The Pharmacist’s Role in Lipid Management
By Jennifer Malinowski, PharmD

Upon completion of this article, the pharmacist should be able to:
1. Discuss the basic pathophysiology of lipid disorders.
2. Identify treatment goals and evaluate heart disease risk for patients with dyslipidemia.
3. Educate patients on therapeutic lifestyle interventions such as diet and exercise.
4. Recommend appropriate initial and add-on treatments for patients with lipid disorders.
5. Identify strategies to prevent and manage adverse events related to lipid lowering therapies.

INTRODUCTION

According to the Centers for Disease Control (CDC), approximately one in every six adults—or 16 percent of the U.S. adult population—has high total cholesterol, defined as total cholesterol of 240 mg/dL and above. High cholesterol and other lipid abnormalities enhance plaque formation that leads to coronary heart disease (CHD) and other atherosclerotic disorders. Patients with high total cholesterol are twice as likely to develop heart disease compared to patients with optimal cholesterol values. Cardiovascular disease is the number one cause of death in American men and women today, claiming one out of every three lives.

The prevalence of high cholesterol in America declined in the past 50 years, largely in part to diets lower in saturated fat and improved pharmacological therapies. In addition, CHD in most cases occurs over a long period of time. Community pharmacists are in a unique position to curb risks and degree of complications associated with CHD, such as poor diet, sedentary lifestyle, and smoking. Their accessibility to patients in the front lines of the pharmacy allows for appropriate identification of screening candidates, and enables them to offer advice on initial and alternative lipid lowering therapies when needed.

The National Cholesterol Education Program (NCEP) recommends that all adults over 20 should have their cholesterol checked at least once every five years. Although nearly three in four Americans are in compliance with this recommendation, approximately 20 percent of adult Americans never had their cholesterol evaluated. Once patients are identified with high cholesterol, therapeutic lifestyle changes (TLCs) are always recommended, regardless of the need for medication. The benefits of TLCs in patients with dyslipidemias are well studied. Numerous animal, clinical, and epidemiologic trials support the correlation of dietary saturated fat and cholesterol to the development and degree of CHD. Pharmacists can offer education and encourage compliance with proper diet and exercise regimens, and/or refer patients to seek out a dietician, physical therapist or other complementary consultant.

Pharmacists can determine if patients would benefit from lipid regulating therapy and communicate action
plans to the patient’s provider. The benefits of statins are well documented in both primary and secondary prevention. Unfortunately, patients sometimes discontinue therapy because of actual or perceived adverse events related to statins. This is a very important role for the pharmacist. Pharmacists can evaluate adverse reactions and establish alternative treatment and monitoring plans for the patient. Pharmacists can help providers navigate the initial and alternative lipid regulating agents for a particular patient and guide the selection of the most appropriate products. Community pharmacists can offer support during patient selection of OTC products designed to enhance or replace existing therapy. This article will focus on background pathophysiology, and nonpharmacologic and pharmacologic treatments for dyslipidemias commonly observed in adults. Common scenarios will be reviewed through patient cases and reviewed with support from the literature.

**PATHOPHYSIOLOGY**
The pathophysiology of dyslipidemia is important for the pharmacist to appreciate to better understand what medications work for different lipid disorders. Cholesterol, a major plasma lipid, is an essential substance made by cells and is used to support the cell wall. Cholesterol is somewhat water insoluble, so it is encapsulated within water-soluble lipoproteins. Lipoproteins move cholesterol through the blood. Lipoproteins are composed of varying amounts of cholesterol and triglycerides (TG). The major lipoproteins, from largest to smallest are: chylomicrons, very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL), low density lipoproteins (LDL), and high density lipoproteins (HDL). Each lipoprotein is characterized by density and size, which are inversely related. For example, high density lipoprotein (HDL) is the smallest lipoprotein, but it is the densest of all lipoprotein particles (hence the name).

Each lipoprotein has surface proteins called apolipoproteins. Apolipoproteins in general help to make and secrete lipoproteins, bind the lipoprotein to cell surfaces, and assist with activation of enzymes needed to breakdown lipoprotein particles into triglycerides. There are different subtypes based on function.

Dietary or biliary cholesterol is transformed by bile salts into micelles in the small intestine. Some of this cholesterol is placed into chylomicrons with phospholipids, apolipoproteins, and triglycerides, which get ejected into the lymphatic circulation. While there, TGs may be removed, creating chylomicron remnants which are removed. Chylomicrons can also engage with HDL particles to share TG and cholesterol.

Cholesterol and TG travel to the liver from the lymph and join phospholipids and apolipoproteins to become VLDL. Lipoprotein lipase, a pharmacologic target of gemfibrozil, interacts with VLDL particles to promote the release of TG and form a VLDL remnant and IDL. IDL can either be cleared or converted by lipases to form LDL. LDL receptors in the liver remove LDL from the blood or other tissues can attract LDL. This is another pharmacologic target for lipid regulation. Atherogenesis develops when LDL is not cleared by the liver, but is attracted to the arterial wall.

**LIPID DISORDERS**
Lipid disorders result from genetic disruptions in the way lipoproteins are formed and metabolized. The most common type is polygenic hypercholesterolemia, a disorder more commonly associated with poor eating and exercise habits. Polygenic hypercholesterolemia is associated with moderate LDL cholesterol concentrations (LDL-C) elevations. Values do not typically exceed 250 mg/dL. LDL-C baseline values that exceed 250 mg/dL are often familial. Severely elevated LDL-C (beyond LDL-C 250 mg/dL) may be associated with overproduction of VLDL or LDL, reduced LDL receptor amounts, or alterations in apolipoproteins bind LDL to the receptor (apo B 100 and apo E2/2, specifically). Although most of the clinical sequelae of dyslipidemia alone is silent, patients with extreme elevations of LDL-C may present with manifestations associated with lipid deposits, such rings around the cornea and xanthomas.

