17, 2008, at the Intercontinental San Francisco in San Francisco, California. Anyone who received CE credit for the live program is not eligible to receive CE credit for this supplement, which represents the same content material.

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Activity Release Date: April 17, 2008
Activity Expiration Date: April 17, 2011
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This educational activity contains discussion of unapproved (investigational) uses of laropiprant in the management of dyslipidemia. The authors have determined to the best of their ability that all other drugs of the statin class (rosuvastatin, pravastatin, atorvastatin, lovastatin, fluvastatin, and simvastatin), purified omega-3 acid ethyl esters, niacin, ezetimibe, and all drugs of the fibrate class (gemfibrozil, bezafibrate, clofibrate, and fenofibrate) discussed in this supplement are FDA approved, either alone or in combination at the doses described, for the management of elevated non-HDL-C associated with hypertriglyceridemia and mixed dyslipidemia. Please refer to the official prescribing information for each product for a description of approved indications, contraindications, and warnings.

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ABSTRACT

OBJECTIVE: To review the role of elevated levels of serum cholesterol and triglycerides in coronary heart disease (CHD) and the increasing recognition of the need to improve the overall lipid profile of patients with mixed dyslipidemia to further mitigate CHD risk.

SUMMARY: Hypercholesterolemia, represented by elevated levels of low-density lipoprotein cholesterol (LDL-C), is a well-known and studied dyslipidemia associated with increased risk for CHD. Statin treatment is highly effective for lowering serum levels of LDL-C. Nevertheless, mixed dyslipidemia associated with low levels of high-density lipoprotein cholesterol (HDL-C) and/or elevated triglycerides, which are risk factors independent of high LDL-C levels, are common. Although interventions using statins are the standard-of-care in mixed dyslipidemia, statin treatment alone does not adequately address these components of the lipid profile in many patients, resulting in residual dyslipidemia and considerable CHD risk. Fibrates, niacin, and omega-3 fatty acids are efficacious additional potential treatment options for patients with mixed dyslipidemia.

J Manag Care Pharm. 2009;15(1)(Suppl S-c):S3-S21
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Causes and Consequences of Mixed Dyslipidemia:
Mitigating Coronary Heart Disease Risk

Matthew Ito, PharmD, FCCP, CLS

Summary

Data from the Framingham Heart Study show a direct relationship between the risk of developing coronary heart disease (CHD) and total serum cholesterol levels. Epidemiologic studies have also established specific lipid parameters as important risk factors for CHD. For example, in the Prospective Cardiovascular Munster (PROCAM) study, the incidence of CHD was positively correlated with increasing serum levels of low-density lipoprotein cholesterol (LDL-C) and triglycerides (TGs) and negatively correlated with increasing high-density lipoprotein cholesterol (HDL-C) serum concentrations. Nevertheless, there are patients with CHD who have plasma LDL-C levels within the normal range. Variation in size, density, and composition of LDL-C particles affect an individual’s likelihood of developing CHD. Smaller, denser LDL-C particles are more prevalent in patients with atherogenic metabolic syndrome (low HDL-C and high TG levels) and in those with CHD. Despite the availability of therapies to reduce dyslipidemia-associated CHD, the risk remains high for many patients. Therapeutic decision making and treatment monitoring for mixed dyslipidemia is complex and, when TGs are elevated, should include assessment of the non–HDL-C level, which is a better predictor of cardiovascular events than the LDL-C level in this patient population.

Overview of Dyslipidemia

Dyslipidemia associated with high levels of LDL-C is a well-known risk factor for CHD and is the primary focus of lipid-lowering therapy with statins. Individuals with mixed dyslipidemia may also have high levels of TGs, low levels of HDL-C, and elevated non–HDL-C.1 In clinical trials, patients treated with statins to normalize LDL-C levels have considerable residual risk for CHD, explained in part by the recognition that elevated TGs and low HDL-C levels are LDL-C–independent risk factors for CHD. Therefore, further CHD risk reduction might be achieved by normalizing TGs and HDL-C levels.

A brief review of the major components of the atherosclerotic process will emphasize the relationship between dyslipidemia and CHD.

In addition to cholesterol, TGs and lipoproteins that constitute the serum lipids play an important role. TGs, the most prevalent fat in the body and diet, are composed of 3 fatty acids linked to a glycerol molecule. Plasma TGs are diet derived or are synthesized...
in the body from carbohydrates and other energy sources. Excess dietary calories are converted to TGs and stored in adipocytes. TGs are a heterogeneous group of compounds because many fatty acids of varying length, branching, and bond saturation exist.

Cholesterol, a waxy, fat-like steroid alcohol, is produced by the liver or ingested from animal-derived food sources. It normally functions as a regulator of membrane fluidity and is also a precursor in the synthesis of biomolecules, such as steroid hormones and bile acids. Pathogenically, when associated with lipoprotein particles, cholesterol is a key component of the atherogenic process.

Lipoproteins are particulate accumulations of proteins and fat that carry lipids and lipid-soluble substances, such as cholesterol, through the blood. Lipoproteins have an outer membrane consisting of phospholipids, unesterified cholesterol, and various surface apolipoproteins; the core of the particle is composed of cholesteryl ester, TGs, and other neutral lipids. Lipoprotein classification is based on density, particle size, surface apolipoproteins, and TG and cholesterol content (Figure 1). The terminology used to describe lipoprotein particle density includes very low (VLDL), low (LDL), intermediate (IDL), and high (HDL). When describing the cholesterol component of lipoprotein, “-C” is added to the acronym (e.g., LDL-C). Non–HDL-C, a measure of atherogenic cholesterol, represents the cholesterol carried by particles other than the HDL-C fraction. Non–HDL-C represents the cholesterol carried by particles other than the HDL-C fraction.

Diet-derived cholesterol as well as other sterols and cholesterol from biliary recirculation enter the gastrointestinal tract and are incorporated into mixed micelles. Cholesterol and other sterols are transported from the micelles into enterocytes by interacting with Niemann-Pick C1-Like 1 transporters. Some cholesterol and most plant sterols, which are structurally similar to cholesterol, are exported back from the enterocyte into the intestinal lumen by the adenosine triphosphate–binding cassette transporters G5 and G8 (ABC G5/G8). Absorbed cholesterol is packaged with TGs and various surface proteins into chylomicrons. These large, buoyant, TG-rich particles are then transported across the enterocytes and secreted into the blood. The content of the chylomicrons is then hydrolyzed by apolipoprotein C-II–activated lipoprotein lipase into chylomicron remnants. During this process, surface lipids and proteins are transferred between chylomicron remnants and HDL particles. Chylomicron remnants are then taken up by endocytosis in the liver by LDL-related protein. In the liver, cholesterol and TGs are incorporated in VLDL together with phospholipids and apolipoprotein B-100. VLDLs are released into the circulation, where they acquire apolipoproteins E and C-II from HDL. A reduction in the TG content of VLDLs occurs in the circulation by the hydrolytic action of lipoprotein lipase to form VLDL remnants and IDLs. IDLs can be cleared from the circulation by hepatic LDL receptors or converted to LDL by further depletion of TGs through the action of hepatic lipases. All of the cholesterol-containing LDLs are atherogenic; however, small dense LDL-C particles are particularly pathogenic. LDL particles can migrate to artery walls and bind to proretentive proteoglycans in the subendothelium where they are oxidized. Oxidized lipoproteins promote endothelial dysfunction, resulting in monocyte entry into the subendothelium. These monocytes differentiate into macrophages and ingest the oxidized lipoproteins to become cholesterol-laden foam cells that form fatty streaks. These streaks can progress to unstable necrotic plaques that block arteries and contribute to cardiovascular disease.

**Lipids, Cholesterol, and Coronary Heart Disease**

Increased levels of total cholesterol are positively correlated with CHD risk. Reduction of LDL-C levels has long been the gold standard for measuring the efficacy of lipid-lowering therapy. However, placebo-controlled trials of various statins (hydroxy-methylglutaryl-coenzyme A reductase inhibitors) have shown that a 20%-40% reduction in LDL-C levels results in a similar reduction in coronary risk over a treatment duration of approximately 5 years. Therefore, considerable coronary risk remains after treatment targets for LDL-C are achieved with statin therapy, yet the potential exists for further risk reduction by modifying other factors associated with dyslipidemia.

