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REPORT®**

Opportunities for Improving Triglyceride Management

**A review of hypertriglyceridemia burden, risk, and
treatment options for improved outcomes**



Jointly sponsored by the University of Cincinnati and the University of Tennessee College of Pharmacy

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Opportunities for Improving Triglyceride Management

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This activity is designed for managed markets physicians and pharmacists.

STATEMENT OF NEED

The high-risk populations for cardiovascular disease (CVD) are diverse, and studies support that all at-risk patients should be managed for best outcomes. Recent studies also support targeted, more aggressive treatment of triglycerides for improved outcomes. A review of the latest data on the benefits and limitations of targeted triglyceride therapy, such as statins, niacin, fibrates, and omega-3 fatty acids, alone or in combination to improve CVD outcomes in real-world applications, is essential for the clinical and managed care communities.

LEARNING OBJECTIVES

After completing this activity, participants should be able to:

- Outline the evidence supporting the treatment of triglycerides as an important target in various populations
- List the triglyceride levels when treatment is recommended, according to clinical guidelines
- Describe the benefits and limitations of targeted strategies used to lower triglycerides, including statins, fibrates, niacin, and omega-3 fatty acids
- Summarize the significance of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) in reducing triglyceride levels
- Apply evidence-based treatment data to real-world applications for reducing triglyceride levels and CVD risk

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There is no fee associated with this activity.

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The faculty reported the following:

Dr. Harper: Speakers bureau—AstraZeneca, Merck/Schering-Plough Pharmaceuticals

Dr. Jones: Research grant—Abbott Laboratories, AstraZeneca, Kos Pharmaceuticals; Consultant—Abbott Laboratories, Pfizer Pharmaceuticals
Mr. Calabrese, Dr. Codario, Dr. Cziraky, and Mr. Kenney disclosed they have no relevant financial relationships with any commercial interests.

Planning Committee Kay Weigand, University of Cincinnati, Office of Continuing Education; Glen E. Farr, PharmD, Associate Dean of Continuing Education, University of Tennessee College of Pharmacy; and Rosemary Hodgson and Erin Phelps, Princeton Media Associates have disclosed they have no relevant financial relationships with any commercial interests.

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Opportunities for Improving Triglyceride Management

Coronary heart disease (CHD) is a major cause of morbidity and mortality in the United States, with significant clinical and economic consequences. Annually, 950,000 Americans die from cardiovascular disease (CVD), 84% of which are 65 years of age or older.¹ Additionally, CVD is estimated to cost \$403.1 billion in 2006.²

One of many factors (eg, metabolic syndrome, obesity, hypertension, and diabetes) contributing to heart disease burden is hypertriglyceridemia, defined as triglyceride levels greater than 200 mg/dL. In fact, hypertriglyceridemia is an independent risk factor for CHD.³ As the US population ages and cardiovascular risk increases, hypertriglyceridemia will become an even greater focus for healthcare providers. Despite recommended lifestyle interventions and effective pharmacologic agents to treat CHD, at-risk populations still must be aggressively identified for appropriate, early treatment and improved outcomes.

A recent symposium titled “Advancing Triglyceride Management” offered a look at the disease burden and populations at risk, summarized clinical research and evidence-based information for identifying high-risk patients, described various pharmacologic interventions for managing triglycerides, and outlined potential evidence-based treatment options. This article highlights the key educational points covered in each presentation.

Populations at Risk: The Role of Triglycerides

Presented by Ronald A. Codario, MD

The atherogenic (plaque causing) dyslipidemia triad—hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-C), and small dense low-density lipoprotein cholesterol (LDL-C)—has been identified as a major risk factor for CHD.⁴ Dr. Codario stated that hypertriglyceridemia has been shown to be a marker for atherogenic lipoproteins. Untreated hypertriglyceridemia is also associated with metabolic syndrome, insulin resistance, and an increased risk of acute pancreatitis.