TG elevations are also familial. The cause is often unknown, but may be related to overproduction of VLDL or changes in apolipoproteins (apo E2/2). TG exceeding 500 mg/dL may cause pancreatitis and xanthomas, though the elevations are usually without symptoms.

**LIPIDS AND CHD**
It is thought that lipoproteins on the arterial wall
produce inflammation, resulting in atherosclerosis. Lipoproteins stick to proteoglycans on the arterial wall, forming a fatty streak. Lipoproteins then enter the intima and are oxidized. Oxidation disturbs the process that maintains vasomotor tone. The smaller, denser LDL particles are attracted to the cell wall more readily and are more at risk for oxidation. Oxidation attracts monocytes, which transform into macrophages. These macrophages express receptors that attract Apo-B containing lipoproteins. Accumulation continues until they become lipid saturated cells called foam cells. Foam cells collect and form a lipid abundant core, which initiates the formation of an atherosclerotic plaque. Smooth muscle cells move from the media to the intima to form a protective fibrous covering. Enzymes are secreted by inflammatory cells that try and break down the fibrin and collagen covering. Patients may experience an ischemic event if this cap breaks off and creates a thrombus. Lipid lowering therapy with statins has been shown to make the plaques more stable.

**LIPID MEASUREMENT AND INTERPRETATION**

When total cholesterol is measured, the total cholesterol molecules within all the major lipoproteins are reported. A typical lipid panel contains results for LDL-C, HDL, TG, and TC. LDL is frequently calculated using the equation: LDL cholesterol mg/dL = total cholesterol - (HDL cholesterol + triglycerides/5). LDL cholesterol (LDL-C) can be directly measured, and must be measured if a patient has triglycerides greater than 400 mg/dL; the calculated test is too inaccurate.

Patients should be advised to fast prior to the lipid panel to obtain a more accurate LDL-C calculation and TG measurement. Fasting allows time for TG carrying chylomicrons to clear the circulation. Fasting does not only involve food, as even coffee with creamer can interfere with test results. Pharmacists can guide the patient to better understanding their lipid panel results. Many patients are confused on the difference between “good” cholesterol (HDL) and “bad” (LDL) cholesterol. Pharmacists can clarify the difference to patients and offer suggestions on how to improve each lipid parameter.

If a lipid panel is deemed valid and not at goal, secondary causes of dyslipidemia should be ruled out (Table 1). Fasting glucose/hemoglobin A1C, liver function, and renal function should be considered before initiating treatment. Diabetes, along with renal and liver disease, may contribute to altered lipid panels. Thyroid stimulating hormone should be evaluated to rule out hypothyroidism. Drug-induced causes of dyslipidemia are important to recognize. Simple removal of an offending medication from the patient’s medication list can correct lipid abnormalities and spare the patient from unnecessary treatment. Consider alternatives when possible.

**TREATMENT GOALS AND RISK STRATIFICATION**

Once an abnormal lipid panel is deemed valid, lipid goals should be established. An overview of treatment goals recommended by the National Cholesterol Education Program is listed in Table 2 and Table 3. The initial treatment target is almost always LDL-C, unless TGs exceed 500 mg/dL.

The Framingham Calculation is useful in establishing the
patient’s 10-year risk for CHD. This is a simple point scale used to evaluate risk, particularly in patients in the LDL-C goal category of < 130 mg/dL. Newer prediction models incorporate additional data points such as Reynold’s risk, United Kingdom Prospective Diabetes Study calculation and Q-Risk, but were developed after the launch of NCEP III. NCEP IV may possibly recommend a newer risk calculation method; full guideline release is expected in 2012.

**PATIENT CASE**

LT is a 65-year-old female currently taking hydrochlorothiazide (HCTZ) 25 mg orally daily, tiotropium bromide inhalation once daily, albuterol inhaler as needed, and omeprazole 20 mg daily. She would like a pharmacist to help her understand her lipid profile. Lipid panel results are: TC 240 mg/dL, LDL 159 mg/dL, HDL 39 mg/dL, and TG 152 mg/dL. What questions should you address prior to evaluating her lipid goals and heart disease risk?

The pharmacist should confirm that LT was fasting for this lipid panel, by scrutinizing when her last meal and beverage occurred. The pharmacist should confirm her past medical history, and prompt for pertinent disease states that would alter her LDL-C goal. LT reveals that she is taking the HCTZ for high blood pressure, which has been averaging 110/78 the past two weeks, and she is using her inhalers as prescribed for chronic obstructive pulmonary disease (COPD). She takes omeprazole for heartburn. The pharmacist confirms that she has no history of heart problems, stroke or Transient Ischemic attacks in the past or has diabetes. To rule out potential secondary causes, the pharmacist is certain to question her about prior history of liver or renal disease or hypothyroidism. LT states her doctor told her everything was normal.

<table>
<thead>
<tr>
<th>LDL-C Goal</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 70 mg/dL</td>
<td>Preexisting CHD at high risk</td>
</tr>
<tr>
<td>&lt; 100 mg/dL</td>
<td>CHD defined as: Myocardial infarction Unstable or chronic stable angina CHD Risk Equivalents defined as: Type 1 and 2 diabetes mellitus Symptomatic carotid artery stenosis (or asymptomatic with &gt; 50% occlusion) Peripheral arterial disease Framingham risk calculation: &gt; 20%</td>
</tr>
<tr>
<td>&lt; 130 mg/dL</td>
<td>Two or more cardiovascular risk factors Evaluate Framingham Risk</td>
</tr>
<tr>
<td>&lt; 160 mg/dL</td>
<td>0–1 cardiovascular risk factors</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>&lt; 150 mg/dL</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>&lt; 200 mg/dL</td>
</tr>
<tr>
<td>HDL-C</td>
<td>&gt; 40 mg/dL (males)</td>
</tr>
<tr>
<td></td>
<td>&gt; 50 mg/dL (females)</td>
</tr>
<tr>
<td>Non-HDL</td>
<td>LDL goal plus 30 mg/dL</td>
</tr>
</tbody>
</table>

LT has NKDA and is without complaint today. Her (blood-related) sister on the other hand, just had a heart attack and cardiac bypass last month. She is only 51 years old. This unfortunate incident has motivated LT to diet, knowing she needs to lose at least 50 pounds (the pharmacist observes that LT does appear obese). She wonders if she must go on a statin, as her sister had a terrible reaction and she heard “horror” stories about people having muscle pain and liver problems. She does not drink and is trying to cut back on smoking. She uses about half a pack per day now, down from one pack daily. She hopes that you can guide her on what to do.