A subgroup analysis of the Framingham Heart Study clarified the role of LDL-C, HDL-C, and TG levels in determining coronary risk. Specifically, study participants with LDL-C levels <100 mg per dL were stratified by increasing TG concentrations. These data showed that, even though LDL-C levels remained fairly constant throughout the various subgroups, the number of LDL-C particles increased with increasing levels of serum TGs, the size of those particles decreased, and the number of...
cholesterol molecules per LDL-C particle decreased—all consistent with the observed increase in small dense LDL-C particles. These changes were accompanied by an increase in non–HDL-C levels. The Prospective Cardiovascular Münster (PROCAM) study was undertaken to assess global CHD risk. The study recruited more than 4,800 middle-aged men between 1979 and 1985 to determine the rate of CHD events over 8 years. The patients’ CHD risk factors were recorded at study entry; those with ratios of LDL-C/HDL-C >5 had a 19.2% chance of experiencing a CHD event. When hypertriglyceridemia was also present, the risk increased to 26.9%. Results of these studies suggest that the existence of large numbers of LDL particles better predicts coronary risk than does high LDL-C levels, that low HDL-C levels and high TG levels are CHD risk factors independent of LDL-C levels, and that non–HDL-C levels may be a better marker for coronary risk than those of LDL-C. The mechanistic roles of LDL-C, HDL-C, and TGs in coronary risk are detailed in the following sections.

**LDL-C.** While the goal of lipid-lowering therapy with statins is the reduction of LDL-C levels, the atherogenicity of LDL-C is determined not only by its concentration, but also by the size and density of the particles. Even though they carry less cholesterol, small dense LDL particles are more atherogenic than their larger counterparts because they bind more tightly to proteoglycans in arterial walls and are more easily oxidized. These particles first need to be oxidized to be taken up by scavenger receptors on macrophages. An increase in foam cell formation occurs and, eventually, so does development of atherosclerotic plaques. Because small dense LDL particles carry fewer cholesterol molecules, there are more of these particles present at any given LDL-C concentration. It is these LDL particles that migrate to the arterial wall, not the LDL itself. Because this is a gradient-driven process, the more particles that are present in the serum, the greater the drive for particles to migrate from the lumen to the arterial wall. In fact, the decreased risk of CHD associated with high HDL-C levels and the increased risk associated with high TG levels probably act as surrogate markers for the primary culprit—an increase in atherogenic small dense LDL-C particles.

The creation of these small dense LDL-C particles occurs when there is an increased flux of free fatty acids delivered to the liver. The liver increases production of TG-rich VLDL particles from fatty acids. These VLDL particles then interact with HDL and LDL through the action of cholesteryl ester transfer protein and exchange the TG content for cholesterol and HDL or LDL. The end result is a TG-rich, cholesterol-depleted LDL or HDL particle; following hydrolysis with hepatic lipase, a small dense LDL particle and a cholesterol-depleted HDL particle are formed. In patients with the metabolic syndrome, after dissociation from HDL particles, apolipoprotein A-1 (apoA-1) is eliminated by the kidneys, further reducing levels of HDL-C and increasing coronary risk. 

Data supporting the differential atherogenicity of various forms of LDL-C were provided by the Quebec Cardiovascular Study, which followed patients initially free of coronary disease to determine CHD risk. Data on the size and number of LDL particles were collected for 5 years, and CHD-related outcomes were analyzed. The results demonstrated that patients with numerous small dense LDL particles had a 6-fold increase in risk of ischemic heart disease compared with patients with fewer, but larger, LDL particles. 

**HDL-C.** In contrast, HDL-C is cardioprotective, and higher levels of HDL-C are associated with reduced CHD risk. The role of HDL-C in reverse cholesterol transport partly explains this effect. In reverse transport, lipid-poor apoA-1 interacts with ABCA1, a specialized transporter, and moves cholesteryl ester out of macrophages to apoA-1, resulting in a discoidal immature HDL particle. With further elution of cholesteryl ester, a mature HDL particle is formed that interacts with scavenger receptors on hepatocytes to deliver their cholesteryl ester content, which is then excreted in bile. Other mechanisms that contribute to the antiatherogenic effects of HDL include its antioxidative effects, inhibition of adhesion molecule expression, platelet activation inhibition, prostacyclin stabilization, and promotion of nitric oxide production. Low HDL-C levels are associated with additional CHD risk factors including smoking, sedentary lifestyle, obesity, insulin resistance and diabetes, hypertriglyceridemia, and chronic inflammatory disorders.

**Triglycerides.** There are a number of primary and secondary causes of elevated serum TG levels. Primary causes include familial disorders of combined hypertriglyceridemia and hypercholesterolemia (e.g., familial combined hyperlipidemia, familial dysbetalipoproteinemia, familial hepatic lipase deficiency) and familial disorders of hypertriglyceridemia, such as familial chylomiconemia (e.g., lipoprotein lipase deficiency, apoC-II deficiency). Secondary causes include physical inactivity, a high-cholesterol diet, excessive alcohol and/or carbohydrate intake, obesity, insulin resistance (type 2 diabetes or the metabolic syndrome), chronic kidney disease, Cushing’s syndrome, nephritic syndrome, hypothyroidism, and use of certain medications (e.g., tamoxifen, steroids, beta-blockers, thiazides, retinoids, atypical antipsychotics, immunosuppressants, human immunodeficiency virus protease inhibitors, isotretinoin). 

The various familial disorders can cause severe elevations in serum TG levels, usually >1,000 mg per dL; the primary target for intervention in individuals with these disorders is to reduce TG levels and the associated risk of pancreatitis. The most worrisome disorders associated with elevated TG levels and CHD risk are those that increase levels of both cholesterol and TGs (insulin resistance and familial combined hyperlipidemia, dysbetalipoproteinemia, and hepatic lipase deficiency). These conditions occur in approximately 1%-6% of the patient population, but are probably associated with 20% of the individuals that present with CHD. Approximately 25% of the patients with elevated TGs are diabetic or have the metabolic syndrome.
Hypert triglyceridem ia contributes to coronary risk in several ways. Excessive TG levels cause the accumulation of cholesterol-rich remnants from the hydrolysis of chylomicrons or VLDL particles. These remnants create a proinflammatory and oxidative environment that may exacerbate the atherosclerotic process by enhancing adhesion molecule expression, foam cell formation, and smooth muscle cell toxicity. High TG levels may also increase the amount of TG-rich HDL particles; evidence suggests that these are less efficient at the reverse transport of cholesterol. There is also an increase in the proportion of atherogenic small dense LDL particles associated with hypertriglyceridemia.27

The Metabolic Syndrome and CHD Risk

Patients with the metabolic syndrome are at an increased risk for cardiovascular death. The metabolic syndrome is a constellation of various lipid abnormalities (low HDL-C levels, elevated TGs, and an increase in small dense LDL-C particles) as well as other factors such as increased waist circumference or visceral adiposity, elevated blood pressure, and an increase in fasting serum glucose levels. The presence of 3 of these factors is necessary to meet the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) diagnostic criteria for the metabolic syndrome.28 The condition is highly prevalent: 1 of 4 adults in the United States meet the NCEP ATP III diagnostic criteria for the metabolic syndrome. By age 60, approximately 40% of individuals have the condition; prevalence is higher in men than in women, and the risk is greater in certain ethnic populations. As rates of obesity continue to rise, the incidence of the metabolic syndrome is expected to increase.29

The association of the metabolic syndrome with cardiovascular risk was demonstrated in a large family study of patients with type 2 diabetes in Finland and Sweden that followed participants for 7 years. After controlling for traditional coronary risk factors, those with the metabolic syndrome had a 6-fold increase in cardiovascular mortality versus patients without the condition.30 Another analysis of data from the Framingham Heart Study stratified male patients by the number of the metabolic syndrome components present (0 to 5) and compared LDL-C levels in each group. As the number of the metabolic syndrome risk factors increased, LDL-C levels remained relatively constant, yet the number of atherogenic small dense LDL-C particles increased; results were similar in women.31