Dr. Codario noted that non-HDL-C, which is an approximate measure of all cholesterol components present (minus HDL-C) and measures the level of triglyceride-containing particles, is superior to LDL-C in predicting risk in patients with elevated triglycerides. According to the National Cholesterol Education Program (NCEP) Adult Treatment Program (ATP) III classification, normal levels of non-HDL-C should be 30 mg/dL higher than LDL-C.⁵

The following NCEP ATP III classifications help identify individuals requiring pharmacologic treatment for raised lipid levels⁵:

- LDL-C (mg/dL) of <100 is optimal, 100 to 129 is near or above optimal, 130 to 159 is borderline high, 160 to 189 is high, and ≥ 190 is very high
- HDL-C (mg/dL) of <40 (men) or <50 (women) is low, and ≥ 60 is high
- Total cholesterol (mg/dL) of <200 is desirable, 200 to 239 is borderline high, and ≥ 240 is high
- Serum triglycerides (mg/dL) of <150 are normal, 150 to 199 are borderline high, 200 to 499 are high, and ≥ 500 are very high

NCEP ATP III also sets the following goals for non-HDL-C for individuals within CHD risk categories:

- For individuals with CHD and 10-year CHD risk, non-HDL-C of <130 mg/dL is goal; for individuals with 2 or more risk factors and 10-year CHD risk, non-HDL-C of <160 mg/dL is goal; and for individuals with 1 or no risk factors, non-HDL-C of <190 mg/dL is goal

Clinical Impact of Hypertriglyceridemia. Strong evidence supports the management of triglycerides for improving outcomes in several disease states.⁶⁻¹² A meta-analysis involving 76,000 individuals indicated that for every triglyceride increase of 89 mg/dL, CHD risk increases by 30% in men and 70% in women, based on univariate analysis.^{6,7} The Prospective Cardiovascular Munster study, which included nearly 5000 middle-age men, found that fasting levels of triglycerides are an independent risk factor for CHD events.⁸ The NCEP guidelines confirm that hypertriglyceridemia is an independent risk factor for coronary atherosclerosis, especially when associated with small dense LDL-C and low HDL-C.⁹ The American Heart Association (AHA) and the American College of Cardiology indicate that hypertriglyceridemia is also associated with cerebral vascular disease and stroke.^{10,11} Furthermore, according to the American Diabetes Association, lowering triglycerides has been shown to reduce macrovascular disease and mortality in patients with type 2 diabetes mellitus.¹²

Hypertriglyceridemia is also associated with an increased risk of metabolic syndrome, found in approximately 47 million Americans.¹³ Metabolic syndrome diagnosis is established when 3 or more of the following risk factors are present: waist circumference >102 cm in men and >88 cm in women, triglyceride levels ≥ 150 mg/dL, HDL-C levels <40 mg/dL in men and <50 mg/dL in women, blood pressure $\geq 130/\geq 85$ mm Hg (treated hypertension is also a risk factor), and fasting glucose ≥ 100 mg/dL.⁵

At-Risk Populations. Triglyceride levels of 200 to 499 mg/dL occur in about 13% of the population and levels of ≥ 500 mg/dL occur in 2.5% to 3% of the population.⁹ Risk factors for hypertriglyceridemia include:

- Genetic patterns: familial hypertriglyceridemia, polygenic hypertriglyceridemia, familial lipoprotein lipase deficiency, familial apolipoprotein creatinine-II deficiency, familial combined hyperlipidemia, familial dysbetalipoproteinemia¹⁴
- Heritage: African American, Pima Indian, Latin American, Mexican American¹⁵
- Acquired causes: overweight/obesity, physical inactivity, smoking, excess alcohol intake, high carbohydrate intake (>60% of total calories)¹⁴
- Medication use: hormones (eg, oral estrogen), corticosteroids, retinoids, beta-blockers, thiazide diuretics, protease inhibitors, antipsychotics¹⁶
- Diseases: chronic renal failure, nephrotic syndrome (caused by diabetes, syphilis, various types of collagen vascular diseases, and renal vein thrombosis), Cushing's disease, lipodystrophy, diabetes¹⁴
- Gender: Women at high risk for CVD are a special concern because of lack of recognition. A study showed that few high-risk women

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attained the AHA's standards for all lipid fractions, and only one third received recommended drug therapy.¹⁵

Strategies for Managing the Hypertriglyceridemic Patient

Presented by Charles Harper, MD

Eighty-four percent of Americans who die from CVD are 65 years of age or older¹; thus, most patients with CVD are Medicare beneficiaries, and preventive CVD screening tests are important for improved outcomes.

