Managing the Hypercholesterolemic Patient: When Statins Are Not Enough

Case Study and Commentary, Robert S. Rosenson, MD

INSTRUCTIONS

The following article, “Managing the Hypercholesterolemic Patient: When Statins Are Not Enough,” is a continuing medical education (CME) article. To earn credit, read the article and complete the CME evaluation form on page 55.

OBJECTIVES

After participating in the CME activity, primary care physicians should be able to:
1. Understand the fundamental concepts in cardiovascular risk stratification in hypercholesterolemic subjects based on new cholesterol guidelines
2. Recognize the common secondary causes of hypercholesterolemia and the choice of laboratory studies to identify patients with these disorders
3. Understand the evidence that supports the efficacy of cholesterol-lowering therapy in the prevention of the initial and recurrent cardiovascular events
4. Recognize the common adverse reactions with the major classes of cholesterol-lowering agents

An estimated 53 million Americans have high cholesterol, a major cause of coronary heart disease (CHD), and nearly 36 million are eligible for cholesterol-lowering drug therapy [1]. However, only about a third receive treatment. Further, many treated patients, especially those at high risk for cardiovascular events, fail to achieve cholesterol goals [2,3].

Updated guidelines on cholesterol management were recently released by the National Cholesterol Education Program’s Adult Treatment Panel III (ATP III) [1]. These update earlier NCEP recommendations (ATP II) [4], in accordance with recent clinical trial evidence. A major feature of ATP III is a focus on primary prevention in persons with multiple risk factors, many of whom are at high risk for CHD and need more intensive LDL cholesterol-lowering than recommended in ATP II; in addition, persons with multiple metabolic risk factors (metabolic syndrome) are identified as candidates for intensified therapeutic lifestyle changes to address underlying causes (obesity and physical inactivity) in addition to treatment of lipid and non-lipid risk factors. Specific new recommendations include screening with a complete fasting lipid profile (total, LDL, and HDL cholesterol) rather than a non-fasting total and HDL cholesterol and multifaceted lifestyle approaches that include weight reduction, increased physical activity, more stringent reductions in saturated fats, and the use of plant stanols/sterols and soluble fiber. In patients with fasting triglycerides of 200 mg/dL or greater, non-HDL cholesterol (total cholesterol – HDL cholesterol) has become a secondary target of cholesterol-lowering therapy after LDL cholesterol.

The practical application of the panel’s recommendations is depicted in the following case study, with an emphasis on utilization of alternate therapies when patients are intolerant of statins or fail to achieve their target on statin monotherapy.

CASE STUDY

Initial Presentation

A 68-year-old hypertensive woman presents to her new primary care physician for a routine check-up.

History

The patient has been hypertensive for 20 years. She reports that she generally feels well and maintains an active lifestyle. Medications include a combination of an angiotensin receptor blocker and low-dose (12.5 mg) hydrochlorothiazide, estradiol 1 mg in the morning, and micronized progestin 2.5 mg in the evening. She also takes nonsteroidal anti-inflammatory agents to treat the joint aches in her hands, wrists, and knees. She denies symptoms compatible with ischemic heart disease, transient neurologic defect, or claudication. She denies symptoms compatible with ischemic heart disease, transient neurologic defect, or claudication.

Family history is notable for a brother who had a myocardial infarction at age 54 years and a 44-year-old daughter with hypercholesterolemia. The patient states that she follows a low-fat diet but finds it difficult to limit portion size when she dines out. She does not engage in regular aerobic exercise, does not smoke, and drinks 2 glasses of wine per week.

From the Preventive Cardiology Center, Division of Cardiology, Departments of Medicine and Preventive Medicine, Northwestern University Medical School, Chicago, IL.
Physical Examination
The patient is a pleasant-appearing female who is 5'0" tall and weighs 144 lb. The blood pressure in the seated position averages 134/92 mm Hg on 3 replicate measurements, and the pulse rate is 68 bpm. The jugular venous pressure is estimated at 6 cm H$_2$O, and the “a” wave is prominent. The thyroid is normal in size. The lungs are clear. The left ventricular impulse is normally placed. The first and second heart sounds are normal in intensity and an S$_4$ gallop is present. The carotid arteries are firm. A bruit is auscultated over the left carotid artery. The pedal pulsations are normal. There is no lower extremity edema.