The first step for establishing therapy for LT would be to evaluate her LDL-C goal. As her TG value is not severely elevated, the initial treatment target should be LDL-C. There are no compelling indications for an LDL-C goal of less than 70 mg/dL or 100 mg/dL, according to Table 2. The next step would be to evaluate her cardiac risk factors and count them, as in Table 4. LT appears to have numerous risk factors: age, family history, high blood pressure, smoking, and low HDL. Five risk factors put her at a minimum LDL-C goal.
of < 130 mg/dL. A Framingham risk evaluation needs to be completed for her, which is calculated to be 6 percent. Since this value does not exceed 20 percent, the percentage that would drive the LDL-C goal to under 100 mg/dL, her LDL treatment goal is < 130 mg/dL.

What should be considered first in LT? Pharmacists should ask patients with dyslipidemia about the presence of stroke and heart attack symptoms. While inquiring, it is helpful to characterize the symptoms for the patients so they can recognize them if they occur. Helping patients understand and develop a plan for how to proceed (call 911, call physician office, etc.) can potentially minimize complications if these unfortunate events occur.

The next step would be to target modifiable cardiac risk factors. Cigarette smoking cessation should be a priority. Smoking increases the Framingham point scale (regardless of amount smoked), is a risk factor for heart disease, and may also contribute to her low HDL. The patient should be asked if they are interested in quitting, and support and encouragement should be offered.

**THERAPEUTIC LIFESTYLE CHANGES**

TLCs are an important component of any dyslipidemia regimen, regardless of any pharmacologic therapy. TLC should be initiated in all patients before consideration of medication therapy and includes reduced intake of saturated fat and cholesterol, increased dietary soluble fiber, increased physical activity and weight reduction. NCEP recommends that TLCs may be used alone as long as the baseline LDL-C does not exceed 30 mg/dL over the target LDL-C. As she just misses this cut off point, TLC alone could be tried for three to six months.

What if her LDL-C was 162 mg/dL? Should pharmacologic therapy be started? What about 190 mg/dL? If the patient appears motivated, and has room for change in diet and exercise, TLC alone may be enough to get the patient to goal. TLC has been shown to reduce LDL-C up to 20 percent in some situations. Plus, since the patient is reluctant to initiate a statin, the drugs of choice for LDL reduction, TLC alone is worth a try. It is important to clarify that the pharmacist should strongly encourage statins along with TLCs for patients with diabetes or CHD for initial treatment, based on compelling evidence.

LT should next be educated to limit dietary cholesterol and saturated fat in her diet, and increase fiber. Table 5 highlights basic dietary recommendations. A thorough diet history is helpful to ascertain the patient’s baseline eating habits. Pharmacists should at minimum screen for high fat foods. Lowering overall fat intake is the first step of TLC. Saturated and trans fat intake should be low. Replacement of saturated fat with unsaturated fat may help to improve TGs if elevated. Simple substitution of high fat dairy/animal meat items to lower fat dairy items (superskim milk has a thickener added to improve the palatability of skim milk; choose leaner meat cuts with less marbling) should be considered. Food preparation is another source for potential substitution. Encourage patients to switch to olive oil from butter/margarine products for a heart-healthy alternative. A six-week trial is encouraged before assessing another fasting lipid panel; up to 12 weeks could be considered.

If the patient is not at goal after six weeks, other interventions such as increased viscous fiber intake could be implemented. Increased fiber, particularly from cereals, is associated with reduced risk for heart disease. A thorough

---

**Table 4. Cardiovascular Risk Factors**

<table>
<thead>
<tr>
<th>Age: Females &gt; 55 years, males &gt; 45 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Family history of premature CHD: Female first degree relative less than 65 years Male first degree relative less than 55 years</td>
</tr>
<tr>
<td>• Hypertension</td>
</tr>
<tr>
<td>SBP &gt; 140 mmHg</td>
</tr>
<tr>
<td>DBP &gt; 90 mmHg</td>
</tr>
<tr>
<td>• HDL &lt; 40 mg/dL (note: greater than 60 mg/dL negates one risk factor)</td>
</tr>
<tr>
<td>• Cigarette smoking in past month</td>
</tr>
</tbody>
</table>

**Table 5. TLC Recommendations**

<table>
<thead>
<tr>
<th>Component</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saturated Fat</td>
<td>Less than 7% total calories</td>
</tr>
<tr>
<td>Total Fat</td>
<td>Less than 25–35% total calories</td>
</tr>
<tr>
<td>Fiber</td>
<td>20–30 grams daily</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>Less than 200 mg daily</td>
</tr>
</tbody>
</table>
dietary history is helpful. The pharmacist can evaluate how the patient is consuming carbohydrates. Carbohydrates should be eaten primarily as whole grains (high fiber variety preferred), and fruits and vegetables. Beyond basic educational tips from the pharmacist, patients would benefit from medical nutrition therapy provided by a licensed nutrition professional. Pharmacists can assist patients when referral is needed.

Phytosterol-containing products may be considered as monotherapy or as a supplement to enhance statin therapy. They block absorption of cholesterol in the gut and have minimal adverse effects. Meaningful outcomes beyond LDL-C lowering, such as reduced death and heart disease, are minimal. LDL-C reductions average 15–18 percent. NCEP recommends two grams daily.

Regular physical activity increases HDL and can lower LDL. The pharmacist should consider the patient’s baseline and ensure that the patient gets medical clearance if needed. If preexisting back/joint problems exist, the pharmacist can suggest the patient talk with a provider about seeing a physical therapist to improve strength and balance.

