Case Studies in the Management of Dyslipidemia
by Shana Lettieri, PharmD, and Tricia M. Russell, PharmD, BCPS, CDE

Upon successful completion of this continuing education activity, the pharmacist should be able to:
1. Determine a patient’s risk for coronary heart disease and treatment goals.
2. Recommend appropriate pharmacotherapy for managing a patient with dyslipidemia.
3. Identify how to treat dyslipidemia in patients taking concurrent interacting medications.
4. Discuss the treatment of dyslipidemia in patients with a history of myalgia or liver dysfunction.
5. Evaluate the treatment options for the treatment of elevated non-high-density lipoprotein cholesterol.

Upon successful completion of this continuing education activity, the pharmacy technician should be able to:
1. Determine which patients would be good candidates for screening heart disease based on observable risk factors.
2. List medications that interact with cholesterol-lowering medications.
3. Determine if a patient may be experiencing an adverse reaction from cholesterol-lowering therapy and should be evaluated by the pharmacist.

INTRODUCTION
Coronary heart disease (CHD) is the narrowing of the coronary arteries and accounts for 16 percent of deaths in the United States each year. According to 2007 mortality data, four patients will experience a coronary event every minute and one of these patients will die. Men and women over 40 have a 49 percent and 32 percent lifetime risk of developing CHD, respectively. A major modifiable risk factor for CHD is dyslipidemia, which affects half of American adults. An array of randomized trials have shown that proper treatment of dyslipidemia can reduce morbidity and mortality associated with coronary artery disease and stroke. A direct relationship has been identified between CHD events and low-density lipoprotein (LDL) cholesterol and total cholesterol (TC). There is also an indirect relationship with high-density lipoprotein (HDL) and CHD risk. According to the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III report, for every 1 mg/dL increment-decrease in LDL, a patient’s relative risk for CHD is decreased by 1 percent. Awareness, treatment, and control of dyslipidemia has increased over the years. However, half of all adults over 20 years of age at borderline high-risk remain unaware of their condition. Despite these alarming statistics, fewer than 50 percent of Americans, including those with a history of CHD, are receiving lipid-lowering medications. Of those receiving lipid-lowering therapy, less than one-third meet the NCEP ATP III parameters for cholesterol control.

RISK ASSESSMENT
Patient Case #1: JB is a 55-year-old white man with a past medical history (PMH) significant for type 2 diabetes mellitus (DM) and dyslipidemia. His current medications include glipizide 10 mg bid and metformin 500 mg bid. His most current lipid panel results were: TC 226 mg/dL, LDL 132 mg/dL, HDL 32 mg/dL and triglycerides (TG) 310 mg/dL. JB’s renal and hepatic functions are within normal limits. JB smokes one pack per day for 26 years and drinks one glass of wine every night. His mother died of breast cancer.
at 69 years of age and his father is living and has a history of myocardial infarction (MI) when he was 49 years old. Today’s vital signs: blood pressure 128/76 mmHg, pulse 72 beats/min. Assess this patient’s risk for heart disease.

The first step when evaluating a patient’s lipid profile is to determine the patient’s lipid goals. The LDL goal is typically the main target when determining your therapeutic plan, unless the patient’s TG exceeds 500 mg/dL. The LDL goal varies from patient to patient. When determining a patient’s LDL goal, first assess if the patient has CHD, a CHD risk equivalent, or risk factors. Use Table 1 and Table 2 to determine a patient’s CHD risk. CHD is defined as a history of myocardial infarction, stable angina, unstable angina, or coronary artery procedure (angioplasty or bypass surgery). Patients with CHD or a CHD risk equivalent (defined in Table 1) are considered high risk and have an LDL goal < 100 mg/dL, with an optional goal of < 70 mg/dL in certain populations. Consider a LDL goal of < 70 mg/dL in patients at very high risk. This would include patients with CHD and multiple risk factors (especially diabetes mellitus), very uncontrolled risk factors (cigarette smoking), or multiple risk factors for metabolic syndrome (elevated triglycerides or non-HDL, or low HDL). For patients without CHD or a CHD risk equivalent, award each risk factor in Table 2 one point and total the CHD risk factors. Patients with zero to one risk factor are considered to be at low risk for CHD in the next 10 years. Calculation of the Framingham risk score in low risk patients is not necessary as it can be assumed their 10-year CHD risk would be < 10 percent. It is also not necessary to perform Framingham in high risk patients, since usually these patients have a 10-year risk of > 20 percent. However, for patients with moderate risk (≥ 2 risk factors) and without CHD or a CHD risk equivalent, a 10-year Framingham risk score should be calculated. The Framingham score predicts the likelihood that a patient will have a heart attack in the next 10 years. Several Web sites, including www.nhlbi.nih.gov/guidelines/cholesterol/index.htm, can aid the pharmacist in the calculation of the Framingham 10-year risk score.

Therapeutic lifestyle changes include smoking cessation, physical activity, dietary changes (low saturated fat, low cholesterol, high fiber and plant stanols/sterols diet), exercise, and weight loss if needed.

When a patient’s TGs are > 500 mg/dL, the patient’s risk of developing pancreatitis increases, thus TG lowering should be the primary target of therapy. The TC goal is < 200 mg/dL. The HDL goal is > 40 mg/dL in patients without DM and in male patients with DM. The HDL goal is > 50 mg/dL in female patients with DM. The TG goal for all patients is < 150 mg/dL.

Referring back to the preceding case, since JB has a history of DM his LDL goal is < 100 mg/dL. The option of a LDL goal < 70 mg/dL should be considered in this patient since he also has an uncontrolled risk factor of current smoking. Once the patient’s LDL goal is determined, the next step is to develop the therapeutic plan. Recommend therapeutic lifestyle changes (TLC) for all patients with abnormali-
ties in their lipid profile. In addition, any patient at moderate-high to high risk of cHD should initiate TLC regardless of their baseline LDL.

The starting point for drug therapy to treat a patient’s LDL is determined by the patient’s baseline LDL, as shown in Table 3. Initially, in patients with low or moderate risk who have baseline LDL < 30 mg/dL over their LDL goal, TLC is the sole treatment. Schedule an appointment to return to the pharmacy and reassess these patients after 6–12 weeks of TLC. If the LDL has not dropped below the goal, consider initiating drug therapy at that time. In moderate-high and high-risk patients, TLC and drug treatment should be initiated simultaneously.

Updated NCEP guidelines are expected this year. Since the publication of the updated NCEP report in 2004, many trials, such as the Treating to New Targets (TNT) and Justification for the use of Statins in Prevention: an intervention trial Evaluating Rosuvastatin (JuPitER) studies, have evaluated the effectiveness of intensive lipid-lowering therapy in patients with a lower baseline LDL (< 130 mg/dL). Post-hoc analysis of patients in both studies showed a relative risk reduction of CHD events in patients achieving very low LDL (LDL < 64 mg/dL in TNT and LDL < 50 mg/dL in JUPITER) without additional adverse effects. It is possible that NCEP may publish even lower cholesterol goals in the next report, increasing the number of patients who will require aggressive lipid-lowering therapy.

**DRUG THERAPY FOR LDL CHOLESTEROL**

**Statins**

Statins, or 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors, are the gold standard for treating patients with elevated LDL. Statins competitively inhibit HMG-CoA reductase, an enzyme needed to convert HMG-CoA to mevalonate. The synthesis of mevalonate is the rate-limiting step in hepatic cholesterol production. Decreasing hepatic cholesterol synthesis up-regulates hepatic LDL receptor activity, which increases clearance of LDL from the circulation. There are also several pleiotropic effects of statins, reducing CHD risk beyond decreasing LDL. These include reducing inflammation, improving endothelial function, and stabilizing atherosclerotic plaque.

Numerous primary and secondary prevention trials in high-risk patients have shown statin use to decrease all cause mortality, coronary events, coronary death, and non-fatal and fatal strokes. Benefits have been shown in men, women, middle-aged, and elderly patients. In primary prevention studies, significant reductions in cardiovascular events have also been shown in populations with normal cholesterol levels randomized to a statin versus placebo.