Treatment Goals. Managed care should understand that the most triglyceride-rich particles in the blood are very low-density lipoproteins (VLDL) and intermediate-density lipoproteins; once a patient's LDL-C goal has been reached, pharmacologic options and lifestyle choices should be recommended to impact and reduce these particles.

The primary goal for patients with borderline-high (150-199 mg/dL) triglycerides is to first achieve the LDL-C goal; first-line therapy should involve lifestyle changes (eg, weight control, physical activity, smoking cessation, alcohol restriction, carbohydrate restriction).⁵ Patients with high triglycerides (200-499 mg/dL) should undertake lifestyle changes to achieve an LDL-C goal complemented with pharmacologic therapy to achieve a triglyceride level goal.⁵ For patients with very high triglycerides (≥ 500 mg/dL), the primary and secondary goals of therapy are the prevention of acute pancreatitis and the prevention of CHD, respectively.⁵ First-line therapy involves medication to lower triglycerides and a very low-fat diet (<15% of calories from fat).⁵

Treatment Options. Triglyceride-lowering pharmacologic options include fibrates, prescription omega-3-acid ethyl esters (P-OM3), niacin, and statins (Table).^{17,18}

Fibrates. Fibrates have been proven effective for lipid management by activating a nuclear receptor called peroxisome proliferator-activated receptor alpha (PPAR α) to affect multiple aspects of lipid metabolism, including increasing HDL-C production and decreasing triglyceride synthesis.¹⁹ Unfortunately, fibrates also decrease the number of LDL-C particles and shift LDL-C particle size from small to large, less atherogenic particles.¹⁹

In patients with lipoprotein disorders, fibrates generally have been shown to decrease triglycerides by 20% to 50% and increase HDL-C by 6% to 15%, although LDL-C may remain neutral or even increase.^{17,18} In patients with triglycerides less than 150 mg/dL, 3 to 6 months of fenofibrate use decreased LDL-C levels by about 31% and triglyceride levels by about 23% versus placebo. Patients with triglycerides higher than 150 mg/dL experienced an LDL-C reduction of about 20% and a triglyceride reduction of about 36%.²⁰

The Helsinki Heart Study,²¹ which used fibrate in a primary prevention setting, found that a fibrate reduced nonfatal myocardial infarction (MI) and cardiac death, and one secondary prevention trial, the Veterans Affairs High-Density Lipoprotein Intervention Trial,²² reported a 22% reduction in events. Results from other secondary prevention trials have been positive but nonsignificant.

Fibrates are generally well tolerated but are contraindicated in patients with hepatic or renal dysfunction and gallbladder disease.²³ Potential adverse effects include an increase in serum creatinine, minor increases in liver transaminases, myopathy, an effect on the action of oral anticoagulants, and an increase in statin blood levels.²³ Dr. Harper cautions clinicians to be aware of dosing and formulation differences among fibrate products.

P-OM3. P-OM3 generally has a neutral to decreasing effect on LDL-C, a neutral to increasing effect on HDL-C, and a 20% to 50% decrease in triglyceride levels. P-OM3 contains eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the active ingredients in fish oil that affect lipid metabolism. Like fibrates, P-OM3 stimulates PPAR α , increases the beta-oxidation of fatty acids, and inhibits triglyceride synthesis.²⁴⁻²⁹ P-OM3 also inhibits diacylglycerol acyltransferase, a key enzyme involved in lipid formation.²⁴⁻²⁹ P-OM3 increases plasma lipolytic activity and triglyceride clearance rates.²⁴⁻²⁹ VLDL particles enriched with P-OM3 are more susceptible to conversion to LDL-C through lipase.²⁴⁻²⁹