LT returns after six weeks and shares her labwork. Her TC is now 210, LDL is 142, TG is 145, and HDL is 40. She is still smoking half a pack per day and isn’t interested in quitting because she needs to focus on one thing at a time. She notices her heartburn symptoms are more frequent. She did switch her coffee creamer to nonfat and switched out butter for olive oil. Her new diet history reveals that she skips breakfast, usually eats a sandwich on white bread with bologna, cheese and mayo for lunch, and usually eats chicken every night with a potato. She snacks mainly on small bite sized chocolates because she heard chocolate is good for cholesterol. She joined a gym but hasn’t had a chance to go as she is helping her sister now that she is home. She is wondering if she should start drinking red wine. What diet recommendations will you make at this time?

LT’s efforts so far should be acknowledged and encouragement should be offered. Her TG’s are at goal on diet alone. The pharmacist can advise the patient to jump start her day with high fiber cereal, which can improve her chances to getting to goal. Lower fat or no fat milk should be used. The pharmacist should determine what lower starch fruits or vegetables the patients enjoys and suggest that she incorporate them as snacks throughout the day. If she needs something on the go, an apple, some red grapes, or baby carrots might be good options. Deeply colored produce is preferred. A handful of heart healthy nuts are also a good snack. Walnut, almond, pecans and pistachio-enhanced diets are associated with improved lipid profiles and reduced risk of fatal and nonfatal CHD and sudden cardiac death. One ounce is the typical serving size used in trials. Switching mustard for mayonnaise, using high fiber bread instead of white bread, and replacing bologna with a leaner lunchmeat such as turkey are heart healthy options for LT.

What would you advise LT on chocolate and red wine? The data on chocolate and red wine for cholesterol is promising. Dark chocolate has been shown to reduce the risk of all cause and CHD-related death, and may lower blood pressure. Serving sizes varied from six grams up to 100 grams a day of chocolate. Caloric and fat content should be considered for all patients. Advise against higher doses; 100 grams of chocolate a day can increase daily calories by 500 kcal. Recommend a small dark chocolate square if the patient is interested (six grams is approximately 1/16 of a candy bar). The pharmacist should discourage the patient from continuing chocolate in this case, as it may be exacerbating her heartburn symptoms.

The link to red wine and reduced CHD risk was observed 30 years ago. It is theorized that red wine delays atherosclerosis because of polyphenols from the skin and seeds of grapes. Polyphenols in red wine inhibit oxidation of LDL particles. Red wine may also boost HDL slightly. When compared to low-polyphenol alcoholic beverages such as white wine and beer, red wine appears to be better for lowering mortality and CHD risk.

There are many confounding factors in these trials, such as lifestyle differences. Furthermore, drinking alcoholic beverages should be balanced with the risks of increased TGs, increased calories, increased blood pressure, heart failure, and liver injury, amongst other problems. The American Heart Association (AHA) suggests that men and women limit alcohol intake to two and one drink daily, respectively. One drink is considered a 12 ounce bottle of beer, four ounces of wine,
and 1.5 ounces of 80 proof spirits. The AHA does not endorse patients to start drinking red wine simply for the perceived cardiovascular benefits at this time. If a patient already consumes alcohol, a switch to red wine makes sense. Keep in mind that the polyphenols are thought to be the active ingredient in red wine, not the alcohol. Snacking on red grapes or consuming grape juice should offer similar benefit if the red wine hypothesis is true. Exercise would be a much more beneficial method of reducing HDL, or in LT’s case, quitting smoking.

The AHA recommends consumption of up to 12 ounces of fatty fish with low mercury content (canned light tuna, salmon, catfish, pollock) twice a week for heart health in patients with and without CHD. Stress low fat preparation (baking, steaming). This recommendation is somewhat controversial, as a Cochrane review of 48 randomized trials did not find a benefit of dietary or supplemental omega 3 fatty acids (the active ingredient in fatty fish) on sudden death, CHD events or cancer. Other reviews did observe a reduction in cardiac death, stroke and CHD with supplemental fish oil. The evidence is stronger for patients using omega-3 fatty acids for secondary prevention. The best studied statins include atorvastatin, pravastatin, and simvastatin. Indirect comparative efficacy evaluations between these agents do not seem to favor one statin over another. Rosuvastatin, the most potent of the statins for lipid-lowering, is accumulating more patient-oriented evidence. Statins are thought to have benefits beyond LDL-C lowering, called pleiotrophic effects. These effects, which include reduced lipoprotein oxidation and reduced clot formation may be partly responsible for statin’s benefits in lowering CHD risk. Statins should be recommended in all patients with CHD (secondary prevention), unless a contraindication exists. Landmark statin trials such as the 4S trial and the Heart Protection Study Patients showed patients with CHD are less likely to die and have a heart attack while on a statin.

Statins reduce heart disease and cardiovascular-related events in patients with diabetes and should be recommended whether they have heart disease or not. One analysis suggests that lowering cholesterol in men and women with diabetes adds 3–3.4 years and 1.6–2.4 years respectively to their life. Nonetheless, it has been debated whether universal statin use is warranted for every single patient with diabetes. It is important to clarify patients not studied in these trials: patients under 40 and over 75 years old, patients with chronic renal insufficiency or organ transplantation, and patients with high baseline triglyceride values on fibrates. In patients with diabetes, statins may be best reserved for those over 40 with additional cardiac risk factors who cannot achieve LDL goals under 100 on their own.

The other important point to consider is that statins are pregnancy category X. It may be prudent to avoid statins in childbearing women until menopause. In the rare event that a statin must be used in a younger woman, be sure to explicitly state that birth control must be used during statin therapy. Verify patient understanding at the end of the counseling session to be sure.