Laboratory Examination
A fasting lipid profile, chemistry panel, and thyroid function studies are ordered by the physician, and the following measures are reported: total cholesterol = 238 mg/dL; LDL cholesterol = 172 mg/dL; triglycerides = 138 mg/dL; and HDL cholesterol = 38 mg/dL. Results of chemistry panel and thyroid function testing are within normal limits.

Table 1. Major Risk Factors That Modify LDL Goals

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>LDL Cholesterol Goals</th>
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<tbody>
<tr>
<td>Cigarette smoking</td>
<td>≥130 mg/dL</td>
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<tr>
<td>Hypertension (blood pressure ≥ 140/90 mm Hg or on antihypertensive</td>
<td>≤100 mg/dL</td>
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<td>medication)</td>
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<tr>
<td>Low HDL cholesterol (&lt; 40 mg/dL)*</td>
<td>&lt;100 mg/dL</td>
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<tr>
<td>Family history of premature CHD (CHD in male first-degree relative &lt; 55</td>
<td>≤130 mg/dL</td>
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<td>years; CHD in female first-degree relative &lt; 65 years)</td>
<td>≤130 mg/dL</td>
</tr>
<tr>
<td>Age (men ≥ 45 years; women ≥ 55 years)</td>
<td>≤100 mg/dL</td>
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</tbody>
</table>

*HDL cholesterol ≥ 60 mg/dL counts as a “negative” risk factor; its presence removes 1 risk factor from the total count.

CHOLESTEROL-LOWERING THERAPY

LDL Cholesterol Goals
ATP III classifies LDL cholesterol levels of 160 mg/dL or greater as high and less than 100 mg/dL as optimal. However, treatment goals are individualized and are based on the patient’s underlying risk profile.

Determining a patient’s risk status begins with an assessment for the presence of clinical CHD or other conditions that confer a similar risk for major coronary events. Persons with CHD or CHD risk equivalents (peripheral arterial disease, abdominal aortic aneurysm, symptomatic carotid artery disease, and diabetes) have a greater than 20% risk of having a CHD event within 10 years and have the lowest LDL goal (< 100 mg/dL). For patients without known CHD (or risk equivalents), risk assessment is based on the presence of major risk factors (Table 1) and an estimate of 10-year CHD risk based on Framingham risk scoring [5]. The LDL goal for patients with multiple (2+) risk factors is less than 130 mg/dL; for patients with 1 or no risk factors, the goal is less than 160 mg/dL (Table 2).

• At what level is LDL cholesterol considered too high?
• How do risk factors modify LDL goals?

Physical Examination
The patient is a pleasant-appearing female who is 5'0" tall and weighs 144 lb. The blood pressure in the seated position averages 134/92 mm Hg on 3 replicate measurements, and the pulse rate is 68 bpm. The jugular venous pressure is estimated at 6 cm H$_2$O, and the “a” wave is prominent. The thyroid is normal in size. The lungs are clear. The left ventricular impulse is normally placed. The first and second heart sounds are normal in intensity and an S$_4$ gallop is present. The carotid arteries are firm. A bruit is auscultated over the left carotid artery. The pedal pulsations are normal. There is no lower extremity edema.

Laboratory Examination
A fasting lipid profile, chemistry panel, and thyroid function studies are ordered by the physician, and the following measures are reported: total cholesterol = 238 mg/dL; LDL cholesterol = 172 mg/dL; triglycerides = 138 mg/dL; and HDL cholesterol = 38 mg/dL. Results of chemistry panel and thyroid function testing are within normal limits.

• Into which risk category does this patient fall?

The patient has several major risk factors other than the elevated LDL cholesterol. These include her age, hypertension, low HDL cholesterol, and a family history of premature CHD. Thus, she appears to fall into the category consisting of persons with 2 or more risk factors. Persons in this category have a 10-year CHD risk of 20% or less. However, 10-year risk estimation using Framingham projections is needed before the patient can be assigned to this category. If her risk is calculated to be greater than 20%, she is considered at highest risk and assigned to the CHD category. The risk factors used in the Framingham calculation are age, total and HDL cholesterol, systolic blood pressure, treatment for hypertension, and smoking; online and downloadable calculators are available from the ATP III Web site (www.nhlbi.nih.gov/guidelines/cholesterol/profmats.htm). Using the risk calculator, this patient’s 10-year risk for a fatal or nonfatal myocardial infarction (MI) is estimated to be 10%. Thus, she remains in the 2+ risk factor category. Her LDL goal is less than 130 mg/dL.