P-OM3 is also comparable to fibrates in efficacy of triglyceride reduction. In a pooled analysis of patients with triglycerides ≥ 500 mg/dL, P-OM3 was found to decrease triglycerides by 45%, VLDL by 42%, and increase LDL-C by 45%; HDL-C increased 9%.^{30,31} The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Prevenzione trial showed that a daily 1-g dose of P-OM3 did not change lipid levels but did reduce sudden death, probably because of antiarrhythmic effects.³² One gram of P-OM3 is not the FDA-approved dose for triglyceride reduction, which is 4 g.³³ Another trial, Omacor Carotid Endarterectomy Intervention (OCEAN), found that patients taking 2 g daily for 21 days prior to endarterectomy had a lower number of foam cells (which form at the earliest stage of atherosclerosis) than patients given placebo ($P=.039$).³⁴

For patients with documented CHD, the AHA recommends a daily 1-g dose of EPA and DHA.^{35,36} Dr. Harper noted that pharmacists should ensure patients understand that the active ingredients in fish oil supplements may be inconsistent. Potential adverse effects of P-OM3 are mild and include eructation, flu-like syndrome, dyspepsia, taste perversion, and back pain.³³

Niacin. Niacin generally decreases LDL-C by 10% to 25%, increases HDL-C by 15% to 35%, and decreases triglycerides by 20% to 50%.^{17,18} Niacin decreases adipose tissue fatty acid mobilization (thus reducing triglyceride synthesis), increases the degradation of apolipoprotein-B, and increases HDL-C.¹⁷

The Coronary Drug Project found that niacin taken for a 5- to 8-year period reduced nonfatal MI by 27%, stroke/transient ischemic attack

Table. Pharmacotherapy: Effect on Serum Lipids^{17,18}

Drug	Total Cholesterol	LDL-C	HDL-C	Triglycerides
Statins	↓15%-60%	↓20%-60%	↑3%-15%	↓10%-40%
Niacin	↓25%	↓10%-25%/Neutral	↑15%-35%	↓20%-50%
Fibrates	↓15%	↓0%-15%	↑6%-15%	↓20%-50%
P-OM3	↓/Neutral	↓/Neutral	↑/Neutral	↓20%-50%

LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; P-OM3 = prescription omega-3-acid ethyl esters.

by 21%, and total mortality by 11%.^{38,39} The Stockholm Ischemic Heart Disease Study found that a combination of niacin and clofibrate reduced total mortality by 26% and CHD mortality by 36%.⁴⁰

Extended-release (ER) niacin is titrated upward from a 500-mg dose during the first 4 weeks to a 1000-mg dose during weeks 5 through 8, and then again to 1500 or 2000 mg, if lower doses produce an inadequate response. The recommended maintenance dose is 1000 to 2000 mg once daily at bedtime.⁴¹ Dosage should not exceed 2000 mg.

The most common adverse effect of ER niacin is flushing, which is reported in as many as 88% of patients.⁴² Practical steps to reduce flushing include taking a regular strength aspirin or a nonsteroidal anti-inflammatory drug up to 30 minutes before ER niacin, taking ER niacin once daily at bedtime, taking the dose with a low-fat snack, and avoiding alcoholic beverages, hot beverages, and spicy foods.⁴¹⁻⁴³

Hepatotoxicity can occur at higher doses of niacin products, particularly with sustained-release, over-the-counter niacin. Niacin is contraindicated in patients with active gout and is relatively contraindicated in patients with poorly controlled type 2 diabetes. Niacin may exacerbate peptic ulcer disease.

Statins. Dr. Harper emphasized that a statin should be given to patients who are not at their LDL-C goal with triglyceride levels of approximately 200 to 300 mg/dL. In patients with hypercholesterolemia, statins have been shown to decrease LDL-C by 20% to 63%, increase HDL-C by 3% to 22%, and decrease triglyceride levels by 5% to 43%.^{19,23,44} Statins' effects on lipids depend on the underlying lipid pathology and are dose-dependent.^{19,23,44} In patients with markedly elevated triglycerides (>500 mg/dL), Dr. Harper indicated that a statin won't always obtain a therapeutic triglyceride target.

Potential adverse events include myopathy, which is dose-dependent, rhabdomyolysis, and an increase in liver function tests; these events should all be noted, but occur in less than 1% of patients.^{23,45,46}

Combination Therapy. Combination therapy in dyslipidemia has 2 roles—to lower LDL-C and to achieve non-HDL-C goals. Dr. Harper discussed evidence from 2 studies of combination therapy.