Statins have evidence for primary prevention (ie, patients that do not have heart disease, or a heart disease

STATIN EFFICACY
Statins are the best choice for LDL-C lowering. They block the enzyme, 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase that is needed for cholesterol synthesis. Statins reduce LDL-C by approximately 25–62 percent. Doubling the dose typically confers an additional 6 percent reduction, known as the rule of 6. Individual patient factors can affect response. The maximum dose of most statins is 80 mg; rosuvastatin’s maximum dose is 40 mg.

The best studied statins include atorvastatin, pravastatin, and simvastatin. Indirect comparative efficacy evaluations between these agents do not seem to favor one statin over another. Rosuvastatin, the most potent of the statins for lipid-lowering, is accumulating more patient-oriented evidence. Statins are thought to have benefits beyond LDL-C lowering, called pleiotrophic effects. These effects, which include reduced lipoprotein oxidation and reduced clot formation may be partly responsible for statin’s benefits in lowering CHD risk. Statins should be recommended in all patients with CHD (secondary prevention), unless a contraindication exists. Landmark statin trials such as the 4S trial and the Heart Protection Study Patients showed patients with CHD are less likely to die and have a heart attack while on a statin.

Statins reduce heart disease and cardiovascular-related events in patients with diabetes and should be recommended whether they have heart disease or not. One analysis suggests that lowering cholesterol in men and women with diabetes adds 3–3.4 years and 1.6–2.4 years respectively to their life. Nonetheless, it has been debated whether universal statin use is warranted for every single patient with diabetes. It is important to clarify patients not studied in these trials: patients under 40 and over 75 years old, patients with chronic renal insufficiency or organ transplantation, and patients with high baseline triglyceride values on fibrates. In patients with diabetes, statins may be best reserved for those over 40 with additional cardiac risk factors who cannot achieve LDL goals under 100 on their own.

The other important point to consider is that statins are pregnancy category X. It may be prudent to avoid statins in childbearing women until menopause. In the rare event that a statin must be used in a younger woman, be sure to explicitly state that birth control must be used during statin therapy. Verify patient understanding at the end of the counseling session to be sure.

Statins have evidence for primary prevention (ie, patients that do not have heart disease, or a heart disease
equivalent). Statins reduce the risk of heart attack and stroke, but men may be more likely to benefit than women. The benefit of statins appears to be associated with a patient’s baseline risk than lipid panel values. Rosuvastatin is associated with a lower death rate overall and a lowered risk of heart attack and stroke in patients with elevated high sensitivity C reactive protein and normal cholesterol values. Pravastatin used in the elderly (up to age 82) reduces the risk of death from heart disease.

**PATIENT CASE 2**

LT’s sister KK comes to your pharmacy and is thinking about stopping her simvastatin that she was started on when she had her heart attack a month ago. She is 51 years old, with a past medical history significant for CABG x 4, hypertension, hyperthyroidism, and osteoarthritis and sciatica. She knows she needs to lose weight and is seeing a nutritionist. She is on lisinopril 20 mg daily, metoprolol tartrate 25 mg twice a day, aspirin enteric coated 81 mg daily, levothyroxine 25 micrograms daily, fish oil 1,000 mg daily, and naprosyn 500 mg once a day as needed. She has a prescription for nitroglycerin sublingual but has never had to use it yet. She would like to stop her simvastatin 40 mg because she feels achy and tired lately, but also wonders if it could be the weather change. What do you advise?

**MEDICATION ADHERENCE AND PERSISTENCE**

Consistent positive clinical outcomes are associated with statin adherence levels of 80 percent or more. Persistence is key, as the cardiovascular benefits of statins do not appear to linger if a patient decides to discontinue treatment. One year persistence with statins is approximately 60 percent in patients with a compelling indication such as CHD; primary prevention rates are lower.

Pharmacists have a pivotal role in patient adherence and persistence. Adherence rates usually decline with initial therapy, but pharmacists can encourage and motivate patients and evaluate potential barriers that may exist. It has been shown that education on disease and medication, good communication between a patient and provider, as well as follow up lipid panels enhance adherence in patients taking statins. One community pharmacy-based program demonstrated a 34 percent reduction in discontinuation rates within the first six months of statin therapy by implementing five individual counseling sessions with predetermined educational material on adherence and lipid levels.

KK should be educated on the benefits of statins beyond lipid-lowering, such as improved lifespan and reduce heart attack risk. She should be cautioned against abruptly stopping the statin without consulting her provider. Patients recently discharged from the hospital for an acute myocardial infarction (MI) of acute ischemic stroke that stopped a statin were at increased risk of mortality (MI) and poorer outcomes (stroke). Discourage her from stopping it right away, especially without speaking to her provider.

**ADVERSE EVENTS**

Like most medications, adverse events can occur with statin use. Pharmacists should educate patients on what to expect and can develop action plans to prevent or manage them. Minor symptoms include stomach upset, headache, insomnia, and fatigue. The pharmacist can recommend taking the statin with food if gastrointestinal comfort occurs. Alteration of administration time may alleviate complaints of tiredness or sleeplessness.

The pharmacist should be aware of the prevention and clinical presentation of more serious adverse events related to statins. Patients should be advised to report new rash or skin changes to their provider when starting a statin. Adverse events such as liver enzyme elevations (AST, ALT) are typically detected objectively with routine lab monitoring. Statins should not be used in patients with acute liver disease. Symptomatic liver failure is extremely rare, but liver enzyme elevations may occur in up to 10 percent of patients within the first year. Fortunately, only about 1 percent experience serious elevations, defined as three times the upper limit of normal. It is associated with all statins and is dose-related. It is theorized that reduced cholesterol amounts within liver cells contributes to enzyme elevation. Liver failure resulting in a liver transplant is rare and may be related to an autoimmune response.

Ironically, statins have been shown to reverse liver enzyme elevation in patients with preexisting nonalcoholic fatty liver disease, a
common concomitant disease in patients with dyslipidemia. Statins may lower hepatic fat and/or reduce hepatic swelling. Statins have been safely used in patients with chronic hepatitis C.