• Is any additional testing indicated in this patient?

Laboratory Testing for Secondary Causes
In the evaluation of any dyslipidemic patient, it is prudent to identify treatable secondary disorders of lipid metabolism. Several essential laboratory studies that should be included in the initial evaluation of dyslipidemic patients are fasting glucose, serum creatinine, and a thyrotropin level. Measuring the thyrotropin level is particularly important in older subjects in whom subclinical hypothyroidism may not be recognized, as many of the manifestations may be attributed to aging. In addition, the residence time of LDL is delayed in hypothyroid patients, resulting in the formation of a particularly atherogenic oxidized LDL particle [6]. It has recently been appreciated that subclinical hypothyroidism is associated with
increased CHD risk [7]. Furthermore, thyroid hormone is necessary for binding of LDL particles to LDL receptors, so subjects with hypothyroidism often have diminished LDL cholesterol lowering with cholesterol-lowering agents.

As the above-mentioned tests were ordered at the time of the lipid profile, no additional testing is needed.

**Initial Management**

The physician reviews the results of the laboratory studies with the patient. He tells her that her cholesterol level is borderline high, which increases her risk for heart disease. As a first step to lowering her cholesterol and reducing her risk, he prescribes diet and exercise therapy. She is advised to continue to avoid high-fat foods, especially foods with saturated fat, and to increase her intake of soluble fiber, found in such foods as beans, oat bran, oatmeal, many fruits and vegetables, and in psyllium and flax seed. To foster weight reduction, he also wants her to limit her portion size and provides a referral to a dietitian to help her with making the dietary changes. The patient agrees to try to modify her diet but expresses reluctance to begin a low-impact aerobic exercise program. The physician asks her to try walking on the track near her home a few times per week for 30 to 45 minutes each time. A follow-up visit is scheduled for 6 weeks.

- What therapeutic lifestyle changes are recommended for the initial management of hypercholesterolemia?
- At what point should the use of LDL-lowering drugs be considered?

**Therapeutic Lifestyle Changes**

Therapeutic lifestyle changes (TLC) should be implemented to reduce risk for CHD. TLC dietary changes include reduced intake of saturated fat (< 7% total calories), reduced intake of cholesterol (< 200 mg per day), and increased intake of soluble fiber (10 to 25 g per day). Weight reduction and increased physical activity is also stressed. Cutpoints for initiating drug therapy differ according to risk class (Table 2). ATP III recommends considering drug therapy for CHD patients (or patients with CHD equivalents) at LDL cholesterol levels of 130 mg/dL or greater. Patients with multiple risk factors whose 10-year risk is 10% to 20% are also considered for drug therapy at LDL levels of 130 mg/dL or greater. If a patient with multiple risk factors has a less than 10% risk, the cutpoint is 160 mg/dL or greater. For patients with 1 or no risk factors, drug therapy is considered at LDL levels of 190 mg/dL or greater. LDL cholesterol-lowering therapies are implemented to prevent the development of initial or recurrent cardiovascular events in hypercholesterolemic adults. In the presence of a major genetic disorder of cholesterol metabolism such as familial hypercholesterolemia, cholesterol-lowering medications are warranted in younger adults with very high LDL cholesterol (≥ 190 mg/dL) because this disorder is associated with early onset of CHD.

- What evidence supports the use of cholesterol-lowering therapies?

**Evidence from Clinical Trials**

Clinical trials of LDL cholesterol-lowering therapies have demonstrated cardiovascular event reduction in subjects with established CHD and as well as in hypercholesterolemic patients who are initially free of CHD. The treatment efficacy of cholesterol-lowering therapies is dependent upon several factors, which include the underlying risk of the population, duration of the intervention, and adherence to the study regimen.