Treatment Goals for Patients with Dyslipidemias

Cholesterol

Desirable serum levels of total cholesterol and LDL-C are <200 mg per dL and <100 mg per dL, respectively. A normal level for serum TGs is considered to be <150 mg per dL and that for HDL-C is ≥40 mg per dL. The goal for non–HDL-C levels is 30 mg per dL higher than the patient’s LDL-C level. A number of traditional coronary risk factors modify specific LDL-C and non–HDL-C goals in patients without preexisting coronary disease. These factors include advancing age, family history of premature CHD, ongoing cigarette smoking, elevated blood pressure (≥140/90 mm Hg), and low levels of HDL-C.32

NCEP ATP III treatment guidelines for LDL-C target levels categorize each patient by their number of CHD risk factors. In general, the threshold to initiate therapeutic lifestyle changes occurs when a patient’s LDL-C level is just above target, whereas the threshold to initiate drug therapy occurs when LDL-C levels are 30 mg per dL over the target. Initiation of therapeutic lifestyle changes is generally recommended for patients with 0-1 CHD risk factor and LDL-C levels ≥160 mg per dL; however, if the LDL-C level is ≥190 mg per dL, drug therapy should be considered. The threshold values for intervention and the LDL-C target levels steadily decline as the CHD risk factors increase. If a patient has 2 risk factors for CHD, the LDL-C goal is <130 mg per dL and the non–HDL-C goal is <160 mg per dL.32,33 In the highest-risk patients, the LDL-C target is <70 mg per dL, and thresholds for lifestyle changes and drug therapy are ≥100 mg per dL and ≥130 mg per dL, respectively.32 These values were derived from results of the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT) trial34 and updated per the Treating to New Targets (TNT) trial.35 In patients with mixed dyslipidemia associated with high levels of LDL-C and TGs, lowering LDL-C levels is the primary goal of intervention and non–HDL-C becomes a secondary target.32

Triglycerides

Patients with TG levels ≥500 mg per dL are at an increased risk for pancreatitis, and lowering TG levels is the primary target for intervention. Once TG levels are normalized, therapy can refocus on LDL-C and, if necessary, non–HDL-C levels.

Management of Mixed Dyslipidemia

Both nonpharmacologic and pharmacologic therapies are available to treat mixed dyslipidemia. Recommended therapeutic lifestyle changes include increased physical activity (moderate exercise sufficient to expend ≥200 kcal per day); increased intake of omega-3 fatty acids, plant stanols/sterols, and soluble fiber; a caloric intake limited to that needed to maintain an appropriate body weight and prevent weight gain; and limited dietary intake of saturated fats, cholesterol, and trans fatty acids. Limiting saturated fat intake to <7% of total calories and dietary cholesterol to <200 mg per day should be the primary recommendation in all patients with elevated LDL-C levels. Other therapeutic options include intake of 2 gm per day of plant sterols/ stanols and 10-25 gm per day of soluble fiber.32,36 In patients with dyslipidemia associated with elevated TG levels, recommendations for lifestyle changes include increasing physical activity and decreasing total caloric intake to levels that reduce weight and maintain an appropriate body weight.32

The American Heart Association (AHA) recommends that all individuals increase the amount of fish incorporated into the
diet as a source of omega-3 fatty acids that may lower CHD risk. People without coronary disease should be consuming at least 2 servings of fish per week. In patients with preexisting CHD, the AHA recommends the equivalent of 1 gm per day of omega-3 fatty acids—a level shown to decrease the risk of cardiovascular death. In patients with very high TG levels (>500 mg per dL), 2-4 grams of omega-3 fatty acids can be ingested daily under the care of a physician to help reduce serum TG levels.

Prescription medications available to treat mixed dyslipidemia include statins, purified omega-3 fatty acids, nicotinic acid, and fibrates. Most patients with mixed dyslipidemia will require combination therapy with a statin plus one or more additional lipid-lowering agents. These pharmacotherapies will be discussed in further detail later in this supplement.

Conclusions

Dyslipidemia increases the risk for CHD. Mixed dyslipidemia with elevated TG levels as a component is commonly seen, especially among patients with the metabolic syndrome or diabetes. As the U.S. population ages and obesity rates increase, a greater number of patients will have elevated TG level–associated lipid disorders. In patients with mixed dyslipidemia associated with increased TG levels, treatment recommendations now include the lowering of non–HDL-C levels as a secondary intervention goal. Patients with TG levels >500 mg per dL should first be treated for hypertriglyceridemia, with secondary goals of lowering LDL-C and non–HDL-C levels.

REFERENCES

Maintaining Cardiovascular Health in Patients With Mixed Dyslipidemia: Optimizing the Management of Hypertriglyceridemia and Non-HDL Cholesterol

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Summary
Atherosclerosis leading to cardiovascular disease (CVD) is the most common cause of death and disability in developed nations. The economic burden of CVD is also significant; in 2006, the estimated total cost of coronary heart disease alone was $142.5 billion in the United States. In addition, the total cost of medical expenses and lost productivity associated with CVD was in excess of $400 billion. Although the lowering of low-density lipoprotein cholesterol (LDL-C) levels is the first step in managing hypercholesterolemia, even when LDL-C is controlled, significant residual cardiovascular risk remains in many patients. Myriad lipid disorders contribute to this risk and are characterized by high levels of triglycerides, very low-density lipoprotein remnant cholesterol, small dense LDL particles, and low levels of high-density lipoprotein cholesterol. The availability of an array of cost-effective lipid-lowering agents enables clinicians to individualize therapy. Thus, fibrates, niacin, and prescription omega-3 fatty acids can be combined with statins to reduce CVD in these patients. Such combination therapy to manage atherogenic dyslipidemia can achieve greater protection against cardiovascular events than is currently realized by statin monotherapy.

Overview of Management of Dyslipidemia
Patients treated with statins to achieve National Cholesterol Education Program (NCEP)—recommended goals for low-density lipoprotein cholesterol (LDL-C) levels may still have an elevated risk for cardiovascular disease (CVD) (Figure 2).1-3 This residual cardiovascular risk may be related to a persistent dyslipidemia, typically characterized by increased triglyceride (TG) levels, low levels of high-density lipoprotein cholesterol (HDL-C) and the presence of LDL particle remnants, small dense LDL particles, and excessive levels of lipoprotein particles in general. Further treatment with more aggressive statin therapy does not directly address the residual dyslipidemia.4 The National Health and Nutrition Examination Survey, conducted between 2003 and 2004, analyzed serum lipid levels of more than 2,800 adults aged ≥20 years. Of those without CVD or related comorbid diseases, 85%-89% were at recommended levels for LDL-C, non–HDL-C, HDL-C, and TGs. Only 36%-37% of individuals with CVD or related comorbidities met goals for LDL-C and non–HDL-C, and only 17% were at recommended levels for all lipids tested. Those undergoing treatment for dyslipidemia had significantly lower LDL-C and non–HDL-C levels compared with untreated individuals; however, HDL-C and TGs remained uncontrolled.5 This survey reinforces the need to address the residual dyslipidemia found in statin-treated mixed dyslipidemia. Fibrates, niacin, and omega-3 fatty acids—agents that lower TGs, reduce remnant cholesterol and particle number, and raise HDL-C levels—are reviewed, with a focus on their utility and cost-effectiveness for reducing coronary heart disease (CHD) risk in patients with mixed dyslipidemia.
Fibrates