Although liver function monitoring does not correlate with improved safety, manufacturer prescribing recommends it. Liver function monitoring is advised at baseline, and 6–12 weeks after starting treatment or increasing dose. Statins should not be started in patients with unexplained elevations in AST/ALT that are three times the normal upper limit. If liver tests are normal after the first three months, once or twice a year testing is appropriate. If liver enzymes exceed three times the upper limit of normal, the test should be repeated. Seventy percent of hepatic elevations resolve on their own even if the same dose and statin are continued. If the elevation persists, be sure to rule out other causes. If alternative etiology is not determined, discontinue or reduce statin dose and repeat in four to six weeks. Although liver enzyme elevations are almost always clinically silent, refer patients to contact their provider if extreme nausea, vomiting or jaundice occurs.

Myopathy, myalgia, and rhabdomyolysis are more serious effects associated with statin use. While myopathy is a general term to define muscle pain, myalgia is muscle pain or weakness. Myositis is myalgia associated with an elevated creatinine kinase 10 times the upper limit of normal. It is estimated that one out of every 10 patients on a statin will experience muscle pain. Myalgia occurs in less than 0.5 percent of patients on available statins. Rhabdomyolysis, myalgia accompanied by an increased serum creatinine and possibly complaints of brown urine, is extremely rare. Risk factors for statin-induced myopathy are highlighted in Table 6.

**PATIENT CASE CONTINUED**

KK’s complaints could correlate to muscle side effects, though she has confounders such as arthritis, sciatica, arthritis, and a recent hospital stay that should be worked up. KK should be referred to her doctor for evaluation and blood work. KK is at increased risk for myalgia from statins based on her recent surgery, hypothyroidism, and relatively high statin dose, though no interactions are present (Table 6).

Lab evaluation that would be helpful for KK would be a complete blood count (anemia post surgery), AST, ALT (hepatotoxicity), CK and SCr (myalgia/rhabdomyolysis), TSH (hypothyroidism is a risk for myalgia) and vitamin D (a common cause of fatigue and myalgias). Her doctor should also perform a physical exam to evaluate if she has worsening arthritis or if her fatigue is cardiac in origin.

KK calls to let you know that all her blood work was normal, except for Vitamin D, and she is now on replacement therapy for two weeks. She still feels that her muscles are aching more, but she did decide to continue simvastatin 40 mg. She is not on any new medications. What do you recommend?

**STATIN-INDUCED MYOPATHY**

The pharmacist can consider calling KK’s doctor to suggest alternative therapy. One study showed that fluvastatin and pravastatin may have a lower risk of myopathy than atorvastatin or simvastatin, though doses used were not equipotent. Theoretically, fluvastatin and pravastatin may have less muscle events secondary to a lower risk of drug interactions with cytochrome 3A4 inhibitors. They are also hydrophilic, so penetration into muscle is expected to be reduced. Fluvastatin has less cardiac outcomes data, though. Rosuvastatin is another option in patients intolerant to simvastatin and atorvastatin based on its hydrophilic properties. The pharmacist can consider a switch to pravastatin or rosuvastatin, based on the level of LDL reduction needed, and insurance coverage. Simvastatin may also be reduced back to 10–20 mg if possible.

Some advisory groups such as the National Lipid Association recommend obtaining a baseline CK level prior to treatment. Repeat CK levels are only warranted

<table>
<thead>
<tr>
<th><strong>Table 6. Risk Factors for Statin-Induced Myopathy</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• High statin dose</td>
</tr>
<tr>
<td>• Small frame/frail</td>
</tr>
<tr>
<td>• Extensive past medical history (diabetes, renal, liver disease)</td>
</tr>
<tr>
<td>• Elderly</td>
</tr>
<tr>
<td>• Perioperative periods</td>
</tr>
<tr>
<td>• Hypothyroidism (untreated)</td>
</tr>
<tr>
<td>• Medications</td>
</tr>
<tr>
<td>Fibrates (gemfibrozil especially)</td>
</tr>
<tr>
<td>Nicotinic acid</td>
</tr>
<tr>
<td>Cytochrome p450 3A4 inhibitors used with statins that are cytochrome p450 3A4 substrates (simvastatin, lovastatin, atorvastatin)</td>
</tr>
</tbody>
</table>

www.americaspharmacist.net
if muscle symptoms develop. KK stated her value was normal, but her pain persists. CK values can be elevated in the absence of statin associated myopathy if the patient increased exercise or received an intramuscular injection. Luckily, her value was normal. If it was elevated, it is advised that as long as the CK level is under 10 times upper limit of normal, and no serum creatinine changes are present, that the statin may be continued. Statin rechallenge in a patient with rhabdomyolysis is not worth the risk.

KK’s doctor informs you that her LDL was 130 mg/dL before starting simvastatin 40 mg. He did not find an alternative cause for her symptoms and would like you to recommend a plan. He heard something about coenzyme q 10 but isn’t sure if it works.

If the patient is willing, a simple dose reduction to 10–20 mg simvastatin could alleviate the symptoms. Symptoms should generally resolve after a week or so, but can take up to two months for full resolution. If symptoms were severe, patients may be reluctant to restarting therapy with the same agent. Consider more hydrophilic statins such as pravastatin and rosuvastatin if the patient’s symptoms persist. These agents theoretically would penetrate the muscle less. Also inquire if the patient has close blood-related family members on a statin. Tolerability to a particular statin may be genetic.

If none of these strategies work, other alternatives to consider are intermittent statin dosing (one, twice, three times a week), pulse dosing (take for three weeks off for one week), or using a lower dose statin supplemented with a non-statin such as fenofibrate or phytosterol. Unfortunately, trial data evaluating alternative dosing regimens effects on meaningful patient outcomes is limited.

Coenzyme Q 10 (coQ10) has been used on the basis that statins deplete natural CoQ10 stores, resulting in muscle pain. There is conflicting evidence on its benefits and overall limited proof that it works. Doses of 100–200 mg divided two to three times daily appear to minimize side effects, which are rare. Dose reduction or statin switch should be tried first, but if the patient wants to try it, no contraindications exist.