**Secondary Prevention Studies**

The Scandinavian Simvastatin Survival Study (4S) was designed to determine whether cholesterol-lowering drugs would improve survival in 4444 patients with established CHD and hypercholesterolemia [8]. After 2 months of diet

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**Table 2. LDL Cholesterol Goals and Cutpoints for Therapy in Different Risk Categories**

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL Goal, mg/dL</th>
<th>LDL Level at Which to Initiate Therapeutic Lifestyle Changes, mg/dL</th>
<th>LDL Level at Which to Consider Drug Therapy, mg/dL</th>
</tr>
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<tr>
<td>CHD or CHD risk equivalents (10-year risk &gt; 20%)</td>
<td>&lt; 100</td>
<td>≥ 100</td>
<td>≥ 130 (100–129: drug optional)</td>
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<tr>
<td>2+ Risk factors (10-year risk ≤ 20%)</td>
<td>&lt; 130</td>
<td>≥ 130</td>
<td>10-year risk 10%–20%; ≥ 130</td>
</tr>
<tr>
<td>0–1 Risk factor</td>
<td>&lt; 160</td>
<td>≥ 160</td>
<td>10-year risk &lt; 10%; ≥ 160</td>
</tr>
</tbody>
</table>
therapy, patients were randomized to simvastatin (20 to 40 mg/day) or placebo. After 5.4 years, among treatment patients there was a 37% decrease in fatal plus nonfatal cerebrovascular events, a 37% decrease in need for revascularization, a 42% decrease in CHD deaths, and a 30% decrease in all-cause mortality.

Like the 4S, the CARE (Cholesterol and Recurrent Events) study [9] involved patients with established CHD, but these patients had lower levels of LDL cholesterol (average, 139 mg/dL). 4159 patients received pravastatin (40 mg/day) or placebo. At 5 years, pravastatin treatment was associated with significant reductions in the combined endpoint of CHD death and nonfatal MI (10.2% versus 13.2%, P = 0.003), need for revascularization (14.1% versus 18.8%, P < 0.001), and frequency of stroke (2.6% versus 3.8%, P = 0.03). When the 2245 patients who underwent revascularization before randomization were analyzed separately, patients on pravastatin had relative risk reductions of 36%, 39%, and 39% for CHD death and nonfatal MI, fatal or nonfatal MI, and stroke, respectively, as compared with placebo [10].

The LIPID study randomized 9014 men and women with a recent myocardial infarction or unstable angina with plasma total cholesterol levels of 155 to 270 mg/dL to therapy with pravastatin or placebo [11]. The primary outcome was CHD death. After a mean follow-up of 5 years, pravastatin therapy was associated with a 24% reduction in CHD mortality (6.4% versus 8.3%). In addition, there was a 22% reduction in total mortality, a 29% reduction in myocardial infarction, a 19% reduction in stroke, and a 20% reduction in the need for revascularization.

More recently, the data from CARE and LIPID were combined in the Pravastatin Pooling Project, a prospectively defined meta-analysis [12]. The analysis showed that pravastatin therapy reduced recurrent cardiac events in subjects with LDL cholesterol of 125 mg/dL or greater, but not in patients with LDL cholesterol levels less than 125 mg/dL. These findings suggest that there is diminishing benefit from additional LDL cholesterol lowering when the LDL cholesterol level is near or above the optimal range.

It should be noted that the optimal LDL cholesterol target for patients with CHD has not been formally established by randomized clinical trials. The Treating to New Targets (TNT) study is an ongoing clinical trial [13] designed to evaluate whether lowering LDL beyond the currently recommended minimum target of less than 100 mg/dL will reduce risk of cardiovascular events in CHD patients. In a study that looked at the effect of LDL cholesterol lowering on progression of atherosclerosis in coronary artery bypass grafts, aggressive cholesterol-lowering therapy (high-dose lovastatin and colesteripol) was more effective in reducing the progression than moderate cholesterol lowering (low-dose lovastatin and colesteripol) [14].

Primary Prevention Studies
One of the first studies to evaluate lipid lowering in primary prevention of CHD was the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) [15]. 3806 middle-aged hypercholesterolemic men were randomized to cholestyramine or placebo. Both groups followed a moderate cholesterol-lowering diet. At year 7, the cholestyramine group had reductions in plasma total and LDL cholesterol of 13.4% and 20.3%, respectively. The cumulative 7-year incidence of the combined endpoint of CHD death and nonfatal myocardial infarction was reduced by 19% in the cholestyramine group (7% versus 8.6%).

