

Lipid-lowering Therapy: A Review for Pharmacists

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Learning Objectives

Upon completion of this CE program, the reader should be able to:

1. Identify the risk factors associated with coronary heart disease.
2. Describe appropriate laboratory screening and monitoring for hyperlipidemia.
3. Recommend initiation and goals of therapy based on established guidelines.
4. Describe the outcomes of the major clinical trials with statins.
5. Discuss the various medications used to treat dyslipidemias.

Abstract: Coronary heart disease (CHD) is the leading cause of death in the United States. Approximately 500,000 Americans die each year of this disease, and associated morbidity costs more than \$100 billion annually. An estimated 52 million adults require dietary changes and 12.7 million need lipid-lowering therapy. The National Cholesterol Education Program developed guidelines and clear objectives with treatment goals to reduce the risk of CHD in patients with lipid abnormalities. Despite the established relationship between lipid abnormalities and CHD morbidity and mortality, disparity exists between established guidelines and clinical practices. The majority of patients eligible for lipid-lowering therapy remain untreated, and those that receive treatment fail to reach target cholesterol values. Pharmacists managing lipid-lowering treatment have recently demonstrated an improvement in lipid-lowering outcomes when they were compared with previously published clinical studies. The primary medications used to treat hyperlipidemia are statins, niacin, bile acid resins, and fibric acid derivatives. Of these agents, the statins are the most effective with relatively few adverse effects and are supported by favorable outcome studies. These studies provide evidence that statin therapy reduces the risk of first-time and recurrent coronary events and death from coronary events and all causes. Pharmacists have already made a significant impact in the area of dyslipidemia disease state management. All pharmacists can contribute to improved lipid therapy outcomes using current clinical guidelines, clinical outcomes data, and their unique knowledge of cholesterol-lowering medications.



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INTRODUCTION

Coronary heart disease (CHD) is the leading cause of death in the United States. Approximately 500,000 Americans die each year of this disease and associated morbidity costs more than \$100 billion annually.¹ The National Cholesterol Education Program (NCEP) developed guidelines to reduce the risk of CHD in patients with lipid abnormalities.^{2,3} Clear objectives were established with treatment goals based largely on low-density lipoprotein (LDL) levels. On the basis of the NCEP goals, an estimated 52 million adults require dietary changes and 12.7 million need lipid-lowering therapy.⁴ Despite the well established relationship between lipid abnormalities and CHD morbidity and mortality,⁵⁻¹⁴ there is a significant gap between NCEP guidelines and clinical practices.

Recent studies suggest that the majority of patients eligible for lipid-lowering therapy remain untreated.^{15,16} Although 53% of patients in one HMO primary care setting were candidates for lipid-lowering drug therapy, only 14% had a cholesterol-lowering drug prescribed during the 5-year study period.¹⁵ After coronary artery bypass grafting at one hospital, 63% of patients were discharged without lipid-lowering treatment.¹⁶ Undertreatment of dyslipidemia is not limited just to a lack of drug therapy; additional studies indicate that those patients receiving lipid-lowering medications are not adequately treated.¹⁷⁻¹⁹ In two Veterans Administration medical center studies, only 33% to 50% of the subjects receiving lipid-lowering therapy achieved NCEP-established LDL goals.^{17,18} A study in the primary care setting showed fewer than 40% of patients achieved target LDL values; for patients without CHD, success rates were 68% among low-risk patients (fewer than 2 CHD risk factors) and 37% among high-risk patients (2 or more CHD risk factors).¹⁹ Patients with CHD had the lowest success rate of 18%. Health care providers are not solely responsible for the low success rates for meeting NCEP goals. Patient compliance is typically poor.²⁰ Results from one study revealed that only 38% of patients remained on their lipid-lowering therapy after 12 months.²¹

Pharmacists managing lipid-lowering treatment have recently demonstrated improvement in patient compliance and persistence.²² Project ImPACT (Improved Persistence and Compliance with Therapy) involved 26 community pharmacies, through which pharmacist-directed care was provided to 397 patients with hyperlipidemia. Patients complied with their lipid-reduction therapies 94% of the time in Project ImPACT, and they persisted with medication therapy 90% of the time. More importantly, Project ImPACT also showed that lipid management by pharmacists produced better NCEP LDL goal outcomes than documented in any previously published national study of patients with dyslipidemia. Among patients with existing CHD, 48% met their NCEP LDL goals,

whereas 67% of patients without CHD met their target. Much attention has been given to community and ambulatory care pharmacists providing care to patients with lipid abnormalities, but opportunities also exist in the hospital setting. A multidisciplinary approach led by pharmacists at one hospital was designed and implemented to improve outcomes in patients with coronary artery disease.²³ The percentage of patients receiving lipid-lowering therapy upon discharge increased from a baseline value of 40% to 72-81%.

Pharmacists with appropriate training, resources, and access to patient data, in collaboration with physicians and other healthcare providers, have demonstrated successful management of lipid disorders. However, formal dyslipidemia management services are not required in order to impact the care of patients receiving antihyperlipidemic therapy. All pharmacists can improve the level of patient care they provide with a working knowledge of the NCEP guidelines, current clinical outcome data, and lipid-lowering therapies.

DYSLIPIDEMIA GUIDELINES

Risk Factors

The NCEP recommends that the intensity of treatment for individual patients depends on risk status (*Table 1*).^{2,3} To determine a patient's risk status, add one point for each positive risk factor and then subtract one risk factor if the patient has an elevated high-density lipoprotein (HDL) cholesterol level (60 mg/dL or greater). Risk factors for CHD are classified as modifiable and nonmodifiable. Age and family history are non-modifiable risk factors and smoking, hypertension, and diabetes are modifiable risk factors. Although obesity and physical inactivity are not listed as official risk factors, they are still targets for intervention.