Table 3: NCEP ATP III LDL and Treatment Goals Based on Patient Risk

<table>
<thead>
<tr>
<th>Patient Risk</th>
<th>NCEP ATP III LDL Goal</th>
<th>Start Drug Treatment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower Risk: Risk Factor 0–1 (10-year risk &lt;10%)</td>
<td>&lt; 160 mg/dL</td>
<td>≥ 190 mg/dL (160–189 mg/dL- drug optional)</td>
</tr>
<tr>
<td>Moderate Risk: Risk Factors ≥ 2 (10-year risk 10–20%)</td>
<td>&lt; 130 mg/dL</td>
<td>&gt; 160 mg/dL</td>
</tr>
<tr>
<td>Moderately High Risk: Risk Factors ≥ 2 (10-year risk 10–20%)</td>
<td>&lt; 130 mg/dL (optional &lt; 100 mg/dL)</td>
<td>≥ 130 mg/dL (100–129 mg/dL- drug optional)</td>
</tr>
<tr>
<td>High Risk: CHD** or CHD Risk Equivalent (10-year risk &gt;20%)</td>
<td>&lt;100 mg/dL (optional &lt; 70 mg/dL-very high risk#)</td>
<td>&gt; 100 mg/dL</td>
</tr>
</tbody>
</table>

*It is recommended that the intensity of LDL reduction when LDL-lowering drug therapy is initiated in high-risk or moderately high-risk patients be at least 30–400 percent.

**CHD is defined as a history of myocardial infarction, stable angina, unstable angina, or coronary artery procedure (angioplasty or bypass surgery).

#Consider a LDL goal of < 70 mg/dL in patients at very high risk. This would include patients with CHD and multiple risk factors (especially diabetes mellitus), very uncontrolled risk factors (cigarette smoking), or multiple risk factors for metabolic syndrome (elevated triglycerides or non-HDL, or low HDL).
Statins reduce LDL cholesterol 18–63 percent, TG 7–30 percent, and increase HDL 5–15 percent. See Table 4 for specific reductions in LDL cholesterol for each statin dose. It is important to note the maximum dose of simvastatin is 40 mg daily, except in patients already taking 80 mg daily without a history of myopathy, due to the increased potential of myopathy. Simvastatin, lovastatin, and fluvastatin work to lower LDL best when administered in the evening since peak activity of HMG-CoA reductase occurs around midnight. Rosuvastatin, pitavastatin, atorvastatin, and pravastatin can be administered any time of the day.

Patients with renal impairment should use some statins cautiously. Atorvastatin is mainly excreted through the liver. Atorvastatin concentrations are not affected by renal impairment, thus no dose adjustments are required when using atorvastatin in patients with renal impairment. In patients with severe renal impairment marked by CrCl < 30 mL/min, the maximum dose of lovastatin is 20 mg daily, pitavastatin is 2 mg daily, and rosuvastatin is 10 mg daily. Product information of other marketed statins recommends starting at low doses and using the agent cautiously in patients with severe renal impairment.

The use of statins is contraindicated in pregnancy or in women trying to become pregnant due to skeletal malformations observed in pregnant mice during trials. Women of childbearing age who are at high risk of CHD should be counseled on the use of contraception if a statin is absolutely required. Women should be counseled to discontinue the statin agent immediately if they become pregnant and contact their provider for further instruction. Statins are also contraindicated in mothers who are breastfeeding and in patients with active decompensated liver disease.

Common adverse events with statin use include headache and gastrointestinal (G.I.) problems, including constipation, diarrhea, and cramping. Rash, proteinuria, myalgias, elevated liver transaminase levels, and rhabdomyolysis have also been reported. Muscle and liver toxicity will be discussed in more detail later in this article.

There is some evidence that using a statin can increase the risk of diabetes in a patient. A meta-analysis of 13 trials showed a 9 percent increased incidence of diabetes with statin use. It appears the risk of developing diabetes is well worth the benefit of statin treatment. A 2011 meta-analysis of five statin trials showed you would have to treat 498 patients with a statin for a mean of 1.9 years to have one additional case of diabetes. However, you would only have to treat 155 patients for a mean of 1.9 years with a statin to prevent one cardiovascular event. As of February 2012, statin labeling now includes a precaution regarding the increase incidence of diabetes with statin use.

According to the American Diabetes Association, patients over 40 years of age with DM and at least one additional CHD risk factor should receive a statin regardless of their baseline LDL. If patients with DM are not able to reach their target LDL goal, an optional target is a LDL reduction of 30–40 percent from baseline. Furthermore, a 30–40 percent reduction should be the target when initiating statin therapy in patients who are close to their target LDL goal. All patients with a history of CHD

| Table 4. Statin Equivalent Doses for LDL Reduction |
|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|
| % LDL Reduction           | 27–33%                   | 34–40%                   | 41–47%                   | 48–54%                   | 55–61%                   | 61–67%                   |
| Rosuvastatin              | 5 mg                     | 10 mg                    | 20 mg                    | 40 mg                    | 80 mg                    | 100 mg                   |
| Atorvastatin              | 10 mg                    | 20 mg                    | 40 mg                    | 80 mg                    | 100 mg                   | 120 mg                   |
| Simvastatin               | 20 mg                    | 40 mg                    | 80 mg                    | 120 mg                   | 160 mg                   | 240 mg                   |
| Lovastatin                | 20 mg                    | 40 mg                    | 80 mg                    | 120 mg                   | 160 mg                   | 240 mg                   |
| Pravastatin               | 1 mg                     | 2 mg                     | 4 mg                     | 8 mg                     | 12 mg                    | 16 mg                    |
| Pitavastatin              | 40 mg                    | 80 mg                    | 120 mg                   | 160 mg                   | 240 mg                   | 320 mg                   |
| Fluvastatin               | 40 mg                    | 80 mg                    | 120 mg                   | 160 mg                   | 240 mg                   | 320 mg                   |

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should also receive a statin regardless of their baseline LDL as long as they do not have an absolute contraindication.

Based on the FDA review of Adverse Event Reporting System (AERS) database, statin use is also associated with memory loss or confusion. This can occur in patients greater than 50 years of age with an onset of one day to years after first statin exposure. Patient’s cognitive function returns to baseline after statin discontinuation.

There are many considerations when choosing which statin is the best choice for your patient, including percent reduction in LDL required to reach goal, concomitant medications, history of adverse effects to statins, and patient’s insurance formulary.

STATIN DRUG INTERACTIONS

Patient Case #2: TM is a 47-year-old African American man with a history of peripheral arterial disease (PAD), type 2 DM, atrial fibrillation and hypertension (HTN). His current medications include simvastatin 40 mg daily, aspirin 81 mg daily, warfarin 2.5 mg daily, diltiazem 240 mg daily, and metformin 500 mg bid. His lipid panel is: LDL, 82 mg/dL; TC 148 mg/dL; TG, 180 mg/dL; and HDL 30 mg dL. His atrial fibrillation is currently rate controlled with diltiazem and his BP is at goal, 126/76 mmHg. His international normalized ration (INR) has been stable for the past eight months on his current dose of warfarin. He denies adverse effects to all of his current medications including muscle pain, soreness or weakness, G.I. symptoms, or headaches from simvastatin use. His hepatic enzymes are within normal limits and his renal function is normal. TM quit smoking three years ago. He plans to start walking daily with his daughter. His weight is 195 pounds and height is six foot. He has been working on decreasing saturated fats in his diet and eating more whole-grain products. Would increasing this patient’s simvastatin to 80 mg daily be the best option for this patient?

The first step in evaluating a patient would be determining the patient’s LDL goal. TM’s LDL goal would be < 100 mg/dL; however, his provider would prefer to target the optional goal of < 70 mg/dL since TM has two CHD risk equivalents, PAD and DM. In order to reach his LDL goal, TM would require an additional 18 percent reduction in LDL. Typically, doubling the dose of a statin provides an additional 7 percent reduction in LDL. Accompanied with TM’s change in diet and increase in exercise he may be able to obtain an LDL of < 70 mg/dL with doubling his simvastatin to 80 mg daily; however, this dose is no longer an option for this patient.

In June 2011, FDA issued a safety announcement which recommended limiting the use of simvastatin 80 mg daily. Simvastatin manufacturers responded accordingly and notified health care professionals of the changed prescribing information. Based on the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial, the incidence of myopathy with simvastatin 80 mg/day was significantly greater when compared to patients taking simvastatin 20 mg/day (0.9 percent versus 0.2 percent, respectively), particularly in the first year of treatment compared to subsequent years. The SEARCH trial led to changes in simvastatin prescribing information, restricting the use of simvastatin 80 mg daily to patients who have already been receiving the medication at this dose for 12 months or more without evidence of muscle toxicity.