The West of Scotland Coronary Prevention Study (WOSCOPS) [16] randomized 6959 middle-aged men with average LDL cholesterol levels greater than 155 mg/dL to pravastatin (40 mg) or placebo. After 5 years, the treatment group showed a 20% reduction in total cholesterol, a 26% reduction in LDL-cholesterol, a 12% reduction in triglycerides, and a 5% increase in HDL cholesterol. In addition, CHD death and nonfatal MI was reduced by 31%, all cardiovascular deaths were reduced by 32%, and total mortality was reduced by 22%, with no excess of deaths from non-cardiovascular causes.

The AirForce/Texas Coronary Atherosclerosis Prevention Study (AFCAPS) [17] trial evaluated a lower-risk population: men and women with average LDL cholesterol levels and below-average HDL levels. Subjects were randomized to lovastatin or placebo. After 5 years, risk for a first acute major coronary event was reduced in the lovastatin group (183 versus 116; relative risk, 0.63). As in WOSCOPS, patients with additional cardiac risk factors derived the greatest benefit from cholesterol lowering; however, the benefit was independent of the absolute level of LDL cholesterol.

Follow-up and Initiation of Drug Therapy
At a follow-up visit 6 weeks later, the patient reports that she is following the diet and walking about 2 times per week. Her weight at this visit is 141 lb. A repeat fasting lipid profile shows a total cholesterol of 237 mg/dL, LDL cholesterol of 168 and an HDL cholesterol of 39 mg/dL. The physician decides to place her on cerivastatin 0.4 mg nightly.

What are the major classes of LDL cholesterol-lowering agents?

Major Classes of LDL-Lowering Agents
There are 3 major classes of drugs for lowering LDL cholesterol: statins, bile acid sequestrants, and nicotinic acid (Table 3).
Statins
Currently available HMG-CoA reductase inhibitors (statins) include lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, and cerivastatin [18]. These agents are competitive inhibitors of HMG-CoA reductase, the rate-limiting step in cholesterol biosynthesis. A reduction in intrahepatic cholesterol leads to an increase in LDL receptor turnover that results from an enhanced rate of hepatic LDL receptor cycling. The statins have modest HDL-raising properties (about 5%), and triglyceride concentrations fall by an average of 20% due to a decrease in VLDL synthesis and to clearance of VLDL remnant particles by apo B/E (LDL) receptors.

The statins are commonly used in the treatment of hypercholesterolemia. They are the most powerful drugs for lowering LDL cholesterol, with reductions in the range of 20% to 60%. Fluvastatin is the least potent, decreasing LDL levels by 20% to 25% at the maximum recommended dose, while atorvastatin is the most potent, reducing LDL levels by 29% to 61% over the dosing range of 5 to 80 mg/day [19].

Adverse reactions occur less frequently with the statins than with the other classes of lipid-lowering agents; however, the incidence of myopathy is variable among the agents and specific subsets of patients. In a study of subjects treated with cerivastatin 0.8 mg, myositis (creatine kinase > 10-fold above the normal range) was more common in women than men at all ages and more frequent in older versus younger women [20]. In rat skeletal muscle, the hydrophilic agent pravastatin was less injurious to the skeletal muscle when compared to the lipophilic agents lovastatin and simvastatin [21]. There has been concern regarding hepatotoxicity with statins, yet hepatic dysfunction does not occur more frequently than with placebo [22].
**Bile Acid Sequestrants**

Conventional bile acid sequestrants include cholestyramine and colesteipol. A newer agent, colesevelam, has recently been approved for subjects with hypercholesterolemia. These agents bind bile acids in the intestine and thereby interrupt the reabsorption of bile acids. The ensuing reduction in the cholesterol pool lowers intrahepatic cholesterol that promotes the synthesis of LDL receptors. LDL receptors bind LDL from the plasma and cause further reduction in blood cholesterol. The bile acid sequestrants also induce minimal elevations in triglycerides, plasma, and HDL cholesterol.

Bile acid sequestrants are effective in patients with mild to moderate elevations of LDL cholesterol. Low doses (8 g/day of cholestyramine or 10 g/day of colesteipol) can lower LDL cholesterol by 10% to 15%. Larger LDL cholesterol reduction (about 24%) can be achieved at maximal recommended doses of conventional bile acid sequestrants (24 and 30 g/day, respectively). A similar reduction in LDL cholesterol can be achieved with 1.5 to 3.75 g/day of colesevelam [23].