In a study of ER niacin and lovastatin, 164 adults with hyperlipidemia were randomized into 5 parallel treatment groups: ER niacin, lovastatin, and 3 combination arms, each with a constant lovastatin dose and escalating ER niacin dose. Mean LDL-C reductions were greater with combination therapy than with lovastatin alone.⁴⁷ The maximum recommended dose (2000 mg niacin and 40 mg lovastatin daily) increased HDL-C levels by 29% and decreased LDL-C and triglyceride levels by 46% and 38%, respectively.⁴⁷

In a randomized drug-drug interaction study in 24 patients with mixed hyperlipidemia, 80 mg simvastatin was administered with or without 4 g of P-OM3 for two 14-day periods; no significant differences were found after coadministration of P-OM3 with simvastatin compared with simvastatin alone.⁴⁸ The study concluded that P-OM3 did not appear to impact the pharmacokinetics of simvastatin, and the combination appeared to be well tolerated.

Dr. Harper added that combination statin/fibrate therapy (particularly with gemfibrozil) increases the risk of rhabdomyolysis and inhibits the hepatic glucuronidation of certain statins.

Dr. Harper cautioned that the lowest efficacious dose of statins/fibrates and niacin/fibrates should be selected when using combination therapy. In addition, managed care pharmacists and clinicians should be aware of the danger of drug-drug interactions (eg, statins with erythromycin or cyclosporine), as well as potential adverse effects and costs.

Strategies for Managing the Patient at Risk for CVD: A Case-Based Approach

Presented by David Calabrese, RPh, MHP

Mr. Calabrese presented 2 evidence-based case studies highlighting various triglyceride management strategies and drawing conclusions regarding the most appropriate care for individual patients.

Case #1: Secondary Prevention and Risk Stratification. The patient is a 65-year-old man recovering from an MI that occurred 6 months ago. Case information is as follows:

- Medical History: Hypertension
- Social History: Nonsmoker, exercises 3 times a week, follows a heart healthy eating plan
- Medications: Lisinopril 10 mg daily, atenolol 50 mg daily, aspirin 81 mg daily
- Vitals: Blood pressure=126/78 mm Hg; weight=182 pounds; height=72 inches; waist circumference=36 inches
- Labs: Fasting labs: Total cholesterol=185 mg/dL; HDL-C=35 mg/dL; LDL-C=95 mg/dL; triglycerides=275 mg/dL; all other labs within normal limits

Specific clinical considerations with this patient include the following:

- The patient is high risk, with known CHD
- LDL-C goal (<100 mg/dL) is attained without lipid-lowering therapy
- Triglycerides are elevated
- HDL-C is low

Given the patient's high risk status, NCEP recommendations further suggest that an appropriate LDL-C goal is <70 mg/dL. Primary and secondary prevention outcome trials involving statin therapy indicate that LDL-C decreases cardiovascular events. For example, the Heart Protection Study,⁴⁹ a landmark study with more than 20,000 patients at high risk for vascular events, randomized subjects to either placebo or 40 mg simvastatin daily for 5 years. Regardless of baseline LDL-C, patients were able to achieve at least a 25% reduction in vascular events.⁴⁹ Additionally, a meta-analysis that combined the results of 14 outcomes trials involving more than 90,000 patients found that statin therapy yielded extremely positive results with regard to reduction in events.⁵⁰

Statin monotherapy was selected to help this patient reduce his cardiovascular risk. LDL-C of >70 mg/dL was attained, and HDL-C was increased to 40 mg/dL.¹⁵ Because the triglyceride levels remained elevated, niacin or fibrate would be an appropriate combination therapy option to lower triglycerides and increase HDL-C.¹⁴

Case #2: Safety Considerations in Combination Therapy. The patient is a 49-year-old man who started statin therapy about a year ago. Case information is as follows:

- Medical History: Hypertension, dyslipidemia
- Social History: 1 to 2 beers/day, smokes, no exercise, kcal diet (low fat and cholesterol) = 2400