KK returns to the pharmacy and is pleased to report that they settled on simvastatin 10 mg daily. Her LDL is 107 mg/dL, but she is doing well diet-wise and just started walking every day. She is taking all her medications without problems. She is encouraged that she can get the LDL to goal within the next two months on the lower dose of simvastatin, and a bit more aggressive TLC now that the weather is warmer.

PATIENT CASE 3

PL is a 67-year-old male reviewing the OTC section for something he can take for his triglycerides. He just came from his doctor’s office and was told that his level was 600. He is looking for something he can take as a daily vitamin instead of filling the prescription he has for gemfibrozil 600 mg twice a day. He is already taking something for his cholesterol and doesn’t understand why he needs both. He is frustrated with all his medications and is hoping to try something more natural.

The pharmacist probes the patient and determines that he has no family history of heart disease but he drinks a six pack of light beer most days of the week, had gout for 10 years, and is supposed to be getting his gall bladder removed but is putting it off until he gets more vacation from work. He is on simvastatin 20 mg daily, allopurinol 100 mg daily, and Losartan 50 mg daily. He is holding bottles of fish oil, no-flush niacin, and garlic in his hand and intends to buy all the products but wants to know what you think. What should the pharmacist advise?

The pharmacist should empathize with the patient and determine what barriers exist to treatment. It sounds like the patient could use some education on the parts of the lipid panel and how the statin differs from gemfibrozil (LDL lowering versus TG lowering). Nonpharmacologic counseling can be offered. The patient should be advised to cut back on drinking beer, which is a large contributor to elevated TGs. The patient should also be counseled on TLCs discussed previously, with an emphasis on reduction in fat and carbohydrate content. Table 1 should be referred to for evaluation of secondary causes.

OTHER LIPID REGULATING AGENTS

The best agents for lowering triglyceride levels are fibrates, niacin, and omega-3 fatty acids. Table 7 highlights lipid parameter reductions associated with each. Bile acid sequestrants should be avoided in patients with elevated
TGs; as they can worsen hypertriglyceridemia. Fibrates reduce the frequency of CHD in patients without heart disease, but less so than statin treatment. Men with CHD, high TG, low HDL and low LDL experience less heart disease-related death, heart attack, and stroke on gemfibrozil. Gastrointestinal upset may occur with fibrates, and liver function test elevations and muscle pain may occur rarely often in association with combined statin use or renal disease.

Was gemfibrozil a good choice for this patient? Fenofibrate would be better, as it is less likely to produce muscle side effects in combination with a statin, compared to gemfibrozil. Plus, the dose of simvastatin in combination with gemfibrozil should not exceed 10 mg. The physician would need to be called for clarification. The other interesting point about this case is that the patient is commenting that he needs his gall bladder out. As fibrates increase cholesterol in the bile and can cause cholelithiasis and cholecystitis, they are all contraindicated in gall bladder disease.

What about niacin for this patient? Niacin is the best product available to increase HDL, though we do not know his current value. Its TG-lowering intensity is about the same or a somewhat less than fibrates. Niacin has also shown benefits beyond lipid lowering, as it reduces total mortality and CHD events. OTC niacin should not be recommended unless a patient does not have insurance coverage for extended release niacin. Immediate release niacin, the better choice of OTC products, is associated with flushing effects. The sustained release niacin, also known as “no flush” niacin, is associated with hepatotoxicity and should not be recommended. Extended release prescription niacin is preferred for safety and tolerability, but may be limited based on patient insurance coverage. Niacin may increase blood glucose levels, though it can be used safely in patients with diabetes with additional monitoring and potential medication adjustment. Niacin should be avoided in this patient, however, due to his gout history and excessive alcohol use. Alcohol enhances the flushing effects associated with niacin and should be avoided. Patients taking niacin should also be counseled to take aspirin 30 minutes before the dose, limit hot and spicy foods, and take with a snack.

The last alternative for this patient would be omega 3 fatty acids. Omega 3’s, typically dispensed as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), may reduce triglycerides when used in higher doses. There is one FDA approved omega 3 product available. Caution should be used when selecting OTC fish oil preparation. USP-verified products are a better choice. The American Heart association notes that doses up to 4 grams EPA/DHA daily have shown effectiveness for reduction of TG. This option will not interact with his current medications and does not contribute to increased hepatotoxicity. The patient should be consulted and the physician contacted to determine the most appropriate omega 3 fatty acid choice. Newer OTC products are more concentrated and less capsules need to be consumed to achieve the desired intake than was previously available. The total daily dose should be split into 2–3 daily doses and taken with food to minimize gastrointestinal upset. Enteric coated versions or freezing capsules may minimize fishy taste. Supplementation has been associated with LDL elevations, rarely up to 75 percent. These elevations may be associated with less dense LDL particles, which are deemed less atherogenic. The effect is more often seen in patients with very high baseline TGs, but may dissipate over time as TG correct. Omega 3 supplements in higher doses may increase the risk for bleeding, especially in patients on warfarin. Caution should be used.

Finally, the patient should be discouraged from purchasing garlic. It is a cytochrome 3A4 inducer so the effectiveness of simvastatin will be reduced. Recent trials have not shown lipid lowering benefit with the use of garlic.

| Table 7. Lipid Parameter Alterations With Non-Statin Lipid-lowering Agents |
|-----------------------------|-------------------|-------------------|
| **Agent**                   | **LDL Reduction** | **TG Reduction**  | **HDL Increase** |
| Fibrates                    | May increase Gemfibrozil-none | 20–50%          | 6–11%            |
| Niacin                      | 12–17%            | 28–35%           | 22–26%           |
| Omega 3 fatty acids         | None or up to 75% increase | 44.9%          | 9.1%             |
| Bile acid sequestrants      | 9–28%             | Up to 28% increase | 0–8%           |
| Ezetimibe                   | 18%               | 8%               | 1%               |
OTHER AGENTS
Bile acid sequestrants such as cholestyramine, colestipol and colesevelam reduce the risk of CHD in patients without heart disease. LDL cholesterol reductions of 15–30 percent are anticipated with use. Adverse effects are gastrointestinal; constipation, bloating, and flatulence are most common and contribute to a high rate of noncompliance. Fluid intake may help counteract some of these effects. Colesevelam is better tolerated but pricey. BAS bind up other medications and must be separated. Advise patients to take a BAS one hour before or four hours after taking another medication.