Bile acid sequestrants are also effective when used in combination with HMG-CoA reductase inhibitors or nicotinic acid in patients with markedly elevated plasma levels of LDL cholesterol. As an example, bile acid sequestrants and HMG-CoA reductase inhibitors have synergistic actions to lower LDL cholesterol (about 50%) and elevate HDL cholesterol (11% to 18%) [24]. Maximal doses of bile acid sequestrants with nicotinic acid (4 g/day) can reduce LDL cholesterol by 32% and elevate HDL cholesterol by 43%. In a study of 91 subjects randomized to atorvastatin 10 mg and colesevelam 3.75 g daily versus atorvastatin 80 mg daily, LDL cholesterol lowering was statistically equivalent (48% versus 53%) [25].

The use of a bile acid sequestrant is often limited by side effects. The major adverse reactions are gastrointestinal. These include nausea, bloating, cramping, and an increase in liver enzymes. Colesevelam was well tolerated in placebo controlled trials in which few gastrointestinal side effects were reported. Dyspepsia was more common in colesevelam treated patients (8%) than placebo treated patients (3%) [25]. Bile acid sequestrants can also bind to and impair the absorption of other drugs, such as digoxin, warfarin, and fat-soluble vitamins. Administering the other drugs 1 hour before or 4 hours after the bile acid sequestrant can minimize this effect. Colesevelam does not bind digoxin, warfarin, lovastatin, or metoprolol. The difference in drug interactions with colesevelam is related to its unique chemical structure in which other medications are unable to bind in the cationic pockets.

**Nicotinic Acid**

Nicotinic acid is available in several formulations that include immediate-release (crystalline) and sustained-release formulations. Nicotinic acid (niacin) has multiple effects on lipid metabolism that include inhibition of hepatic production of VLDL and consequently its metabolite LDL [18]. It raises HDL levels by as much as 30% to 35%, both by reducing lipid transfer of cholesterol from HDL to VLDL and by delaying HDL clearance, and it can lower lipoprotein (a) levels by as much as 35% at higher doses [26].

Nicotinic acid is effective in patients with hypercholesterolemia and in combined hyperlipidemia associated with normal and low levels of HDL cholesterol, lipoprotein (a) excess, and low HDL disorders. The VLDL and LDL lowering effects are typically seen with higher doses (3 g/day) [18,26]. In contrast, the HDL-raising properties of nicotinic acid occur with dosages as low as 1 to 1.5 g/day.

The use of nicotinic acid is often limited by poor tolerability. At standard doses of crystalline nicotinic acid (1.5 to 4.5 g/day), flushing occurs in 80% of cases, and pruritus, paresthesias, and nausea each occur in about 20% [26]. Elevations in hepatocellular enzymes are common and may lead to severe hepatotoxicity, jaundice, and fulminant hepatitis. The onset of hepatocellular injury is not predictable; therefore regular monitoring of biochemical studies is mandatory. Nicotinic acid also causes insulin resistance. As a result, hyperglycemia may develop in susceptible patients, and the glycemic state may be worsened in those already being treated for overt diabetes mellitus [27]. In type 2 diabetes mellitus, low doses of crystalline nicotinic acid (1.5 g/day) do not worsen glycemic control [28]. A similar safety profile was established for extended-release (ER) nicotinic acid (Niaspan) at doses of 1 g/day [29]. Most subjects (71%) treated with higher doses of ER nicotinic acid did not have deterioration in glycemic status or require intensification of hypoglycemic therapy. Nicotinic acid can induce hyperuricemia and precipitate acute gouty arthritis.

ER nicotinic acid is better tolerated than the immediate-release formulations. In 1 study of 269 patients receiving a median dose of 2000 mg/day for 48 weeks, 4.8% discontinued the drug because of flushing [30]. In a comparative study in which both formulations of nicotinic acid were given in a dose of 1500 mg/day for 4 months, ER nicotinic acid was accompanied by fewer flushing episodes per month than immediate-release nicotinic acid (1.9 versus 8.6).