Fibrates have been used to lower serum TG levels for many years; however, their mechanism of action is complex and remains only partially elucidated. It is known that fibrates stimulate the nuclear receptor peroxisome proliferator-activated receptor-alpha (PPAR-alpha), resulting in the transcriptional regulation of a family of genes. Fibrates bind to PPAR-alpha, which forms a complex with the retinoid X receptor (RXR) ligand. This complex then binds to a PPAR response element in DNA to either suppress or enhance the transcription of many genes. In the liver, the fibrate/PPAR-alpha/RXR ligand complex upregulates acyl-coenzyme A (CoA) synthase, an enzyme in hepatocytes that reduces free fatty acids to produce acetyl-CoA. This process results in reduced cholesterol from within the cell to the cell surface where they may be picked up by circulating HDL particles for transport to the liver for elimination. A modest increase in apolipoprotein A-1 (apoA-1) production has also been demonstrated. The net effect of fibrate treatment is a modest increase in HDL-C levels, a substantial reduction in VLDL-C levels, and a decrease in number and size of LDL particles. Fenofibrate treatment may increase LDL-C levels because it results in an increase of apoA-1 production.11 However, fibrates are associated with several poorly understood limitations: (a) increases in creatinine and/or homocysteine levels and hence a need for caution in use in patients with impaired renal function, especially the elderly; (b) increased rates of myopathy, rhabdomyolysis, cholelithiasis, and cholecystectomy; and (c) a trend toward an increased risk of noncardiovascular mortality.10 When fibrates are coadministered with a statin, an additive myotoxic effect is possible. Furthermore, fibrate treatment is associated with an increased risk for venothromboembolic disease (e.g., pulmonary embolism, deep venous thrombosis) potentially due to increased homocysteine levels.12

Gemfibrozil can interfere with the glucuronidation of statins, resulting in increased serum concentrations of lovastatin, pravastatin, rosuvastatin, and simvastatin; this effect is not significant with atorvastatin and fluvastatin. Because such interactions do not occur with fenofibrate, it is often used when combination therapy with statins is indicated. The effects of fibrates on mortality were mixed in 4 placebo-controlled, randomized end-point studies that enrolled a combined total of more than 19,000 patients. CHD-related and total mortality increased with fenofibrate use by 19% and 11%, respectively, in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study and increased by 7% and 5%, respectively, with bezafibrate in the Bezafibrate Infarction Prevention (BIP) study. In contrast, mortality was reduced by 22% and 11%, respectively, with gemfibrozil in the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) and decreased by 26% and increased by 7%, respectively, with gemfibrozil in the Helsinki Heart Study fibrate trial (Figure 3). Although these differences were not statistically significant, there is a troubling trend toward increased mortality with fibrate therapy. In the World Health Organization cooperative trial of primary prevention of ischemic heart disease, clofibrate use was associated with 25% more deaths than in the control groups (P<0.01), with excess mortality attributable to cancer and diseases of the gallbladder, liver, and intestines—further adding to the controversy surrounding the use of fibrates.13 A meta-analysis of 10 placebo-controlled trials examined the role of long-term fibrate treatment in the prevention of CVD. Results indicated that, compared with placebo, fibrate treatment was associated with an increased risk of all-cause mortality that was not statistically significant and a significantly increased risk of noncardiovascular mortality (P=0.004). When clofibrate trials were removed from the analysis, there was no significant difference in either value. This analysis also demonstrated that fibrates did not significantly lower the risk of cardiovascular mortality, fatal myocardial infarction (MI), or stroke, but did reduce the risk of nonfatal MI by approximately one-fifth (P<0.001).17

Currently, there is a lack of data concerning the incremental cost-benefit of adding fibrates to statin therapy for primary and secondary prevention of CHD. Outcome studies are needed specifically to assess the pharmacoeconomics of this treatment strategy.

Niacin

Although niacin has been used to lower TG levels for approximately 50 years, little was known about its mechanism of action. However, we now appreciate that niacin acts during the last step in the hepatocytic synthesis of TGs by inhibiting the conversion of diacylglycerols to TGs by the enzyme diacylglycerol acyltransferase-2. Normally, the body anticipates the production of TGs and thus begins to produce apolipoprotein B (apoB) to form

<table>
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<th>FIGURE 3 Mortality Rate Changes in Large Fibrate Trials</th>
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<tr>
<td><strong>Fibrates</strong></td>
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<tr>
<td><strong>FIELD</strong> (n=9,795)</td>
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<tr>
<td><strong>BIP</strong> (n=3,090)</td>
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<tr>
<td><strong>VA-HIT</strong> (n=2,531)</td>
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<td><strong>Helsinki</strong> (n=4,081)</td>
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Source: McKenney JM. Future Lipidol. 2006;1:275-81. No change was statistically significant.

BIP = Bezafibrate Infarction Prevention study; CHD = coronary heart disease; FIELD = Fenofibrate Intervention and Event Lowering in Diabetes study; VA-HIT = Veterans Affairs High-Density Lipoprotein Intervention Trial.
Niacin is thought to raise HDL-C levels via a unique mechanism. Kinetic studies of niacin-treated patients indicate a decreased catabolism of apoA-I. At least 2 liver receptors are responsible for the metabolism of HDL particles: the scavenger receptor B1 facilitates HDL-C uptake, and the HDL holoparticle catabolism receptor takes up HDL–apoA-1 particles by endocytosis. Niacin interferes with the latter receptor and leads to a reduced removal of HDL, thus preserving HDL–apoA-1 for reverse cholesterol transport from macrophage cells to the liver. In this manner, apoA-1 rises—not because more is produced, but because the apoA-1 that has been produced is retained longer.

Niacin was evaluated as part of the Coronary Drug Project study for secondary prevention of cardiovascular events in men with previous MI. In this study, niacin was associated with a small but significant reduction in nonfatal MI and CHD-related death versus placebo (Figure 4). In a side-by-side comparison study, niacin was shown to be the better HDL-raising agent, while gemfibrozil was a better TG-lowering agent. Niacin usually does not increase LDL-C levels, and both therapies have a positive effect on non–HDL-C. In the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2 study, 167 patients with prior MI were first treated with statins to achieve a mean LDL-C level of approximately 90 mg per dL (below the <100-mg-per-dL treatment goal) and an HDL-C level of approximately 40 mg per dL. Extended-release (ER) niacin at a dose of 1,000 mg per day or placebo was then randomly added to the statin therapy. Progression of atherosclerosis, as measured by carotid artery intima-media thickness (IMT), was followed for 12 months. There was less increase from baseline to study end in IMT in patients who received a statin plus ER niacin (P=0.23) compared with those who received the statin-plus-placebo regimen (P<0.001); however, the between-group difference was not statistically significant (P=0.08). There was an additional 2.3% decrease in LDL-C, a 21.0% increase in HDL-C, and a 7% decrease in non–HDL-C when ER niacin was part of the treatment regimen.

Niacin is associated with an increased risk of hepatotoxicity and a 4-mg-per-dL increase in fasting blood glucose (FBG); the latter may be important when managing patients with impaired FBG. Flushing is the most common side effect of niacin and, while not dangerous, can lead to noncompliance or discontinuation of the drug. Recent research on the mechanism of niacin-induced flushing may reduce the impact of this side effect. A niacin receptor has been identified on adipocytes as well as on immune and skin cells. Flushing is triggered by stimulation of the niacin receptor in epidermal Langerhans cells, resulting in increased production of arachidonic acid and, subsequently, an array of prostaglandins (PG), including PGD2. Flushing is caused by the dilation of capillary vessels due to the binding of PGD2 to peripheral DP-1 receptors. Laropiprant, a DP-1 receptor antagonist, was developed to block the niacin-induced flushing response. When laropiprant was added to ER niacin therapy, approximately 90% of patients had moderate to no flushing compared with 65% of patients on ER niacin alone in the first week of niacin therapy, the period when flushing is usually most severe.

A cost-effectiveness analysis of ER niacin–augmented statin therapy was undertaken using the Framingham Heart Study dataset and data from a population of ARBITER 2 patients of similar age, gender, and lipid profile. Rates of MI, angina, and death from CHD were compared for both therapies. The incidence of all 3 measures declined modestly when ER niacin was added to therapy. The patients who received both a statin and ER niacin therapy gained an average of 0.17 life-years, which translates to approximately €20,645 in incremental costs per life-year gained. This figure is within the acceptable range for expenditures to prevent cardiovascular disease.