Ezetimibe is associated with LDL reductions up to 18 percent. Like statins, it should be avoided in patients with active liver disease. Ezetimibe is considered a second line treatment due to limited meaningful efficacy data, but may be used to lower LDL-C in patients intolerant of statins or who are limited by statin dose and require further reduction. Additional outcome data is anticipated in 2012.

CONCLUSION
Numerous therapeutic options exist for patients with dyslipidemia. Well designed trials justify the use of many of these interventions to reduce CHD, CHD recurrence, and death. The ongoing relationships pharmacists cultivate in the pharmacy create an ideal environment to reduce cardiovascular risk in patients with dyslipidemia over time. Pharmacists, along with other providers, can educate and motivate patients to establish good TLC. Pharmacists can help providers navigate the numerous OTC and prescription products available to patients with dyslipidemia. Pharmacists can assist patients with prevention, identification, and management of adverse events associated with lipid regulating agents to promote adherence and persistence with lipid regulating treatments.

Jennifer Malinowski, PharmD, is an associate professor of pharmacy practice at Wilkes University, Wilkes Barre, Pa. She is also a clinical pharmacist in lipid management at Geisinger Lake Scranton Clinic in Scranton, Pa.

CONTINUING EDUCATION QUIZ
Select the correct answer.

1. NCEP recommends screening cholesterol:
   a. Annually in patients over 65 years old
   b. Three years in patients over 40 years
   c. Five years in patients over 20 years
   d. Ten years in patients over 50 years

2. The most common type of lipid disorder is:
   a. Polygenic hypercholesterolemia
   b. Familial hypercholesterolemia
   c. Familial hypertriglyceridemia
   d. Apolipoproteinemia

3. An LDL-C goal of < 100 mg/dL is warranted in patients with:
   a. Liver disease
   b. Framingham risk score < 5%
   c. Diabetes
   d. Migraines

4. The main components of TLC include all of the following except:
   a. Decreased saturated fat
   b. Increased fiber intake
   c. Increased trans fat intake
   d. Increased physical activity

5. All of the following were associated with a reduced incidence of CHD-related death in trials except:
   a. Red wine
   b. Nuts
   c. Dark chocolate
   d. Garlic

6. Statins are the first-line pharmacologic choice for LDL-C lowering in most patients:
   a. True
   b. False
7. The initial lipid parameter target in most cases should be:
   a. LDL-C
   b. HDL
   c. Triglycerides
   d. Non-HDL

8. Appropriate management strategies for statin-induced myalgias include:
   a. Reduce the dose
   b. Switch to a hydrophilic statin
   c. Reduce the frequency
   d. All of the above

9. The most appropriate baseline monitoring plan to prevent adverse events before initiating a statin includes:
   a. Potassium, chloride, BUN, albumin
   b. AST, ALT, TSH, CK, SCr
   c. Phosphate, BUN, SCr, indirect bilirubin
   d. Glucose, magnesium, iron, AST, ALT

10. Hydrophilic statins are:
    a. Lovastatin and atorvastatin
    b. Simvastatin and atorvastatin
    c. Pravastatin and fluvastatin
    d. Fluvastatin and atorvastatin

11. Cytochrome p450 3A4 substrates that should be used with caution in patients on CYP 3A4 inhibitors are:
    a. Simvastatin
    b. Atorvastatin
    c. Lovastatin
    d. All of the above

12. All of the following are true about niacin except:
    a. Immediate release formulations OTC are associated with a high degree of flushing.
    b. It is the best LDL reducer amongst all lipid regulators.
    c. Sustained release formulations should not be recommended.
    d. Aspirin 30 minutes prior to dose minimizes flushing.

13. Appropriate counseling for a patient taking fish oil supplements should include:
    a. Take with food to minimize upset.
    b. Avoid hot or spicy foods with administration.
    c. Separate from other medications by at least four hours.
    d. Liver testing should be done every three months.

14. A patient has recently filled a prescription for pravastatin 10 mg and returns to your pharmacy two weeks later seeking additional education. He is considering stopping the medication because he doesn’t think it works and had heard there are bad side effects with it. What advice makes sense at this time?
    a. Pravastatin has no benefits beyond cholesterol-lowering and should be stopped.
    b. One in 10 statin users develop severe hepatotoxicity. The patient should be educated about this and allowed to decide to continue.
    c. The patient should be educated on the benefits of statins and reassured that he is on a statin that is at a lower dose and may be associated with less side effects.
    d. He should continue it for another two days and call his doctor to get his lipid panel checked.

15. Foods considered heart healthy include all of the following EXCEPT:
    a. Nuts such as walnuts, pistachios, almonds
    b. Fish such as salmon, tuna
    c. Dark chocolate
    d. Higher fat dairy items

16. An incorrect lipid goal for a female patient with a history of TIA is:
    a. LDL < 100 mg/dL
    b. HDL > 40 mg/dL
    c. TC < 200 mg/dL
    d. TG < 150 mg/dL

17. Statins may be used safely in patients with chronic nonalcoholic fatty liver disease.
    a. True
    b. False
18. A therapeutic option in patients intolerant to statins or who need additional LDL lowering while on a statin is:
   a. Ezetimibe
   b. Omega 3 fatty acids
   c. Niacin
   d. Coenzyme Q 10

19. Gemfibrozil is the preferred fibrate in combination with statins.
   a. True
   b. False

20. Medications associated with drug-induced alterations of lipids include:
   a. Hydrochlorothiazide
   b. Estrogen
   c. Beta blockers
   d. All of the above