In addition, the maximum allowable dose of simvastatin when combined with other medications has been decreased, particularly when simvastatin is used concomitantly with amiodarone, verapamil, diltiazem, ranolazine, and amloidipine. The use of simvastatin with gemfibrozil, cyclosporine, danazol and strong CYP 3A4 inhibitors (posaconazole, itraconazole, ketoconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone) is now contraindicated. Many of the other statins also carry dose limitations when combined with fibrates or strong CYP 3A4 inhibitors such as cyclosporine. See Table 5 for a list of statin maximum dose restrictions when used concurrently with interacting medications. Many patients who are at high risk for cardiovascular disease take interacting medications concomitantly with statins, so it is important for a pharmacist to be aware of the interactions and dose limitations associated with concurrent use and appropriately counsel the patient to watch for adverse effects.

With the exception of pravastatin, all statins undergo phase I metabolism by the hepatic cytochrome P450
(CYP P450) isoenzyme system. The CYP 3A4 isoenzymes are responsible for metabolizing lovastatin, simvastatin, and atorvastatin. Pitavastatin and fluvastatin, and to a much smaller extent rosuvastatin, are metabolized by 2C9 isoenzymes. Inhibition of these isoenzymes through concurrent drug interactions can lead to higher concentrations of statins in the circulation and in turn more adverse effects. The mechanism of the gemfibrozil-statins interaction is not mediated by the CYP P450 system. Statins are substrates of organic anion transporting polypeptide (OATP), a hepatic uptake transporter, which is inhibited by gemfibrozil. Inhibition of OATP by gemfibrozil increases statin plasma concentrations. Unlike fenofibrate, gemfibrozil also inhibits glucuronidation of lipophilic statins, simvastatin, atorvastatin, lovastatin, and pitavastatin. Glucuronidation is necessary in order to make these statins more hydrophilic for elimination. Finally, with the exception of rosvustatin, statins are substrates of p-glycoprotein, a drug transporter present in the small intestine that reduces statin bioavailability. Some drugs, such as cyclosporine, are strong inhibitors of p-glycoprotein and concurrent use leads to increased concentrations of statins.

When treating patients with dyslipidemia taking interacting medications, most providers will choose to temporarily discontinue statin treatment when a patient requires use of a macrolide or azole antifungal to treat infections. However, for patients taking a chronic concomitant interacting medication, switching to another statin with desired LDL-lowering effects may be warranted. Let’s refer back to TM in the patient case and assume he was taking simvastatin 10 mg/day instead of 40 mg/day. The provider would not be able to increase his simvastatin dose to 20 mg daily due to the maximum dose limitation with concurrent diltiazem use. The best option would be to change his simvastatin to another statin agent with LDL-lowering effects equivalent to simvastatin 20 mg daily, such as atorvastatin 10 mg daily, pravastatin 40 mg daily, pitavastatin 2 mg daily or fluvastatin 80 mg daily. Recall, lovastatin 40 mg daily is contraindicated with diltiazem.

<table>
<thead>
<tr>
<th>Statin</th>
<th>Primary Metabolic Pathway: Primary Metabolic Pathway:</th>
<th>Maximum Daily Dose</th>
<th>Concomitant Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin</td>
<td>CYP 3A4</td>
<td>Contraindicated</td>
<td>Gemfibrozil, erythromycin, clarithromycin, danazol, cyclosporine, telithromycin, posaconazole, ketoconazole, itraconazole, nefazodone, HIV protease inhibitors, grapefruit juice &gt;1 quart/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 mg</td>
<td>Diltiazem, verapamil</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 mg</td>
<td>Amiodarone, amlodipine, ranolazine</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>CYP 3A4</td>
<td>10 mg</td>
<td>Use cautiously if &gt; 20 mg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 mg</td>
<td>Clarithromycin, itraconazole, ritonavir/saquinavir, ritonavir/lopinavir</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>Only 10% by CYP 2C9</td>
<td>5 mg</td>
<td>Cyclosporine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 mg</td>
<td>Cyclosporine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 mg</td>
<td>Gemfibrozil, ritonavir/lopinavir, ritonavir/atazanavir</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>CYP 3A4</td>
<td>Contraindicated</td>
<td>Itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir, nefazodone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Avoid with lovastatin</td>
<td>Gemfibrozil, cyclosporine, grapefruit juice &gt;1 quart/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 mg</td>
<td>Danazol, diltiazem, verapamil</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40 mg</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>CYP 2C9</td>
<td>20 mg</td>
<td>Cyclosporine, fluconazole</td>
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<tr>
<td>Pravastatin</td>
<td>No significant liver metabolism</td>
<td>20 mg</td>
<td>Cyclosporine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40 mg</td>
<td>Clarithromycin</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>CYP 2C9</td>
<td>1 mg</td>
<td>Erythromycin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 mg</td>
<td>Rifampin</td>
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</table>
STATIN-INDUCED HEPATOTOXICITY

Patient Case #3: AL is a 57-year-old African American man with chronically elevated liver transaminases. He also has a history of type 2 DM and stroke. His physician calls your pharmacy asking if you have any idea if he can use a statin medication in this patient. Currently he is taking colestipol for hyperlipidemia, but has discontinued this medication due to severe constipation. Patient denies any other complaints, including nausea, vomiting, abdominal pain or jaundice. AL’s labs are as follows: LDL 168 mg/dL, TC 276 mg/dL, TG 332 mg/dL, and HDL 42 mg/dL. Patient’s AST and ALT have been consistently elevated between 1.1-1.4 times the upper limit of normal (ULN) for years. His total and direct bilirubin, INR, platelets, and albumin are all normal. Ultrasound of liver shows probable non-alcoholic fatty liver disease (NAFLD).

Elevations in liver aminotransferases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) have been demonstrated with all statins at all doses.

The association between elevated aminotransferase levels and statin use is affirmed by the Liver Expert Panel of the National Lipid Association (NLA). Less than 1 percent of patients taking a statin across dose ranges will experience aminotransferase levels > 3 times the ULN for years. His total and direct bilirubin, INR, platelets, and albumin are all normal. Ultrasound of liver shows probable non-alcoholic fatty liver disease (NAFLD).

Thus due to the rarity of this occurrence it is difficult to establish a direct relationship between the two. Of the > 50,000 patients who had a liver transplant in the United States between 1990 and 2002, three were presumed to be in liver failure due to statin therapy. In addition, data from the Food and Drug Administration (FDA) Adverse Event Report system estimated that one case of liver failure occurred per 1 million statin prescriptions.

The NLA Statin Safety Taskforce does not support the routine monitoring of liver enzymes in asymptomatic patients receiving treatment with statins. The Taskforce believes that transient AST and ALT elevations may prompt providers to inappropriately discontinue statin therapy placing the patient at an increased risk of cardiovascular disease. Recent changes have been made to statin package labeling to support the NLA belief. In February of this year, the FDA issued a Safety Communication stating routine monitoring of LFTs in patients taking statins is not effective at detecting or preventing serious liver damage. Thus, LFT monitoring for statins is now only recommended at baseline and when clinically appropriate. Any patient receiving a statin should be advised to alert their provider if they experience any signs of hepatic dysfunction such as jaundice (yellowing of the skin and sclera of the eyes), fatigue, lightened stool or darkened urine. Patients should also be instructed to avoid excessive alcohol consumption (> 2 alcoholic drinks daily) since this can increase the patient’s risk of liver impairment.

If elevations in AST and ALT are seen prior to statin initiation, the etiology should be determined and referral to a hepatologist or gastroenterologist may be necessary. If AST and ALT become elevated at any time during statin therapy, it remains prudent to determine the etiology of the abnormal tests to avoid discontinuation of statin therapy in high risk individuals. Question the patient about alcohol consumption prior to the lab draw. If the AST and ALT are elevated between one to three times the ULN, then there is no need to change the patient’s lipid-lowering regimen. When liver enzymes return to normal, statin therapy can be reinitiated at a lower dose of the same statin or a different statin agent.
There is evidence to support the use of statins in certain patients with baseline elevated liver enzymes. The Liver Expert Panel states that patients with NAFLD or non-alcoholic steatohepatitis (NASH) should be targets for statin therapies because these patients are at higher risk for CHD. Several case-controlled studies have shown that patients with baseline elevations in liver enzymes and presumed NAFLD do not have an increased risk of statin liver impairment compared to those who had normal baseline liver enzymes. A post-hoc analysis of the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study evaluated 437 patients with moderately elevated baseline liver tests (< 3 times the ULN) possibly associated with NAFLD. The 227 patients who received atorvastatin had significant improvements in liver tests. The 210 patients who received placebo had further increases in LFTs or progression of NAFLD. In addition, there were a significantly greater number of cardiovascular events in patients with abnormal liver enzymes who received placebo compared to those who received atorvastatin. Thus, statin therapy may not only reduce cardiovascular events in patients with NAFLD, but may also help to improve the condition. Returning back to the patient case, AL already has elevated liver aminotransferase levels (between 1 to 3 times the ULN), possibly due to NAFLD. He is also at an increased risk of a cardiovascular event due to his history of stroke and diabetes, thus it would be appropriate to advise the physician that the patient would likely benefit from treatment with statin therapy.