Omega-3 Fatty Acids
Populations with fish-rich diets have a lower risk of heart disease. This phenomenon has been linked to the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are naturally found in fish. Omega-3 fatty acids may lower cholesterol levels by reducing the number of LDL particles, as well as increasing the number of HDL particles. The Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2 study found that ER niacin added to statin therapy further reduced LDL-C levels, increased HDL-C levels, and reduced non–HDL levels compared to statin therapy alone.
which are present in high concentrations in fatty fish. EPA and DHA lower serum TG levels, but also have a number of other effects that may explain their cardiovascular benefits. Linolenic acid, a plant-derived omega-3 fatty acid, can be converted to DHA, but the rate at which this occurs is neither sufficient to raise DHA levels significantly nor contribute to TG lowering. Although the primary dietary source of EPA and DHA is fatty fish, fish oil supplements are sold over-the-counter, and a purified and concentrated form of omega-3 fatty acids is available as a pharmaceutical-grade product by prescription.

Omega-3 fatty acids are thought to lower TG levels by acting early in the TG biosynthetic pathway, most likely by stimulating sterol regulatory element binding protein-1c (SREBP-1c), a transcriptional activator. When stimulated, SREBP-1c upregulates the transcription of the enzymes—acyl-CoA carboxylase and fatty acid synthase—needed for the production of fatty acids, which in turn are used to produce TGs. Omega-3 fatty acids apparently inhibit binding of the liver X receptor (LXR) alpha/ RXR alpha heterodimer to the LXR-responsive elements in the SREBP-1c promoter region, which suppresses SREBP-1c expression and ultimately leads to decreased TG levels.

The American Heart Association (AHA) recommendation for omega-3 fatty acid intake in individuals who do not have CHD is consumption of a variety of fatty fish about twice a week, which provides approximately 1 gm per day of omega-3 fatty acids. For patients with CHD, the recommended AHA dose is also EPA/DHA 1 gm per day from either fatty fish or supplements in consultation with their physician. For treatment of patients with very high TG levels (≥ 500 mg per dL), 2-4 gm per day of omega-3 fatty acids is recommended to prevent pancreatitis.

Potential adverse effects associated with the consumption of omega-3 fatty acids include increased caloric intake, consumption of cholesterol from low-potency dietary fish oil supplements, and gastrointestinal disturbances, such as dyspepsia. Fishy aftertaste and belching are common complaints associated with prescription-grade products. In the manufacture of supplements, omega-3 fatty acids are extracted from fish, raising the potential concern of consumer exposure to environmental toxins (e.g., methylmercury, polychlorinated biphenyls, organochlorine pesticides) found in the waters from which the fish were caught. However, because they are water soluble, mercury and other heavy metals are eliminated when the oil is extracted from the fish during the manufacturing process; therefore, exposure to these toxins is generally not a problem with supplement use. On the other hand, if eating fish is a person’s sole source of omega-3 fatty acids, exposure to toxins may occur because of the large quantity of fish required to obtain the appropriate amount of fatty acids.

Several products are available to supplement the intake of omega-3 fatty acids other than consumption of fatty fish. Over-the-counter fish oil supplements generally deliver 200-300 mg of EPA/DHA in a 1-gram tablet; the remainder (700-800 mg) is composed of saturated fats, other fatty acids, and cholesterol. A major issue with these supplements is the large number of tablets or capsules that the patient must consume to receive the 4-gm-per-day dosage required to lower TG levels. A second problem is the consumption of saturated fats, cholesterol, and calories derived from the 80% of the dose that is not composed of omega-3 fatty acids.

The U.S. Food and Drug Administration (FDA) approved a concentrated, highly purified form of omega-3 fatty acids (P-OM3) in November of 2004. P-OM3 is available by prescription and provides at least 900 mg of omega-3 fatty acid ethyl esters per capsule (predominantly EPA/DHA) with only 10% derived from other fatty acids, saturated fats, and cholesterol. Two randomized, double-blind, placebo-controlled 6- and 16-week studies of 4 gm per day (recommended dosage) of P-OM3 were undertaken in 84 patients whose median TG level was 792 mg per dL. In this population, P-OM3 reduced median TG, VLDL-C, and non–HDL-C levels and increased median HDL-C levels compared with placebo. P-OM3 is indicated as an adjunct to diet modification for patients with very high TG levels (≥ 500 mg per dL) associated with a high risk for pancreatitis. The FDA-monitored manufacturing process ensures a known source of fish oil in a consistent, stable product with all contents analyzed and reported.

A large, long-term trial was conducted to determine the effects of omega-3 fatty acid therapy on secondary prevention of CVD. The open-label Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico (GISSI)-Prevenzione study followed 11,324 patients for 3.5 years who had suffered an MI within 3

![Figure 5](image-url)
months prior to study entry. Patients were randomly assigned to supplements of P-OM3, vitamin E, both supplements, or no treatment (controls), and all patients were maintained on standard care of pharmacologic treatment and lifestyle recommendations that included a Mediterranean diet for most patients. The primary combined efficacy end points of the study were (a) the cumulative rate of all-cause death, non-fatal MI, and non-fatal stroke, and (b) the cumulative rate of cardiovascular death, non-fatal MI, and non-fatal stroke. Using a 4-way factorial analysis comparing the efficacy of P-OM3 supplements, vitamin E supplements, combined treatment versus controls, and combined treatment versus individual interventions, the addition of P-OM3 therapy reduced end point 1 from 14.6% to 12.3%, which indicates a 15% reduction in risk ($P=0.023$). End point 2 was 11.4% and 9.2% in the control and P-OM3 treatment groups, respectively, which represents a risk reduction of 20% ($P=0.008$) (Figure 5). When the components of the end points were analyzed separately, significant reductions were found in the risk for cardiovascular mortality ($P=0.024$), coronary mortality ($P=0.023$), fatal plus non-fatal coronary events ($P=0.024$), and sudden death ($P=0.010$). The total mortality rate was 10.4% with standard care alone and 8.3% with the addition of P-OM3, a reduction of 20%. The rate of sudden death was 3.5% with standard care alone and 1.9% with standard care plus P-OM3, a 45% reduction. In addition, the cardiovascular event rate decreased from 26.3% with standard care alone to 18.9% with the addition of P-OM3, a reduction of 30%. Time-course analysis of the results from the GISSI-Prevenzione trial showed that total mortality was reduced by 41% after 3 months of treatment with P-OM3 ($P=0.037$). The risk reduction for sudden death contributed to this decrease in total mortality, consistent with either an antiarrhythmic or antiatherothrombotic effect.

A comparison study of P-OM3 (4 gm per day) and gemfibrozil (1,200 mg per day) demonstrated similar efficacy for both agents in terms of lowering TG (37%-40%) and VLDL-C (33%-39%) levels. Both also raised LDL-C levels slightly; however, there was also a net reduction in non–HDL-C with omega-3 fatty acids.

Furthermore, P-OM3 has been studied in patients scheduled for coronary artery bypass graft without concomitant cardiac surgery, in which it reduced the incidence of vein graft occlusion. Also, progression of renal insufficiency was slowed by P-OM3 in patients with immunoglobulin A (IgA) nephropathy. In contrast, P-OM3 had no effect on restenosis in elective coronary angioplasty patients.

A pharmacoeconomic analysis of P-OM3 therapy was undertaken using data from the GISSI CHD Secondary Prevention Trial. Patients who experienced a recent MI received either P-OM3 or standard secondary prevention therapy (antplatelet agents, beta-blockers, angiotensin-converting enzyme inhibitors, and/or lipid-lowering agents) for 3.5 years. Results indicated that the cost-effectiveness of P-OM3 was comparable with recently introduced medications in routine use for the secondary prevention of MI. The authors concluded that P-OM3 should be added to currently employed secondary prevention measures because of its potential additive benefits. Similar cost-benefits were found using comparable study methodologies applied to patients in Australia, Belgium, Canada, Germany, Poland, and the United Kingdom. In addition, investigators in the United States found that P-OM3 can be expected to reduce overall costs and improve outcomes when used for secondary prevention of cardiovascular disease.