**Fibric Acid Derivatives (Fibrates)**

The major effects of the fibrates are to lower plasma triglyceride and raise HDL levels [31,32]. In subjects with type IIa and IIb hyperlipoproteinemia, LDL cholesterol may fall by 20% [33]. Thus, fenofibrate may be useful for hypercholesterolemic patients who are intolerant to statins and nicotinic acid. In addition, fenofibrate lowers lipoprotein (a) whereas gemfibrozil has a variable effect [34]. The fibric acid derivatives have not been considered effective in LDL cholesterol, but fenofibrate has been shown to have a moderate effect on lowering LDL cholesterol.
Myositis Episode and Follow-up

Several days after starting the cerivastatin, the patient develops weakness and tenderness in her upper arms. A creatine kinase level is minimally elevated at 320 U/L (normal range < 200 U/L). The cerivastatin is discontinued, and the muscle aches improve after several days. Due to her intolerance to the lipophilic statin, a hydrophilic statin is tried (pravastatin 20 mg/day). LDL cholesterol is reduced to 142 mg/dL after 6 weeks. After she demonstrates tolerability to low-dose pravastatin, the dose is increased to 40 mg daily. Six weeks later, a repeat fasting lipid profile shows a total cholesterol of 203 mg/dL, LDL cholesterol of 136 mg/dL, triglycerides of 126 mg/dL, and HDL cholesterol of 42 mg/dL. The alanine aminotransferase and creatinine kinase levels are within the normal range. She continues to adhere to a low-fat diet but is finding it difficult to lose weight. Her exercise has been interrupted by the winter season, but she claims that she is active in her volunteer work and social obligations.

> What are treatment options in this patient who has not achieved her LDL goal?

Follow-up Treatment

The options available for patients who have LDL cholesterol levels within 30 mg/dL of their target level include intensification of TLC or additional lipid altering therapy. Counseling on intensification of TLC is dependent on the patient’s perceived ability to make further changes in their diet or exercise program. Some patients may find that their diets have become unpalatable, and these comments should prompt involvement of the dietitian, who may be able to suggest new recipes. A more intensive and frequent exercise program may be limited by social factors such as employment, care of children or elderly relatives, and other conditions such as lung disease or arthritis. Again, the health care professional should suggest options in order to minimize musculoskeletal injury such as performing different types of exercise on different days of the week such as walking, use of a stationary bicycle, and water aerobics.

It is imperative that the patient be queried about treatment adherence. For example, statin agents are most often recommended for use at bedtime, but some patients fall asleep before taking their medication. It may be advisable for patients to place the vial of medication by their toothbrush or on their nightstand. In WOSCOPS, there were significantly fewer cardiovascular events in subjects who were more than 75% adherent with their medication than in those who were less adherent. All-cause mortality was reduced an additional 10% (22% to 32%) in those who were adherent to the study medication [35].

Addition of Bile Acid Sequestrant

The physician recommends that the patient initiate therapy with colesevelam 3 tablets with dinner in combination with pravastatin. Six weeks later, the total and LDL cholesterols are reduced to 196 mg/dL and 106 mg/dL, respectively. Triglycerides and HDL cholesterol are 134 mg/dL and 46 mg/dL, respectively. She will be maintained on this regimen. She is advised to implement a more regular and structured walking program and to consider contingency plans for her exercise, such as mall walking, when the weather prohibits exercise outdoors.

SUMMARY

LDL cholesterol-lowering therapy is underutilized in high-risk subjects despite clinical trial evidence, and many treated patients fail to achieve LDL cholesterol treatment goals. With the availability of more potent LDL cholesterol-lowering statins, more patients successfully achieve their LDL target. Patients intolerant of statins or certain agents within the class may require alternative approaches.

References

7. Hak AE, Pols HA, Visser TJ, et al. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam

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Financial disclosure: Dr. Rosenson is a member of the Speakers Bureau, Sankyo Pharma.
CHOLESTEROL-LOWERING THERAPY


The Journal of Clinical Outcomes Management acknowledges Sankyo Pharma Inc., who provided an unrestricted educational grant to support the development of this article.
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Part 1. Please respond to each statement. Strongly Agree Strongly Disagree

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Part 2. Please complete the following sentence.
As a result of reading this case study, I . . .
- see no need to change my practice.
- will seek more information before modifying my practice.
- intend to change the following aspect(s) of my practice: (Briefly describe)

Signature: __________________________ Date: __________________________

Part 4. Identifying information: Please PRINT legibly or type the following:
Name: __________________________ Fax number __________________________
Address: __________________________ Telephone number __________________________
________________________________________________ Social Security number: __________________________
(Required and confidential)
Medical specialty: __________________________

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