The frequency of liver aminotransferase elevations appears to be the same in patients with chronic liver disease or compensated cirrhosis whether they are or are not taking a statin. Thus, the Liver Expert Panel does not consider either of these conditions a contraindication to statin use. However, the panel does believe decompensated cirrhosis and acute liver impairment are contraindications to statin therapy. Decompensated cirrhosis is cirrhosis associated with impaired liver function. Patients would not only have elevated liver aminotransferases, but also have elevated indirect bilirubin, decreased albumin, decreased platelets, increased INR, and possibly bleeding varices.

STATIN-ASSOCIATED MYALGIA

Patient Case #4: GH is a 65-year-old woman with a history of PAD and CHD. She had three stents placed in the last five years. She currently smokes and her HTN is controlled with lisinopril and metoprolol. Her last lipid panel showed an LDL of 62 mg/dL, TC of 143 mg/dL, HDL of 45 mg/dL, and TG of 178 mg/dL. She currently takes atorvastatin 40 mg daily for her cholesterol and has been on this medication for seven years. Today she notes that she started to have muscle cramping in both legs. She denies any strenuous activity. She was recently started on clarithromycin for an upper respiratory infection. Her creatine kinase was checked today and was 4.5 times the ULN.

Statins have been in the spotlight for causing rhabdomyolysis since Bayer withdrew cerivastatin (Baycol) four years after it was approved due to an increased incidence of myopathy, including rhabdomyolysis and deaths. In clinical trials, about 5 percent of patients have reported myalgias, or generalized muscle aches without elevations in creatine kinase (cK) when using a statin. This incidence of myalgias is similar in placebo groups; however, many patients discontinue statin treatment because of the temporal relationship between the initiation of the statin and time of muscle symptoms. Myopathy, on the other hand, is muscle pain associated with elevations in cK and is rare with statin use (0.1 percent). Rhabdomyolysis is a serious adverse event associated with severe muscle pain, CK > 10 times the ULN, and elevation in serum creatinine (Scr). It is caused by the leakage of muscle cells into the circulation which can lead to renal failure, cardiac arrhythmias, and death. The FDA reported the incidence of rhabdomyolysis was 16 to 80 times more frequent with cerivastatin compared to use with other available statins. The incidence of fatal rhabdomyolysis reported to the FDA as of June 2001 was one death per million prescriptions dispensed.

Myopathy occurs more frequently in patients who have hypothyroidism or when statins are combined with interacting medications such as fibrates, niacin, red yeast rice, cyclosporine, and erythromycin. Other risks of statin-associated myopathy include use of statins in the elderly.
(over 80 years of age), female patients, frail patients, patients with multiple disease states (especially renal insufficiency due to diabetes), and statin use during perioperative periods. A drug holiday during a hospitalization for major surgery may be considered. In addition, higher doses of statins are more commonly associated with myalgias. The incidence of myopathy is one case per 10,000 patients per year with standard statin dosing (20 and 40 mg), but increases with higher doses of statins (80 mg).

All patients taking a statin should be advised to report any muscle pain or muscle weakness prior to statin initiation. It is reasonable to obtain a baseline CK in patients prior to statin use. Other rheumatologic conditions or routine exercise can cause elevations in CK. Although routine CK monitoring is not recommended, a baseline level will aid in the evaluation of a patient who complains of muscle pain in the future. Patients with an elevated baseline CK can start statin therapy if the CK is < 10 times the ULN. CK should be monitored soon after initiation of the statin in these patients, regardless of whether they are reporting myalgias. Statins should be immediately stopped in these patients if they complain of myalgias or CK raises to > 10 times the ULN.

Muscle symptoms can occur at any point with statin use. Patients do not develop a tolerance to muscle symptoms. Any patient reporting muscle pain, weakness or soreness should have a subsequent CK drawn and the result should be compared to the patient’s baseline, if available. Some experts also recommend monitoring the patient’s thyroid function since hypothyroidism can lead to muscle pain. If a patient complains of muscle symptoms and CK is mildly elevated (< 3 times ULN), the statin can be continued and CK should be repeated in six weeks. If CK continues to increase or myalgia does not resolve, the patient’s statin dose can be decreased or the patient can take a drug holiday, temporarily discontinuing the statin until myalgias resolve. If the patient’s CK is moderately elevated (3–10 times the ULN) and they are experiencing muscle symptoms, the statin can be continued with weekly CK monitoring. However, clinicians may practice a more conservative approach by stopping the statin. Once the CK normalizes, you can start the patient on the same statin at a lower dose or use another statin agent. If a patient’s CK is > 10 times the ULN, the statin should be immediately discontinued.

Let’s refer back to GH in the previous case. She would be at a greater risk for developing statin-induced myopathy due to concurrent clarithromycin therapy. It would be prudent to stop the atorvastatin in this patient case while the patient is taking clarithromycin. If GH were taking a chronic interacting medication instead, such as verapamil, CK should be checked weekly and atorvastatin can be continued or, the clinician can consider a temporary drug holiday until symptoms improve. When CK returns to baseline, the patient can be changed to another statin or restarted on atorvastatin at a lower dose.

Asymptomatic patients with CK elevations are treated similarly to symptomatic patients. If a CK is mildly elevated (< 3 times the ULN) and a patient is asymptomatic, rule out other causes. The statin can be continued and CK should be repeated in six weeks. If the CK is between three and 10 times the ULN, you can consider decreasing the statin dose or giving the patient a statin holiday. Like other scenarios, the statin should be stopped when a patient’s CK is > 10 times the ULN.

Statin-induced myopathy is probably related to high concentrations of statins in the circulation, which can result from drug interactions, concomitant disease states such as renal impairment, and advanced age. The exact mechanism of statin-induced myopathy is unknown. It has been proposed that statins impair the stability of muscle cell membranes leading to decreased cell proliferation. Statins may also interfere with skeletal muscle membrane conduction resulting in myotoxicity. There is a possible genetic component to statin-induced myopathy. The SLC01B1 C variant is strongly associated with increased risk of statin-induced myopathy. The SLC01B1 C variant encodes for the system that controls hepatic uptake of statins, thus patients with the C variant have increased concentrations of circulating statins. Another proposed mechanism for statin-induced myopathy is the inhibition of a precursor in the cholesterol biosynthesis pathway, which may lead to ubiquinone deficiency. Ubiquinone is an intracellular energy component in the mitochondria. A
decrease in ubiquinone may lead to changes in intracellular respiration.

There are several strategies that can be attempted to prevent statin-induced myalgias. Supplementation with coenzyme Q10 (ubiquinone) has been a proposed antidote for statin-induced myopathy. Evidence supporting this claim is contradictory.

More research is needed before routine supplementation with coenzyme Q10 can be recommended to patients taking statins. However, there are no known risks to supplementation with coenzyme Q10. In high-risk patients who consistently report myalgias with various statins, a trial of coenzyme Q10 supplementation of 100 or 200 mg daily may be an option to allow continued use of statin therapy.

According to the Prediction of Muscular Risk in Observational conditions (PRiMo) study, both fluvastatin and pravastatin may carry a lower risk of statin-induced myalgia. The PRiMo study was an observational study which enrolled more than 7,000 patients taking high-dose statins for three or more months. A total of 10.5 percent of patients report muscle symptoms in this study. This is at least two times greater than that reported in clinical trials. Myalgia occurred in approximately 5 percent of patients receiving fluvastatin, 10 percent of patients receiving pravastatin, 15 percent taking atorvastatin, and 18 percent taking simvastatin. The lower incidence of myalgia with fluvastatin and pravastatin can possibly be explained by the lower incidence of drug interactions.

Both pravastatin and rosuvastatin are hydrophilic, which decreases the distribution of these medications to the muscle compared to other lipophilic statins. Theoretically, these agents may be associated with a lower incidence of statin-induced myopathy. However, rosuvastatin has a long half-life which, despite its hydrophilicity, may negate its ability to decrease the risk of statin-induced myopathy.

Some patients who experience myalgias on several different statins may benefit from using a low dose of a highly potent statin, such as atorvastatin or rosuvastatin every other day, several times a week, or even once weekly. Several small studies and some case reports have shown increased tolerability with alternative statin dosing and up to 35 percent reduction in LDL. However, it is not known if alternative statin dosing has cardiovascular benefits as seen with daily dosing of statins.