## Conclusions

Optimum lipid management strategies for patients with mixed dyslipidemia associated with hypertriglyceridemia will lower TG and non–HDL-C levels, in addition to lowering remnant VLDL-C and LDL-C and raising HDL-C levels. Addressing this dyslipidemia should further reduce CHD risk in patients whose statin treatment has brought LDL-C levels to goal; however, this risk reduction has yet to be demonstrated in controlled clinical trials. Fibrates, niacin, and omega-3 fatty acids are all useful agents for improving lipid profiles in patients with mixed dyslipidemia. Nevertheless, the TG-lowering effects of fibrates are accompanied by considerable tolerability issues, and there is concern over the increase in mortality seen with these agents. Niacin is effective for lowering VLDL-C and LDL-C levels and is the best agent available to raise HDL-C levels; its potential may be maximized if the bothersome flushing seen with this agent can be controlled with novel formulations or coadministered agents. P-OM3 is generally well tolerated and offers significant improvement in serum lipid profiles by reducing TG, VLDL-C, and non–HDL-C levels and increasing levels of HDL-C. P-OM3 has also been shown to be efficacious and cost-effective when added to usual care for the secondary prevention of cardiovascular and cerebrovascular events including sudden death, MI, and stroke.

## REFERENCES


Outcomes for Patients With Mixed Dyslipidemia

Eliot A. Brinton, MD

Summary
Pharmacologic management of dyslipidemia reduces atherosclerotic coronary heart disease (CHD) risk and prolongs patient survival. Statins are often the treatment of choice for patients with elevated levels of low-density lipoprotein cholesterol (LDL-C); however, many statin-treated individuals do not achieve the target LDL-C goals set by the National Cholesterol Education Program. In addition, many patients have mixed dyslipidemia typified by elevated LDL-C and triglyceride (TG) levels. Because statin monotherapy is only modestly effective in treating TG elevations, combination modalities are often required for optimal management of mixed dyslipidemia. Several recent clinical trials have evaluated the potential clinical benefits of combination therapy for CHD risk reduction. For example, the COMBOS (COMBination of prescription Omega-3 with Simvastatin) study demonstrated the safety and efficacy of statins in combination with purified omega-3 acid ethyl esters for improving lipid parameters and achieving non–high-density lipoprotein cholesterol goals in patients with mixed dyslipidemia. The HDL-Atherosclerosis Treatment Study (HATS) trial showed that the combination of a statin plus niacin reduced the progression of atherosclerosis and incidence of cardiovascular events. Several large clinical trials are under way to assess the value of adding either a fibrate (ACCORD) or extended-release niacin (AIM-HIGH, HPS2-THRIVE) to a statin to reduce cardiovascular events in high-risk patients.

Overview
There is increasing recognition, supported by clinical studies, that elevated serum triglyceride (TG) levels are associated with an increased risk for cardiovascular disease (CVD), independent of the risk due to high levels of low-density lipoprotein cholesterol (LDL-C) and low levels of high-density lipoprotein cholesterol (HDL-C). Hypertriglyceridemia is usually associated with a number of proatherogenic conditions such as insulin resistance, endothelial dysfunction, inflammation, and thrombosis. Often, hypertriglyceridemia occurs with elevated LDL-C levels and is termed “mixed dyslipidemia.” Frequently, the high TG component of mixed dyslipidemia is undertreated because the usual treatment is statin monotherapy. There is growing evidence that the addition of fibrates, niacin, or purified omega-3 fatty acids (P-OM3) to statin therapy is safe and effective not only for control of lipid abnormalities but also for prevention of atherosclerosis. A review of this evidence and treatment recommendations for mixed dyslipidemia are included in this article.

Coronary Risk Associated With Hypertriglyceridemia
A widespread misconception exists that high TG levels are not associated with an increased risk for CVD. Although it is true that the TG level itself does not contribute directly to atherogenesis, TG-rich lipoproteins do carry cholesterol and can directly promote atherosclerosis. There appear to be at least 3 ways in which hypertriglyceridemia makes lipoproteins more atherogenic—or less antiatherogenic. First, in the presence of high TG levels, the action of cholesteryl ester transfer protein drives excess TGs from very low-density lipoproteins (VLDLs) into low-density lipoproteins (LDLs) and high-density lipoproteins (HDLs) in exchange for excess transfer of cholesteryl ester (CE) into VLDLs. CE enrichment of VLDLs appears to make it more atherogenic. Second, the resulting CE depletion and TG enrichment of LDLs result in greater susceptibility to TG lipolysis of LDLs by lipoprotein lipase and hepatic lipase, which in turn results in shrinkage of both the lipid core and the lipoprotein itself. The resulting small dense LDL particles are thought to be more atherogenic than larger, less dense particles. Finally, the same sequence of core lipid exchange and TG lipolysis also occurs in HDLs, resulting not only in smaller, denser particles, but also, more importantly, in the shedding of lipid-free or lipid-poor apolipoprotein A-I from HDLs, resulting in its permanent loss through renal glomerular filtration. This loss is associated with the reduction of HDL levels and its antiatherogenic effects.

The strong metabolic connection between TGs and HDLs (mentioned previously) results in a strong inverse relationship between their levels; nevertheless, several studies have confirmed the direct association of hypertriglyceridemia to increased coronary risk. One study compared the serum lipid profiles of 653 patients who had premature familial coronary artery disease (CAD) with those of 1,029 control subjects. Results indicate that the risk associated with high TG levels is independent of the risk related to high levels of LDL-C; therefore, patients with elevated TG levels and average or high HDL-C values also have an increased risk for CAD. The CAD risk for a patient with TG levels ≥500 mg per dL is more than 10 times that of a person with a TG level <100 mg per dL. At TG levels between 200 and 299 mg per dL (levels commonly seen in patients with dyslipidemia), the CAD risk is double that of patients with TG levels <100 mg per dL. The Prospective Cardiovascular Münster (PROCAM) study followed 4,849 middle-aged men for 8 years to determine the incidence of coronary heart disease (CHD) events in accordance with the risk factors present at the start of the study. Results indicated that TG levels have an impact on coronary risk that is independent of LDL-C or HDL-C levels. The Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial, one of the classic studies of statin therapy, compared treatment with pravastatin 40 mg per day and atorvastatin 80 mg per day. Data indicated that LDL-C levels achieved with statins predicted the...
risk for death, myocardial infarction (MI), or recurrent acute coronary syndrome. However, when TG levels were considered, a substantial elevation of risk for future cardiovascular events remained among patients with levels >150 mg per dL who were receiving aggressive statin monotherapy—a fact that is often missed in clinical practice.7 Therefore, lipid-lowering treatments that target elevated TG levels should be considered when developing a comprehensive therapeutic plan for reducing CVD risk in patients with mixed dyslipidemia.

Because all lipoproteins other than HDLs are probably atherogenic, the total amount of cholesterol carried by these particles, termed non–HDL-C, is a powerful and convenient index of atherosclerosis risk. Non–HDL-C is invariably elevated in hypertriglyceridemia, with or without mixed dyslipidemia, and predicts CVD risk more strongly than does LDL-C.8 In addition (and at least partially independent of the above), a number of lipid-related proatherogenic conditions are linked to high TG levels including insulin resistance, endothelial dysfunction, inflammation, thrombosis, and increased oxidation of lipoproteins and other components of atherosclerotic plaque.7,9,10

The Role of Statins in the Treatment of Mixed Dyslipidemia
Patients with mixed dyslipidemia are often undertreated. Many patients with dyslipidemia and TG levels ≥200 mg per dL are not at their LDL-C and non–HDL-C treatment goals. A survey using electronic data-capture was undertaken to determine the success rates of dyslipidemia treatment, as defined in the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines. For patients with hypertriglyceridemia, both treatment goals were reached by 64% of the patients who had ≤1 risk factor for CHD, by 52% of those with ≥2 risk factors, and by only 27% of patients with CHD and CHD risk equivalents (Figure 6). Lipid therapies tend to be more effective at reducing LDL-C levels than non–HDL-C levels, especially on a percentage basis.11 Because non–HDL-C levels predict CVD risk better than LDL-C levels, lipid therapy in mixed dyslipidemia should focus on closing this gap in efficacy; meeting the LDL-C goal may leave the patient inadequately treated with regard to achievement of the non–HDL-C goal.12

Increasing the dosage in statin monotherapy is one approach to achieve additional reduction of TG levels in mixed dyslipidemia. However, the dose-response curve of statins is relatively flat, and higher statin doses are not always well tolerated. Statin intolerance due to myopathy and other causes tends to be more prevalent in elderly patients, and lower statin doses should be considered for this population.13 For example, half of the normal statin dose might be used in patients aged ≥75 years. Similar considerations apply to females and to patients with a small body frame, multisystem disease, or a family history of statin intolerance.14 Patients who have hepatitis,15 myopathy,16 or fibromyalgia prior to statin administration are at a higher risk for statin-induced muscle and liver problems. Polypharmacy also increases risk because of a greater potential for drug-drug interactions.17 Strenuous physical activity also increases the risk for myopathy,17,18 which is problematic because most patients are encouraged to exercise regularly.19,20 The most common liabilities associated with statin therapy are reviewed in the following sections.