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- Medications: Hydrochlorothiazide 25 mg daily, simvastatin 20 mg daily
- Vitals: Blood pressure=136/84 mm Hg; weight=190 pounds; height=70 inches; waist circumference=39 inches
- Labs: Fasting labs: Total cholesterol=187 mg/dL; HDL-C=40 mg/dL; LDL-C=135 mg/dL; triglycerides=535 mg/dL; glucose=105 mg/dL; high-sensitivity C-reactive protein=4.1 mg/L; all other labs within normal limits

Specific clinical considerations with this patient include the following:

- The patient has very high triglycerides
- The patient is at moderately high risk with multiple cardiovascular risk factors and a Framingham Risk Score of 15%⁵¹
- The patient has metabolic syndrome and an elevated C-reactive protein
- The patient's LDL-C goal should be <100 mg/dL

Primary clinical management should focus on a 60% initial reduction in triglycerides to obtain the NCEP goal of <200 mg/dL⁵² and secondary reduction of LDL-C by 30% to 40%.

Niacin and fibrate would be options for this patient, who has already started on a statin. Additionally, because the triglyceride levels are elevated higher than 500 mg/dL, P-OM3 may be considered. For the LDL-C reduction, the lipid-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial⁵³ included more than 10,000

primary prevention patients with multiple cardiovascular risk factors and a mean baseline LDL-C of 133 mg/dL who received either atorvastatin 10 mg per day or placebo for a mean of 3.3 years. The atorvastatin group reduced LDL-C to 90 mg/dL and achieved a 36% reduction in nonfatal MI and cardiovascular death.⁵³

Several therapies are available, but managed care pharmacists and clinicians should consider changing to a higher potency statin regimen to ensure LDL-C reduction.⁵

Conclusion: Implications for Care

LDL-C continues to be the primary target of lipid management for most providers today. However, many patients present with multiple lipid abnormalities; therefore, other factors, such as HDL-C and triglycerides, must also be a focus of treatment for improved outcomes. In particular, high triglycerides are considered to be an independent risk factor for CHD and are a major component of the metabolic syndrome. Lifestyle interventions are critical and pharmacologic intervention is necessary in some patients at risk of developing CHD or having another cardiovascular event. Clinicians can select from among a variety of effective options to help achieve lipid level goals. Additionally, multiple medications are often needed to control a patient's full lipid panel, so it is essential that managed care is familiar with efficacious and safe combination therapy options. ■

Complete list of references available through Princeton Media Associates, LLC. Call 609-371-1137 or e-mail info@princetoncme.com

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Clinical Commentary

Peter H. Jones, MD, Associate Professor, Center for Cardiovascular Disease Prevention, Methodist DeBakey Heart Center

Closing Knowledge Gaps

It is not well recognized that the non-high-density-lipoprotein cholesterol (non-HDL-C) value, which is simply the total cholesterol level minus the HDL-C level, captures the contribution to risk of low HDL-C and high triglycerides. Elevated triglycerides are frequently seen in patients with type 2 diabetes and the metabolic syndrome, and have been shown to be independent predictors of cardiovascular risk in women more than men. Healthcare professionals need to target both LDL-C and non-HDL-C goals in patients with mixed dyslipidemias, and the drug treatments commonly involve combinations of statins with fibrates, niacin, and/or omega-3 fatty acids.

Targeted learning with case studies illustrates how to assess cardiovascular risk and how to apply lifestyle and drug treatment regimens based on national guidelines. With specific regard to lipid management, case studies can demonstrate how to assess primary and secondary lipid targets of therapy and how to safely use drug monotherapy or combinations. Real-life case studies have been extremely valuable over many years to reinforce the analytical decision-making process that is the basis of clinical medicine.

Targeting High Triglycerides

Triglyceride levels are used as one of the metabolic syndrome defining criteria if they are >150 mg/dL. Most physicians are aware that triglyceride levels >200 mg/dL should be treated, but I don't believe they are stringently committed to achieving levels <150 mg/dL, most

likely because there are no clinical cardiovascular end point trials that firmly establish that as a target associated with reduced risk. Exercise and weight reduction are very effective in reducing triglyceride levels, particularly in the metabolic syndrome and diabetes. Physicians should emphasize and encourage participation in, at a minimum, a walking program of 150 minutes per week, and a calorie-restricted diet that achieves a 10% weight reduction.