Vitamin D deficiency can cause myopathy. Reports have shown patients who are treated with statins and experience myalgias have lower vitamin D levels than those treated with statins who are symptom-free. Small studies have shown that vitamin D supplementation may decrease statin-induced myalgias in patients with a history of these symptoms. However, some patients who had vitamin D repletion eventually developed myopathy when the statin was restarted. Results are conflicting, thus more studies are required prior to routinely recommending vitamin D for this use. From a clinical standpoint, it may be warranted to measure and monitor a vitamin D level in patients who report statin-associated myalgias. Recommend supplementation if the patient’s vitamin D level is low.

**CHOLESTEROL ABSORPTION INHIBITOR**

Ezetimibe, the only currently available cholesterol absorption inhibitor, is mainly used as adjunctive therapy for patients receiving statin therapy requiring additional reduction in LDL cholesterol. Ezetimibe works by inhibiting cholesterol absorption from the brush border of the small intestine. Hepatic stores of cholesterol are decreased when cholesterol absorption is decreased. This in turn causes increased hepatic cholesterol uptake from the bloodstream. When ezetimibe is used as monotherapy as adjunctive therapy to TLC in patients who cannot tolerate a statin or in whom statin use is contraindicated, ezetimibe provides ~ 18 percent lowering of LDL, 10 percent lowering of TG and raises HDL by 1 percent. When added to statin therapy, ezetimibe can provide an additional 25 percent reduction in LDL, 14 percent reduction in TG and 3 percent increase in HDL.

According to prescribing information, ezetimibe is dosed 10 mg daily with or without food. However, a small study of 272 patients evaluated LDL-lowering effects of ezetimibe half dose, 5 mg daily, versus ezetimibe full dose, 10 mg daily. The full dose of ezetimibe only decreased LDL by an additional 0.3 percent. In addition, the percentage of patients
reaching LDL goal was practically the same, 61.8 percent (5 mg) versus 60.5 percent (10 mg). Some providers may choose to recommend a 5 mg daily dose to their patients as a cost-saving alternative. Ezetimibe dose adjustment for patients with mild hepatic or renal impairment is not needed.

Ezetimibe is contraindicated in patients with active liver disease or unexplained persistent liver transaminases, and women who are pregnant or breastfeeding.

The most commonly reported adverse events with ezetimibe monotherapy are respiratory infections, arthralgia, and diarrhea. Rates of liver transaminase elevations, myopathy, and rhabdomyolysis are comparable to placebo when ezetimibe is used as monotherapy. When combined with a statin the incidence of transaminase elevations, although small, is slightly increased compared to monotherapy with a statin. 0.4 percent with statin monotherapy versus 1.4 percent with ezetimibe/statin combination. Withdrawal of ezetimibe and/or statin is recommended when transaminase elevations > 3 times ULN persist. Creatine kinase > 10 times ULN was reported in 0.2 percent of patients taking ezetimibe monotherapy versus 0.1 percent taking placebo. When combined with statins, 0.1 percent of patients experience CK > 10 times ULN versus 0.4 percent receiving statin monotherapy. There have been post-marketing reports of myopathy with ezetimibe use when used in combination with statins and also when used as monotherapy. Patients should be advised to report any muscle pain or weakness to their providers and ezetimibe should be discontinued if patients have a CK > 10 times ULN.

When cyclosporine and ezetimibe are administered concurrently, levels of both agents may increase. Cyclosporine levels should be monitored when the combination is used. In patients taking a bile acid sequestrant (BAS) with ezetimibe, ezetimibe should be given two hours prior to or four hours after the BAS to avoid decreased ezetimibe absorption. There is some controversy regarding the utilization of ezetimibe as adjunctive therapy. The Study of Heart and Renal Protection (SHARP) trial did show significant reductions in stroke and revascularization in patients with chronic kidney disease taking the combination simvastatin 20 mg/ezetimibe 10 mg daily versus placebo. However, it cannot be ruled out that this result would be seen with simvastatin monotherapy since this was not a study group in the trial. The Enhances Atherosclerosis Regression Cholesterol (ENHANCE) study evaluated the effectiveness of ezetimibe in decreasing carotid intima-media thickness (CIMT), a surrogate marker for cardiovascular disease. In this double-blind trial, 720 patients with familial hypercholesterolemia were randomized to simvastatin 80 mg daily plus placebo or simvastatin 80 mg daily plus ezetimibe 10 mg daily.

Although there was a significant reduction in LDL in the combination group compared to the simvastatin-only group, there was an insignificant change in CIMT at the end of the trial. Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies in Atherosclerosis (ARBITER 6-HALTS), an open-label trial, compared niacin to ezetimibe in patients with CHD or a CHD risk equivalent who were already taking a statin and had a LDL < 100 mg/dL and HDL < 50 mg/dL in men and < 55 mg/dL in women. Although ezetimibe had a greater effect on lowering LDL compared to niacin, there was a greater reduction in CIMT, and fewer composite cardiovascular events (myocardial infarction, revascularization, acute coronary syndrome, and death from CHD) in the niacin group. Ezetimibe is often well tolerated. However, some clinicians prefer to use other agents as adjunctive therapy to statins in order to lower a patient’s LDL cholesterol due to the lack of clinical evidence supporting its effectiveness in primary and secondary cardiovascular prevention.

NIACIN
Niacin is an appropriate adjunctive agent to decrease a patient’s LDL cholesterol if it remains elevated with statin therapy. Niacin can also be used in patients who have contraindications to statins or cannot tolerate statin treatment. Because niacin has the capability to treat multiple lipid abnormalities, high TG and low HDL, the use of this agent will be discussed later in this article under the treatment of non-HDL cholesterol.
**BILE ACID SEQUESTRANTS**

Bile acids sequestrants (BAS) are appropriate agents to use in patients with increased LDL who cannot tolerate statin therapy or require additional LDL reduction despite treatment with a statin. Bile acids are synthesized from cholesterol. Endogenous bile acid is secreted into the intestine to aid in the absorption of fat from food. Once absorbed from the small intestine, the vast majority of bile acid is then reabsorbed by the liver through enterohepatic portal circulation. Bile acid sequestrants bind this bile acid in the intestine to increase bile acid excretion. In order to compensate for the loss of bile acid reabsorption, the liver increases conversion of stored cholesterol into bile acid. The loss of hepatic cholesterol stores stimulates LDL receptor activity, increasing the uptake of LDL cholesterol from the circulation.

BAS therapy decreases LDL by 15–28 percent, increases HDL by 3–8 percent, and can increase TG in some patients. Colestipol has been shown to decrease atherosclerotic plaque progression in addition to lowering LDL cholesterol when combined with nicotinic acid or lovastatin. A primary prevention study with cholestyramine monotherapy versus placebo has been shown to significantly decrease the risk of definite CHD death and/or nonfatal myocardial infarction in middle-aged men with primary hypercholesterolemia.

There are three available BASs currently available, colestipol, cholestyramine, and colesevelam. Constipation commonly occurs in patients taking these agents. This adverse effect occurs less frequently in patients taking colesevelam. These agents should be started at a low dose and titrated in order to avoid common side effects such as constipation. Advise patients to increase fluid and dietary fiber intake. Patients may also consider taking a stool softener with these agents. Other G.I. adverse effects such as flatulence, abdominal discomfort and hemorrhoids can occur. Cholestyramine is typically dosed between 4–16 grams daily in divided doses, colestipol 5–20 grams daily in divided doses, and colesevelam 2.6–3.8 grams daily in divided doses. These agents should be administered before or during meals. BASs can decrease the absorption of many other medications and fat-soluble vitamins, such as vitamin A, D, E and K. Patients should be advised to take BASs one hour prior to or four hours after other medications. Colesevelam does not appear to affect absorption of other medications and can be administered at the same time as others, except when given with drugs that have a narrow therapeutic index, such as levothyroxine, phenytoin, and warfarin.

As BASs can raise TG, the use of these agents is contraindicated in patients who have TG > 400 mg/dL. Use cautiously in patients with moderately elevated TG >200 mg/dL or in patients with persistent G.I. complaints, such as irritable bowel syndrome. The agents can be used in pregnancy because they are not absorbed through the intestine, thus they lack systemic toxicity. Compliance can be an obstacle with this class of agents, primarily due to the G.I. adverse effects. Many patients may have decreased compliance due to the large pill burden as well. Liver enzymes can increase with BASs and should be monitored, especially when used in combination with a statin.