Muscle Effects. Muscle-related problems with statin therapy are well known and include muscle weakness, pain, inflammation, and, in some cases, rhabdomyolysis. While rhabdomyolysis is rare, it is associated with myoglobinuria and acute renal failure and is fatal in approximately 10% of cases.21

Liver Effects. A reversible elevation of liver transaminase is sometimes seen with the use of statins, although serious cases of liver damage are rarely, if ever, reported.22

Kidney Effects. The perspective on statin-related renal effects has gradually evolved. Some studies, especially those involving rosvustatin, suggested proteinuria and hematuria.23 Because it is highly water soluble, early concerns were raised that rosuvastatin could cause renal damage; indeed, the highest dose requested was not approved by the U.S. Food and Drug Administration due to evidence of proteinuria. However, since then, accumulated evidence suggests that rosuvastatin and other statins may actually improve renal function.24

Neurologic Effects. Statin-related effects on sleep disorders and cognition are controversial due to conflicting evidence.25-31

Drug-Drug Interactions. As discussed, drug-drug interactions
interactions between the statins and gemfibrozil may increase the risk of myopathy. Other agents, such as cyclosporine and certain anti-infective agents, may interact adversely with statins; thus, caution is required when combining such treatments. Likewise, cardiac medicines, such as amiodarone and verapamil as well as the antidepressant nefazodone, are known to interact negatively with statins. Finally, if a patient consumes a large quantity of grapefruit juice (i.e., more than 1 quart per day), the naringenin contained in the juice can delay statin catabolism and thus increase blood levels and potential toxicity.32-35

**Medication Adherence With Statin Therapy.** A number of factors can negatively influence a patient’s adherence to statin therapy, which has been reported to drop to 50% or lower after 1 year of treatment.36,37 For example, medication phobia due primarily to perceived, rather than actual, safety issues can impact adherence. Numerous factors contribute to statin phobia. Patients who use the Internet or consult nonmedical professionals are often misinformed about the safety of statins. Those who are skeptical of Western medicine may assume that they will have a bad reaction to any drug, and others may be reluctant to take statins if they subscribe to “conspiracy theories” about the pharmaceutical industry. Others may overemphasize the use of natural products and dietary supplements, falsely assuming that anything derived from plant or animal sources must be safe.38-41 Some patients rely on dietary supplements and trust the claims made about these products, yet they can be reluctant to believe the benefits of prescription drugs.32 Nonadherence to statin therapy is a major problem. All medical professionals should strive to overcome the misconceptions and other factors that are common to medication nonadherence in general.

**Combination Therapy for Mixed Dyslipidemia**

Increasing the statin dose for patients with mixed dyslipidemia may improve lipid levels to some extent, but not necessarily to recommended goals. Ezetimibe, an agent with a distinct mechanism of action from that of the statins, was shown to reduce LDL-C levels by inhibiting intestinal absorption of dietary cholesterol. However, when added to statin therapy in the Effect of Ezetimibe Plus Simvastatin Versus Simvastatin Alone on Atherosclerosis in the Carotid Artery (ENHANCE) trial, ezetimibe failed to show additional antiatherosclerotic benefits beyond statin use alone.43 An array of therapies is available to improve lipid levels in patients with mixed dyslipidemia. Nonpharmacologic approaches involve therapeutic lifestyle changes, such as increased exercise and dietary changes.44-46 A number of diverse agents, such as interferon,47 olanzapine,48 propofol,49 and human immunodeficiency virus protease inhibitors,50 have the potential to promote hypertriglyceridemia; therefore, removal and replacement of these agents should be considered in therapeutic planning. Statins have only modest effects on lowering TG and raising HDL-C levels; thus, in treating mixed dyslipidemia, the addition of fibrates, niacin, or P-OM3 is often required to bring TGs and HDL-C to target levels. Combination regimens that are useful for the treatment of hypertriglyceridemia are summarized in the following sections.

**Fibrates Plus Statins.** While fibrates have long been used for the successful treatment of hypertriglyceridemia, evidence of their cardiovascular benefits is inconsistent. Further research on fibrate/statin combination therapy is ongoing and includes the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which may help to clarify the current and sometimes conflicting evidence regarding the efficacy and cardioprotective effects of fibrates. This study is investigating the control of coronary events in more than 10,000 high-risk patients with type 2 diabetes. Approximately half of the subjects are receiving lipid treatment with simvastatin either with or without fibrates, while the other half is being treated with various blood pressure–lowering agents. The outcome under investigation in the ACCORD trial is the rate of major cardiovascular disease events (i.e., nonfatal MI, stroke, or CVD death).51-55

**Niacin Plus Statins.** Niacin and the statins have different and complementary effects on lipid profiles; therefore, combinations of these agents would be expected to improve LDL-C, HDL-C, and TG levels and further reduce coronary risk.56 The Comparative Effects on Lipid Levels (COMPELL) study compared statin monotherapy using rosuvastatin (40 mg per day) with combination therapy using atorvastatin (40 mg per day) plus niacin (2,000 mg per day) and rosuvastatin (20 mg per day) plus niacin (1,000 mg per day). When niacin was added to statins, TG and HDL-C levels improved significantly compared with statin monotherapy. HDL-C levels approximately tripled with combination therapy versus monotherapy, and TG levels were reduced by 33%-41% with combination therapy versus 19% with rosuvastatin alone.57 The Safety and Efficacy of a Combination of Extended-Release Niacin and Simvastatin in Patients with Dyslipidemia (SEACOAST) trial compared the effects of simvastatin 20 mg per day alone with simvastatin 20 mg per day plus extended-release niacin either 1 gm or 2 gm per day. The included patients were at goal for LDL-C but not non–HDL-C levels. After 24 weeks of therapy, niacin provided as much incremental improvement in HDL-C and TG levels as simvastatin achieved in lowering LDL-C levels. Compared with patients with normal TG levels, those with elevated TG levels demonstrated a greater reduction in non–HDL-C levels with niacin treatment. These data predict, but do not prove, better cardiovascular outcomes with combination therapy.56

The cardiovascular benefits of treatment with simvastatin plus niacin were compared with placebo in the HDL Atherosclerosis Treatment Study (HATS). A major improvement in atherosclerosis was seen with the combination therapy; regression of stenosis was demonstrated in the group treated with combination therapy compared with progression in those who received placebo. While these results are positive, the drug combination was not compared with statin monotherapy; thus, in this trial, nothing can be
concluded about the superiority of either therapy. The double-blind, randomized, placebo-controlled Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2 trial studied extended-release niacin added to statin therapy in 167 patients with known CHD and low HDL-C levels. The results demonstrated a downward trend in cardiovascular events, but the difference in this very small study was not statistically significant.

Two large ongoing studies of similar design should help verify the efficacy of niacin plus statin combination therapy. In both trials, all participants are treated with a statin; half of these groups also receive niacin and the other half is randomized to placebo treatment. The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH) trial is being undertaken in the United States with the target of following cardiovascular end points in 3,300 patients with vascular disease for 3 to 5 years. The Heart Protection Study 2, a much larger European trial enrolling 20,000 patients, has a similar design, but compares simvastatin monotherapy with simvastatin combined with niacin plus laropiprant (an agent under investigation for the control of niacin-related flushing), with follow-up planned for 3-6 years.