Effectively Using Pharmacologic Agents

When lifestyle modification isn't enough, there are also effective and safe drugs that reduce triglycerides by 25% to 50%, including fibrates, niacin, and omega-3 fatty acids. HDL-C levels, which are frequently low in people with high triglycerides, can increase significantly with the same lifestyle and drug treatments.

Physicians may find that compliance to niacin can be limited by flushing episodes, while the other drugs are usually well tolerated. For example, most over-the-counter (OTC) omega-3 fatty acid products contain 240 to 500 mg of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) per capsule, which would require a minimum of 4 to 8 capsules, and a maximum of 10 to 14 capsules per day (2000-4000 mg/day). Prescription omega-3-acid ethyl esters contain 840 mg EPA and DHA per capsule, and I have found that the recommended 4 capsules per day for triglyceride lowering are more cost efficient and tolerable with the prescription than the OTC supplements.

Combination Therapy

In my experience, for patients with severe hypertriglyceridemia (>500 mg/dL) monotherapy is usually insufficient to achieve acceptable control. It is frequent that the LDL-C level increases when treating severe hypertriglyceridemia with niacin, fibrates, or omega-3 fatty acids; in most instances, this is not the result of increased LDL

particles, but rather, an increase in the LDL particle size. However, for some high-risk patients, the addition of a statin may be indicated, and it is not recommended that gemfibrozil be combined with statins because of an observed higher risk of myositis. Fenofibrate, niacin, and omega-3 fatty acids combined with statins can be safe and efficacious. ■

Managed Care Commentary

James T. Kenney, Jr, RPh, MBA, Pharmacy Operations Manager, Harvard Pilgrim Health Care

Emerging Cardiovascular Risk Factors

For more than 10 years, cholesterol management has centered on low-density lipoprotein cholesterol as the primary target for pharmacologic treatment. Statins have been heavily promoted to physicians and managed care plans as the primary pharmacologic agents for the effective management of high cholesterol in the patient population at risk for cardiovascular disease (CVD). Recently, the focus has expanded to include additional markers as important predictors of coronary heart disease (CHD) risk, including high-density lipoprotein cholesterol, triglycerides, and other fractions of the lipid profile, including very low-density lipoprotein cholesterol.

An educational need exists to identify and characterize all elements of the lipid profile and their relative risk in the development of CHD, as well as knowing the various pharmacologic agents that are appropriate for treating patients with abnormal lipid profiles.

Formulary Decision-Making

The formulary decision-making process focuses primarily on the efficacy and safety. It is imperative that the pharmacy and therapeutics committee has a clinical understanding of the influence of high triglycerides on conditions such as CHD and metabolic syndrome, and the potential impact on clinical outcomes in the at-risk population. The review of agents to treat CVD is particularly challenging because of the broad number of disease states the cardiovascular cat-

egory encompasses and the extensive drug classes employed in managing these complex conditions. Multiple drug combinations compound the treatment of these patients and demand a thorough understanding of their various uses and interactions. Evidence-based case studies are a useful tool in evaluating agents for formulary inclusion because they allow for a real-world assessment of the role new pharmacologic agents play in the treatment algorithms used for total cholesterol management in the cardiovascular at-risk population.

Differentiating Efficacy of Current and New Treatments

Although there are several pharmacologic agents that can be used for triglyceride lowering, including niacin, statins, fibrates, and the approved prescription omega-3-acid ethyl esters, managed care needs to clearly differentiate these options when selecting appropriate agents for the CHD patient and developing effective cardiovascular formularies. Each agent offers a unique clinical profile, and the combination of these products with a statin is a common indication that requires outcomes data to support appropriate use.

Knowledge of the clinical differences among these agents is an important factor to differentiate those most effective in triglyceride lowering from those that are less effective. Available clinical studies to support the efficacy and safety of these agents are useful in determining their role in the treatment of hypertriglyceridemia. ■

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