**NON-HDL CHOLESTEROL**

**Patient Case #5: SL is a 62-year-old man who approaches your pharmacy with a question about fish oil. He takes simvastatin 40 mg daily for dyslipidemia, metformin 1 gm twice daily for type 2 DM, and aspirin 81 mg daily for heart protection. He also has a history of gout. He denies muscle pain, weakness or soreness. His last lipid panel was as follows: LDL 86 mg/dL, TC 192 mg/dL, TG 360 mg/dL and HDL 34 mg/dL. Kidney and liver function are within normal limits. His physician mentioned some prescription medications that he could consider to further control his lipids, but he only recalled fish oil. With fish oil available over the counter, SL wanted to try this option first. What is this patient’s non-HDL cholesterol? What would you recommend for the management of this patient’s dyslipidemia?**

Once a patient’s LDL goal has been met, the non-HDL cholesterol becomes a secondary goal if TG are 200 mg/dL or greater according to NCEP ATP III guidelines. The exception to this rule would be if TG were > 500 mg/dL; this makes the patient’s TG, and not the LDL, the primary target of therapy. With elevated TG,
the patient is at risk of pancreatitis as well as CHD. Non-HDL cholesterol is calculated as total cholesterol minus HDL cholesterol. (See Table 6.) It constitutes the concentration of cholesterol within all atherogenic lipoprotein particles. See Table 7 for a comparison of the non-HDL cholesterol goal to LDL goal at various patient risk categories. The non-HDL cholesterol goal is set 30 mg/dL higher than LDL goal, as a TG level of 150 mg/dL corresponds to a very-low density lipoprotein (VLDL) of 30 mg/dL. Very low-density lipoprotein (VLDL), another atherogenic lipoprotein, is calculated as TG divided by five. Non-HDL cholesterol was found to be a better predictor of CHD risk than LDL in some studies, especially in patients treated with statin therapy. Non-HDL cholesterol does not require additional testing if regular lipid panels are being tested in a patient and it can be calculated using a nonfasting TG.

With patient SL, his LDL goal would be < 100 mg/dL based on his CHD risk equivalent, DM. His non-HDL cholesterol goal would be < 130 mg/dL (30 mg/dL higher than LDL goal). SL’s non-HDL cholesterol is currently 156 mg/dL (TC of 192 mg/dL - HDL of 34 mg/dL = 158 mg/dL). This is above the goal of < 130 mg/dL, therefore, additional therapy would be indicated in this patient. Aggressive lifestyle changes are recommended, including exercise, weight loss, a high fiber diet, and a diet low in fat, cholesterol, and carbohydrates. Smoking cessation and alcohol restriction (if excessive) are important too if indicated. Medications recommended by NCEP ATP III include fibrate or niacin therapy. These agents help to lower TG, raise HDL, and therefore, improve non-HDL-C. Fish oil is another option to help lower TG, and thus non-HDL-C.

If the patient had a normal TG and LDL, but only had a low HDL (< 40 mg/dL) as the lipid abnormality, this is considered a tertiary goal of treatment for some patients. New NCEP guidelines may address this treatment goal further. There is still limited evidence on the benefits of treating low HDL by itself.

Table 6. Non-HDL Cholesterol Calculation

| Non-HDL Cholesterol = Total Cholesterol – HDL Cholesterol |

FIBRATES

Fibrates, or fibric acids, activate peroxisome proliferator activated receptor alpha (PPARα). They change the composition of apolipoproteins (proteins attached to lipoproteins), which enhances the clearance of TG-rich lipoproteins by activating lipoprotein lipase. Lower triglyceride levels leads to smaller and less-dense LDL particles which increases LDL particle affinity for cholesterol receptors. Fibrates lower TG 20–50 percent, and raise HDL 10–20 percent. In patients with normal TG, fibrates lower LDL by 5–20 percent and may raise LDL in patients with high TG. Fibrates are an attractive option for patients with elevated TG and/or low HDL.

There are two marketed fibrates, gemfibrozil and fenofibrate. Gemfibrozil is dosed 600 mg twice daily before meals. Multiple fenofibrate products are available with varying daily doses, given with or without meals depending on the specific formulation. Tricor is one branded fenofibrate product available, and the usual daily dose is 145 mg daily. Other fenofibrate branded products include Antara, Fenoglide, Fibricor, Lipofen, Lofibra, Triglide, and Trilipix. Fenoglide, Lipofen, and Lofibra should be taken with a meal, whereas the other products may be taken without regard to meals. Fenofibrate formulations are dose-adjusted in patients with kidney impairment (mild to moderate impairment) or in the elderly. Fenofibrate should be avoided in patients with severe kidney impairment. The choice of a fenofibrate product should be based on insurance formulary and costs to the patient. Fibrates are contraindicated in patients with a hypersensitivity to the product, liver impairment, severe kidney

<table>
<thead>
<tr>
<th>Table 7. LDL and Non-HDL Cholesterol Goals Based on CHD Risk Categories</th>
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<tr>
<td>Risk Category</td>
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<tr>
<td>Lower Risk: 0–1 Risk Factor</td>
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<tr>
<td>Moderate and Moderately High Risk: Multiple (2+) Risk Factors and 10-year risk 10–20%</td>
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<tr>
<td>High Risk: CHD or CHD Risk Equivalent (10-year risk for CHD &gt; 20%)</td>
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</tbody>
</table>

Table 7. LDL and Non-HDL Cholesterol Goals Based on CHD Risk Categories
impairment, gallbladder disease and nursing mothers. Common adverse reactions include increased G.I. events, elevated liver enzymes, increased CK, or rhinitis. Although fibrates can increase the risk of myopathy when administered with statins, fenofibrate may carry less risk of myopathy and rhabdomyolysis than gemfibrozil when used in combination with a statin. Patient education is essential regarding potential myopathy with fibrate monotherapy, as well as in combination with a statin. Fibrates also may interact with warfarin and can potentiate its effects; caution should be used and dosage of warfarin should be reduced. Gemfibrozil is also contraindicated in patients taking repaglinide, as severe hypoglycemia can occur. Fibrates should be given one hour before or 4–6 hours after a BAS, if used concomitantly. Use caution in patients receiving fenofibrate and immunosuppressant agents, such as cyclosporine and tacrolimus, as they can cause nephrotoxicity and renal elimination is the primary route of excretion of fenofibrate.

Landmark studies, the Helsinki Heart Study (HHS) and the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT), demonstrated a reduction in cardiovascular events with the use of gemfibrozil in primary and secondary prevention populations, respectively. Recently, an 18-year mortality follow-up of the HHS, showed long-term CHD mortality benefits in early initiation of gemfibrozil for patients with dyslipidemia, especially if related to the metabolic syndrome.

With the availability of a once-daily fibrate, fenofibrate, research has focused on this agent. Several studies evaluated the additional lipid effects of adding fenofibrate to statin therapy, primarily resulting in further HDL-raising and TG-lowering effects, with minimal effects on LDL. However, when fenofibrate was evaluated in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, long-term use did not reduce the composite outcome of fatal MI or CHD mortality in patients with type 2 diabetes who were not receiving a statin. Secondary outcomes of non-fatal MI, coronary revascularization, progression to albuminuria, and laser treatments for retinopathy were reduced. There was a significant higher use of statins in the placebo arm compared to the fenofibrate arm of the study. HDL varied between treatment arms of the study. These factors could have contributed to the results of the study.

Fenofibrate was also evaluated in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid trial for 4.7 years, which found no significant difference in the risk of experiencing a major adverse cardiac event between the fenofibrate plus simvastatin arm of the study compared with simvastatin alone in patients with type 2 diabetes. Subgroup analyses describe a potential benefit of fenofibrate in men and potential harm in women, as well as a possible benefit in patients having elevated baseline TG of at least 204 mg/dL and a low baseline HDL of 34 mg/dL or less. Questions still remain as to the results of these studies and role of fibrates, specifically fenofibrate, in CHD prevention. Despite a lack of CHD and mortality outcome data of fenofibrate in trials, clinicians and patients may prefer this fibrate due to its daily dosing and its safety preference in combination with statins for patients with mixed dyslipidemia or elevated non-HDL cholesterol.

In addition to therapeutic lifestyle changes, fenofibrate would be a good addition in the above patient case having high TG, low HDL and elevated non-HDL-C, despite treatment with a statin. A fasting lipid panel should be monitored in approximately four to six weeks to assess efficacy, and LFTs and Scr should be monitored periodically. Patients should be educated to report any myalgia to their pharmacist or provider, as well as any signs or symptoms of G.I., liver or gallbladder disease.