Omega-3 Fatty Acids Plus Statins. The Japan Eicosapentaenoic Acid (EPA) Lipid Intervention Study (JELIS) compared statin monotherapy with statins plus a purified form of EPA (not available in the United States). Nearly 19,000 patients received either usual therapy with statins or 1.8 gm per day of EPA added to their statin therapy and were followed for 4.6 years. A 19% reduction in major coronary events was seen with combination therapy compared with statin monotherapy, driven mainly by lower incidence rates of unstable angina. However, because this trial was performed in Japan where the diet is typically rich in fish and because the study product used (containing only EPA) is unavailable in the United States, the results may be difficult to translate to the American population. Despite these factors, it is encouraging evidence that higher doses of P-OM3 acids added to statin therapy can provide further cardiovascular risk reduction.

When P-OM3 was added to simvastatin in the COMBination of prescription Omega-3 with Simvastatin (COMBOS) trial, statistically significant improvements were seen in non–HDL-C, TG, VLDL-C, and LDL-C levels compared with simvastatin monotherapy. The proportion of patients who achieved non–HDL-C treatment goals in this study is illustrated in Figure 7. Combination therapy also increased HDL levels comparable with those seen with statins, but did not elicit as much improvement as seen with niacin combinations. The COMBOS trial also demonstrated that the combined agents increase the size of LDL particles, thereby decreasing atherogenicity—an effect not seen with fish oil alone.

A meta-analysis of 97 randomized, controlled clinical trials was undertaken to assess the efficacy and safety of lipid-lowering interventions based on all-cause, cardiac, and noncardiovascular mortality data. The studies included a combined total of more than 270,000 patients. Results of this analysis are summarized in Figures 8 and 9. The authors concluded that statins and omega-3 fatty acids offer the best lipid-lowering interventions and reduce the risk of overall and cardiac mortality. The reduction in cardiac mortality that was demonstrated by the use of fibrates is offset by increased mortality from noncardiovascular causes.

Several trials of omega-3 fatty acids are ongoing, primarily studying cardiovascular end points in addition to other

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"Favors Treatment" and "Favors Control" regarding the effect of adding P-OM3 to simvastatin therapy over placebo.

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**FIGURE 7** Effect of Adding P-OM3 to Simvastatin Therapy (COMBOS Trial)

<table>
<thead>
<tr>
<th>Patients achieving non–HDL-C goal (%)</th>
<th>P-OM3 (4 gm per day) + simvastatin</th>
<th>Placebo + simvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>51.6</td>
<td>23.8</td>
</tr>
</tbody>
</table>

**FIGURE 8** Effect of Antilipidemic Agents and Diet on Cardiac Mortality

<table>
<thead>
<tr>
<th>Favors Treatment</th>
<th>Favors Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk ratio (95% CI)</td>
</tr>
<tr>
<td>P-OM3 (n=12)</td>
<td>0.68 (0.52-0.90), P&lt;0.001</td>
</tr>
<tr>
<td>Statins (n=33)</td>
<td>0.78 (0.72-0.84), P=0.42</td>
</tr>
<tr>
<td>Diet (n=18)</td>
<td>0.91 (0.82-1.02), P=0.14</td>
</tr>
<tr>
<td>Fibrates (n=17)</td>
<td>0.95 (0.81-1.08), P=0.13</td>
</tr>
<tr>
<td>Niacin (n=2)</td>
<td>0.95 (0.82-1.10), P=0.75</td>
</tr>
</tbody>
</table>

Adapted from Studer M et al. Arch Intern Med. 2005;165:725-30. Copyright (2005), American Medical Association; all rights reserved.

n = number of studies; P-OM3 = purified omega-3. Trial of P-OM3 used different dietary and nondietary sources with food supplements of n-3 fatty acids or n-3 fatty acid precursors.
potential benefits. Clinical research is currently being undertaken to study the effects of P-OM3 on congestive heart failure mortality (Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico [GISSI]-Heart Failure [HF]), CVD in prediabetes (Outcome Reduction With An Initial Glargine Intervention [ORIGIN] trial), and primary prevention of CVD in metabolic syndrome (A Study of Cardiovascular Events in Diabetes [ASCEND]).

This evolving field of study has the potential to provide clinically relevant developments.

Conclusions
Hypertriglyceridemia is associated with an increased risk for pancreatitis and CVD. Mixed dyslipidemia with high LDL-C levels associated with high TG and low HDL-C levels are common. Medications for lowering TGs are available as monotherapy or in varying combinations of statins, fibrates, P-OM3, and niacin. When LDL-C levels are reduced to treatment goals with statin monotherapy, considerable cardiovascular risk still remains. Published evidence already suggests that the addition of niacin or P-OM3 to a statin may improve cardiovascular outcomes over statin monotherapy; however, definitive data are lacking. Meanwhile, at present, there is no published evidence for additional cardiovascular benefits when either fibrates or ezetimibe are added to statins compared with statin monotherapy. Ongoing clinical trials should soon provide more conclusive data regarding these clinically important questions.

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59. McKenney JM, Jones PH, Bays HE, et al., Comparative effects on lipid levels of combination therapy with a statin and extended-release niacin or ezetimibe versus a statin alone (the COMPelli study). Atherosclerosis. 2007;192(2):432-37.


Maintaining Cardiovascular Health in Patients With Mixed Dyslipidemia: Optimizing the Management of Hypertriglyceridemia and Non-HDL Cholesterol

Activity Release Date: April 17, 2008
Activity Expiration Date: April 17, 2011

Accreditation Statement and Credit Designation
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Upon successful completion of this activity, you will automatically receive your CE statement. Your CE credits will be automatically archived and tracked for you on the AMCP.org (CE/CME Center) site. All information is kept confidential.

Note: There is no fee to participate in this activity.
1. Which of the following is not a diagnostic criterion for the metabolic syndrome?  
   a. Increased waist circumference  
   b. Elevated blood pressure  
   c. Low triglyceride levels  
   d. Low levels of HDL-C  

2. According to the NCEP ATP-III guidelines, a normal triglyceride level is  
   a. <300 mg per dL  
   b. <250 mg per dL  
   c. <200 mg per dL  
   d. <150 mg per dL  

3. Which of the following describes non–HDL-C?  
   a. It is a primary target for intervention in patients with elevated LDL-C.  
   b. It may be a better marker of cardiovascular risk than LDL-C.  
   c. Increased levels are consistently associated with increases in LDL-C.  
   d. It is measured by calculating total cholesterol minus LDL-C.  

4. Approximately what percentage of patients with cardiovascular disease is at LDL-C and non–HDL-C treatment goals?  
   a. 10%  
   b. 20%  
   c. 40%  
   d. 60%  

5. According to American Heart Association recommendations, what amount of omega-3 fatty acids should be ingested by individuals with cardiovascular disease?  
   a. 0.5 gm EPA/DHA per day  
   b. 1 gm EPA/DHA per day  
   c. 4 gm EPA/DHA per day  
   d. 6 gm EPA/DHA per day  

6. Over-the-counter fish oil supplements generally contain about ____% EPA/DHA.  
   a. 30  
   b. 50  
   c. 70  
   d. 90  

7. Which of the following is not thought to be involved in the triglyceride-lowering effects of the fibrates?  
   a. Peroxisome proliferator-activated receptor-alpha  
   b. Retinoid X receptor ligand  
   c. Acyl-CoA synthase  
   d. HMG-CoA reductase  

8. A flushing reaction is commonly associated with which of the following medications?  
   a. P-OM3  
   b. Naringenin  
   c. Laropiprant  
   d. Niacin  

9. Which of the following is not a proatherogenic condition associated with hypertriglyceridemia?  
   a. Insulin resistance  
   b. Decreased lipoprotein oxidation  
   c. Endothelial dysfunction  
   d. Inflammation  

10. When P-OM3 was added to statin therapy, significant improvement was seen in which of the following lipid parameters?  
    a. Triglycerides  
    b. Non–HDL-C  
    c. HDL-C  
    d. All of the above  

To complete this activity, go to http://www.amcp.org, where you will access the posttest and evaluation form.