NIACIN

Niacin, also known as Vitamin B3, inhibits the production of fatty acids and TG production in the liver, resulting in less VLDL production. It also decreases HDL clearance. Niacin lowers LDL 5–25 percent, lowers TG 20–50 percent, and raises HDL 15–35 percent. It is the lipid-lowering agent that raises HDL cholesterol the most.

Although niacin has demonstrated efficacy and safety in randomized clinical trials, questions remain about the different niacin products. Niacin is available over the counter and by prescription. Niacin formulations include immediate-release (IR) available OTC or prescription; sustained-release (SR) available OTC, and extended-release
(ER) available by prescription. The IR and SR OTC formulations of niacin, including “no-flush” or “flush-free” products, are dietary supplements and not subject to the same FDA regulations as prescription drugs. In fact, the “no-flush” or “flush-free” niacin products contain minimal or no active niacin. The American Heart Association and the American Pharmacists Association do not recommend the use of dietary supplement niacin over prescription niacin. If an OTC product is selected due to financial reasons, then the immediate-release product is preferred. The sustained-release product causes more liver toxicity of all available niacin products, whereas the prescription extended-release formulation given once daily at bedtime, causes less liver toxicity.

Niacin should be slowly titrated to effective doses. Initiate the prescription immediate-release at one-half of 500 mg tablet (250 mg) after the evening meal and slowly titrate dose and increase dosing frequency every four to seven days until 1.5–2 g/day is reached in divided doses two or three times a day. After two months on this dose, further upward dosage titration in two to four week intervals up to 1–2 g two to three times a day, is appropriate if necessary. Prescription extended-release niacin should be started at 500 mg at bedtime after a low-fat snack and then slowly titrated at 500-mg increments at monthly intervals up to 2000 mg/day. Extended-release tablets should be swallowed whole and not be broken, crushed or chewed.

Niacin is contraindicated in patients with a known hypersensitivity to product, active liver disease, peptic ulcer disease, or arterial bleeding. Although niacin has favorable effects on various lipid parameters, its use is limited by adverse events, including flushing, itching, liver effects, metabolic abnormalities (including increases in uric acid and gout and hyperglycemia), and G.I. complaints.

Patients should be educated that niacin can cause itching or flushing, which may subside with continued use. Avoidance of alcohol, spicy foods, and hot foods or drinks at the time of administration can help minimize flushing. Patients without contraindications should also be counseled that administration of aspirin up to 325 mg or another non-steroidal anti-inflammatory drug (NSAID) 30 minutes prior to niacin helps minimize the prostaglandin-mediated vasodilation and associated flushing. Niacin can also cause myopathy, and the risk is increased in combination with statins; therefore, educate and monitor patients closely when used together.

The ARBITER 6-HALTS trial, mentioned previously in this article, was stopped 14 months early after extended-release niacin (target dose of 2,000 mg/day) was superior to ezetimibe 10 mg/day in demonstrating a reduction (or regression) of CIMT. In this small study, patients with CHD or CHD equivalent were taking a statin and had LDL < 100 mg/dL and HDL < 50 mg/dL in men or HDL < 55 mg/dL in women. More recently, extended-release niacin (up to 2,000 mg/day) was studied in patients with CHD and LDL levels < 70 mg/dL, receiving statin therapy and also ezetimibe if needed to reach LDL goal, to determine if there was additional benefit in residual cardiovascular risk, in the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health (AIM-HIGH) trial. This NIH-sponsored study was discontinued early due to a lack of efficacy of extended-release niacin in reducing cardiovascular events. These results are surprising and an ongoing, large extended-release niacin study should provide more information. These results should not be extrapolated to patients with more acute CHD and less controlled LDL levels. The use of statins and lifestyle changes should be stressed as we learn more about the management of non-HDL-cholesterol.

Although niacin would be an acceptable therapy in a patient with dyslipidemia (alterations in all lipid parameters), it isn’t a good choice in the above patient case due to the patient’s history of gout, when alternatives are available.

**FISH OIL**

Fish oil, specifically omega-3 fatty acids, can prevent heart disease and lower TG 20–50 percent by reducing TG production in the liver and increasing TG clearance. However, fish oil may also increase LDL. Two omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are of most interest. The best source of omega-3 fatty acids is fatty fish, such as salmon. Flax seed and dietary supplements are other
Due to the strong evidence of heart protection and TG lowering with omega-3 fatty acids, specifically EPA and DHA, the American Heart Association (AHA) recommends 1 g/day of omega-3 fatty acids for the prevention of cardiovascular events in patients already having CHD, preferably by eating fatty fish. However, fish oil in capsules or liquid form is also acceptable. The AHA encourages consumption of at least two servings of fatty fish per week for cardiovascular prevention. However, in patients with heart disease, the recommendation is to try to eat fish daily.

Fish oil is available OTC in various amounts as well as by prescription. The prescription formulation, omega-3-acid ethyl esters (Lovaza, formerly Omacor), has FDA-approval and is indicated for patients with hypertriglyceridemia of 500 mg/dL or more. Lovaza is a highly concentrated formulation of ethyl esters of omega-3 fatty acids, EPA and DHA, and thus allows fewer capsules per day versus OTC formulations. Advise patients that Lovaza should not be opened, crushed, dissolved or chewed. OTC fish oil products have the option of verification by USP noted by the “USP Verified Mark” on the label. Refer to the label to also determine how much EPA and DHA are in the specific product to recommend how many capsules a patient should take per day.

Table 8. Some Patient Counseling Points of Lipid-Lowering Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Instructions</th>
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<tbody>
<tr>
<td>Statin</td>
<td>• Avoid excessive alcohol consumption (&gt; 2 drinks/day).</td>
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<tr>
<td></td>
<td>• Notify a health care professional if you experience any yellowing of the skin or whites of eyes, excessive itching, or darkened urine or stool.</td>
</tr>
<tr>
<td></td>
<td>• For women: use contraception and stop the statin medication immediately if you become pregnant.</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>• Notify a health care professional if you experience unusual muscle pain, soreness, or weakness.</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>• Take with food 1 hour before or 4 hours after other medications.</td>
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<tr>
<td></td>
<td>• Increase fluid and dietary fiber intake. Use a stool softener if constipation occurs.</td>
</tr>
<tr>
<td>Fibrates</td>
<td>• Notify a health care professional if you experience any unusual muscle pain, soreness, weakness, nausea, vomiting, abdominal pain, yellowing of the skin or whites of eyes, excessive itching, or darkened urine or stool.</td>
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<tr>
<td></td>
<td>• Consider taking aspirin up to 325 mg or other NSAID 30 minutes prior to taking niacin.</td>
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<td></td>
<td>• Avoid alcohol, spicy or hot foods or hot drinks at night when taking niacin.</td>
</tr>
<tr>
<td></td>
<td>• Take Niacor with meals and Niaspan after a low fat snack.</td>
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<td>• Slowly titrate niacin to effective dose.</td>
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<td>• Slowly titrate niacin to effective dose.</td>
</tr>
<tr>
<td>Fish oil</td>
<td>• Use with caution in patients with known hypersensitivity or allergy to fish and/or shellfish.</td>
</tr>
<tr>
<td></td>
<td>• Patients should be advised to not break open, crush, dissolve or chew Lovaza.</td>
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Children and pregnant or nursing women should avoid fish high in mercury, specifically king mackerel, shark, swordfish, and tile fish. Fortunately, commonly consumed fish containing omega-3 fatty acids, such as salmon, shrimp, sardines, and herring, are very low in mercury. OTC USP Verified fish oil products and Lovaza should not contain mercury. Common adverse effects of omega-3 fatty acids include nausea, dyspepsia, eructation, diarrhea, and fishy taste. Some counseling tips to offer patients to minimize burping and improve compliance include taking omega-3 fatty acid at bedtime or with meals, using enteric-coated formulations, or storing capsules in the freezer. With higher doses used for treating hypertriglyceridemia, bleeding can occur, and it is imperative to monitor for this if a patient is also taking aspirin, an anticoagulant or other drug that can cause bleeding. Fish oil can raise LDL; therefore, it should be monitored regularly.

The use of prescription omega-3 fatty acids in combination with statins in patients with hypertriglyceridemia has demonstrated further lowering of non-HDL cholesterol in several studies. Recommending fish oil for the patient in the above case would be an acceptable alternative to fibrate or niacin therapy.
ADHERENCE
Although clinical trials demonstrate that LDL-lowering medications can decrease CHD risk, patients must adhere to treatment recommendations to reap these benefits. It takes six months to one year for CHD benefits to be achieved with lipid lowering medications. Unfortunately only half of patients started on medications to treat dyslipidemia remain on the same regimen after six months. Patients are non-adherent for a number of reasons, including cost of medications, fear of adverse effects, and belief that medication is not needed.

As pharmacists, we have a unique opportunity to assess patient’s adherence as we have a direct recording of the patient’s refill history. Recommend medication boxes or alarms to help the patient remember their medications. Use phone call reminders to help the patient refill their medications at the appropriate time. Encourage the patient to assess his or her own progress through home testing systems. Praise any progress, little as it may be, that the patient has made towards his or her cholesterol goals. A collaborative program can be set up with local providers in your community pharmacy. Through appointments or at each refill a pharmacist can use desktop analyzers to monitor the patient’s cholesterol levels. The pharmacist can provide feedback to the patient regarding their progress toward their cholesterol goals and address any concerns the patient may have about their therapy. This model has been shown to be one of the strongest to maintain patient adherence and achieve cholesterol goals.

CONCLUSION
Dyslipidemia increases a patient’s risk of developing CHD and pharmacists have an important role in assessing and treating this condition. Assessing a patient’s risk for CHD is important in determining the appropriate lipid goals and treatment. LDL is the primary target of therapy. There is an array of treatment choices and statin therapy is first-line in many patients. With proper patient education and screening for myopathy, patients can use statin therapy safely. Pharmacists can prevent and identify drug interactions and manage them appropriately. A number of other medications can also be considered in patients with dyslipidemia. Non-HDL cholesterol is a secondary target of therapy after achieving goal LDL concentrations. Refer to Table 8 for some patient education tips for the various treatment options of dyslipidemia. Table 9: Useful Web Sites for Patients and Pharmacists About Cholesterol.

Table 9: Useful Web Sites for Patients and Pharmacists About Cholesterol.

<table>
<thead>
<tr>
<th>Web Site</th>
<th>Description</th>
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<tbody>
<tr>
<td><a href="http://www.heart.org/HEARTORG/Conditions/Conditions_UCM_001087_SubHomePage.jsp">www.heart.org/HEARTORG/Conditions/Conditions_UCM_001087_SubHomePage.jsp</a></td>
<td>American Heart Association Learn and Live. Cholesterol, risk assessment and treatment information for patients.</td>
</tr>
<tr>
<td><a href="http://www.CardioSmart.org">www.CardioSmart.org</a></td>
<td>American College of Cardiology. Patient education and support program.</td>
</tr>
<tr>
<td><a href="http://www.lipidfoundation.org">www.lipidfoundation.org</a></td>
<td>Foundation of the National Lipid Association. Patient and provider information about lipids, diseases and resources to locate a lipid specialist in your area.</td>
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Note: The opinions in the article are the opinions of the author and not reflective of the opinions of the Department of Veterans Affairs.

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CONTINUING EDUCATION QUIZ
Select the correct answer.

1. A patient with a history of myocardial infarction (MI) should have a low-density lipoprotein (LDL) goal of which one of the following?
   a. < 50 mg/dL
   b. < 100 mg/dL
   c. < 130 mg/dL
   d. < 160 mg/dL

2. Which one of the following is a coronary heart disease (CHD) risk equivalent?
   a. History of transient ischemic attack
   b. Congestive heart failure
   c. Framingham 10-year risk score of 10 percent
   d. Hypothyroidism

Use the following patient case to answer questions 3 and 4:
NK is a 38-year-old woman who smokes half a pack of cigarettes per day and has a history of hypertension (HTN). She takes lisinopril for HTN. Her most recent blood pressure is 120/78 mmHg. Her mother is alive with a history of breast cancer at 52 years of age and her father is alive with a history of a MI at 58 years of age. NK has no CHD risk equivalents and her Framingham 10-year risk is 12 percent. Her total cholesterol (TC) is 242 mg/dL, triglycerides (TG) are 320 mg/dL and her high-density lipoprotein (HDL) is 52 mg/dL.

3. Which one of the following risk factors for CHD does NK have?
   a. Family history
   b. Age
   c. Low HDL
   d. Smoking

4. Which one of the following is NK’s LDL goal?
   a. < 70 mg/dL
   b. < 100 mg/dL
   c. < 130 mg/dL
   d. < 160 mg/dL

5. Which one of the following statements is true?
   a. A patient taking lovastatin with a creatine kinase (CK) of four times the upper limit of normal should immediately stop treatment with the statin.
   b. Coenzyme Q10 has strong evidence supporting its use in preventing statin-induced myopathy and should be recommended in all patients.
   c. Vitamin D deficiency is the cause of statin-induced myopathy and all patients should be screened prior to statin initiation.
   d. Some patients have an elevated baseline CK, so obtaining a CK prior to statin initiation is helpful if myopathy occurs during treatment.

6. Simvastatin will work best when administered:
   a. With meals
   b. Without meals
   c. In the morning
   d. In the evening

7. The maximum dose of simvastatin when administered with amiodarone is:
   a. 10 mg/day
   b. 20 mg/day
   c. 40 mg/day
   d. 80 mg/day

8. Which one of the following agents is safest to use in patients with severe renal impairment?
   a. Atorvastatin
   b. Lovastatin
   c. Pitavastatin
   d. Rosuvastatin

9. If a patient develops muscle cramping while taking simvastatin 40 mg daily and a provider wants to switch to another statin with equivalent LDL-lowering properties, what would be the best option?
   a. Rosuvastatin 20 mg daily
   b. Atorvastatin 20 mg daily
   c. Lovastatin 40 mg daily
   d. Pravastatin 40 mg daily
10. Which one of the following statements is true?
a. There is no clinical evidence supporting statin use in elderly patients.
b. There is no clinical benefit to lowering LDL below 70 mg/dL.
c. Statin use is associated with an increased risk of developing diabetes mellitus.
d. Pravastatin is lipophilic, thus more likely to cause statin-induced myalgias.

11. The use of a statin is contraindicated in a patient with Hepatitis C, in whom liver transaminase levels have been consistently elevated at 1.2 times the upper limit of normal, biopsy showed no signs of cirrhosis, and bilirubin, albumin, international normalized ratio (INR), and platelets are within normal limits.
   a. True
   b. False

12. As elevations in liver transaminase levels are often transient and clinically insignificant, routine monitoring of transaminases with statin therapy is not recommended.
   a. True
   b. False

13. Which one of the following statements is true?
   a. Ezetimibe can effectively lower LDL when given 5 mg daily.
   b. Ezetimibe has secondary cardiovascular prevention data supporting its effectiveness.
   c. Ezetimibe is as effective as atorvastatin 40 mg daily in lowering LDL.
   d. Ezetimibe in an appropriate adjunctive agent to help lower a patient’s non-HDL cholesterol.

14. Which one of the following statements is true about bile acid sequestrants?
   a. Can be used to treat hypertriglyceridemia
   b. Can commonly cause diarrhea
   c. Should be taken one hour before or four hours after other medications
   d. Should not be combined with other lipid-lowering medications

15. A statin should be stopped immediately if a patient’s CK is:
   a. Two times the ULN
   b. Five times the ULN
   c. Eight times the ULN
   d. Ten times the ULN

16. CT is a 46-year-old African American man. He is taking gemfibrozil 600 mg bid and atorvastatin 80 mg daily to treated mixed hyperlipidemia. He also has a history of HTN and hypothyroidism. Which risk factors for statin-induced myopathy does CT exhibit?
   a. Age and male
   b. Fibrate use and hypothyroidism
   c. Male and fibrate use
   d. Age and hypothyroidism

17. Although a patient presents to clinic for a follow up visit and denies complaints of myalgia, the provider checks a CK level and it is 1.2 times the ULN. The patient has DM and a history of triple coronary bypass one year ago. What would be the most appropriate way to manage this patient?
   a. Continue the same statin and repeat CK within six weeks.
   b. Change to a different statin and repeat CK in six months.
   c. Lower the dose of the statin.
   d. Discontinue the statin.

18. Which one of the following is the non-HDL cholesterol goal for a patient with a LDL goal of < 100 mg/dL?
   a. < 70 mg/dL
   b. < 100 mg/dL
   c. < 130 mg/dL
   d. < 160 mg/dL
19. Which one of the following is more likely to cause flushing?
   a. Gemfibrozil
   b. Niacin
   c. Fenofibrate
   d. Fish oil

20. Which one of the following is more likely to cause gallstones?
   a. Lovastatin
   b. Gemfibrozil
   c. Niacin
   d. Ezetimibe