Laboratory Screening and Monitoring

All adults 20 years of age or older should be screened for hyperlipidemia at least once every 5 years (*Table 2*).^{2,3,24} Serum total cholesterol and HDL should be measured for patients with fewer than 2 risk factors, and these measurements can be made in the non-fasting state. Initial classification of cholesterol and triglyceride concentrations for adults without evidence of CHD are listed in *Table 3*. Higher risk patients (e.g., HDL less than 35 mg/dL) and those with CHD require evaluation with a fasting lipid profile. The LDL value can be estimated from the lipid profile using the Friedewald equation: $LDL = Total\ cholesterol - [HDL + (triglycerides/5)]$.³ If the triglyceride value is greater than 400 mg/dL, the equation is not accurate, and direct LDL measurement should then be used. Patients should be fasting for at least 9-12 hours for lipid profiles because plasma triglyceride concentrations are affected by recent food intake, and will affect the calculation of LDL. The Cholestech LDX Analyzer[®] is a point-of-care laboratory instrument that measures lipid profiles for determination LDL values within 5 minutes of obtaining a blood sample by fingerstick. The availability of efficient and reliable lipid profile results allow pharmacists to be directly involved in the management of lipid-lowering therapies.²² Cholestech has a continuing education program designed for community pharmacists interested in expanding patient care services to dyslipidemia management (510-732-7200 or <http://www.cholesteck.com>).

Treatment Guidelines

The threshold LDL levels above which diet and drug therapy should be initiated, as well as the goals of therapy, are outlined in *Table 4*.^{2,3,25,26} The target serum LDL concentration is less than 160 mg/dL for patients with no risk factors or only 1 risk factor, less than 130 mg/dL for patients with 2 or more risk factors, and less than 100 mg/dL for those with CHD.^{2,3,25,26} Patients with any form of clinically evident atherosclerosis, such as peripheral or carotid vascular disease, should be treated as if they have CHD.^{2,3} Persons with diabetes also fall in this third category, even if they have no apparent cardiovascular disease.²⁷ Type 2 diabetes is associated with a 2- to 4-fold excess risk of CHD, and patients with diabetes also have a higher fatality rate once they have CHD.²⁷ Drug therapy is not recommended for men under 35 years of age or premenopausal women unless they have serum LDL levels of more than 220 mg/dL because their immediate risk of heart disease is low.^{2,3} The presence of risk factors and a family history of CHD could lower this threshold.

There are increasing data to support that high triglyceride and/or low HDL levels are risk factors for CHD, but the major atherogenic lipoprotein is LDL, and high LDL levels remain the primary target for lipid-lowering therapy.^{2,3,28-34} The NCEP guidelines for patients with elevated serum triglyceride levels rely primarily on lifestyle modifications (*Table 5*).^{2,3} Drug therapy should be considered when a patient who has hypertriglyceridemia also has established CHD or pancreatitis.

Secondary Causes of Hyperlipidemia

Many conditions can cause hyperlipidemia including obesity, diabetes, hypothyroidism, obstructive liver disease, and nephrotic syndrome.³⁵ In general, each condition should be treated before lipid-lowering therapy is introduced. Several medications can also cause changes in lipid concentrations, including protease inhibitors, glucocorticoids, alcohol, oral estrogen, and isotretinoin (*Table 6*).^{35,36} Medications that have adverse effects on serum lipids may need to be discontinued. However, the effects may only be mild or transient and the benefits of the medication may outweigh any potential increased risk of CHD.

Non-Pharmacologic Treatment

Lifestyle modification is the foundation of hyperlipidemia treatment. All patients should begin dietary therapy and exercise and should also attempt to alleviate any modifiable risk factors (i.e., smoking and hypertension) for CHD. Depending on the degree of hyperlipidemia, the Step I and Step II diets can be introduced sequentially, or the Step II diet can be started immediately if the risk of CHD is high (*Table 7*).^{2,3} Patients with existing cardiovascular disease should be managed aggressively; therefore, a dietary trial without medication may not be recommended. Pharmacists can emphasize the importance of dietary therapy, provide basic nutritional education, and facilitate referral to a dietician.

Although physical inactivity is not listed as a risk factor in the NCEP guidelines, it is indeed an important target for intervention.^{2,3,40} Regular aerobic physical activity plays a role in both primary and secondary prevention of cardiovascular disease. The American Heart Association has recommendations for the implementation of exercise programs that may be a useful starting point for pharmacists to learn how to counsel patients on the benefits of physical activity.^{39,40}

Dietary treatment and exercise are effective for lowering LDL values.^{2,3,41} However, they are often difficult to accomplish or sustain and are seldom successful without the addition of a pharmacologic agent.⁴¹ There are several classes of cholesterol-lowering agents for patients that cannot be controlled with lifestyle modifications alone.

STATINS

The primary medications used to treat hyperlipidemia are statins, niacin, bile acid resins (BARs), and fibric acid derivatives. Of these agents, the statins are the most effective with relatively few adverse effects and are supported by favorable outcome studies.^{9-13,17,19} The statins are competitive inhibitors of HMG-CoA (3-hydroxy-3-methyl-glutaryl-coenzyme A) reductase, the enzyme that catalyzes the rate-limiting step in cholesterol synthesis.⁴² The currently available statins are atorvastatin (Lipitor[®]), cerivastatin (Baycol[®]), fluvastatin (Lescol[®]), lovastatin (Mevacor[®]), pravastatin (Pravachol[®]), and simvastatin (Zocor[®]). Additionally, an investigational statin, ZD4522, is now in phase III clinical trials.

Clinical Outcomes with Statins

For pharmacists to become more effective in managing lipid disorders and communicating with other health care professionals, it is important to know the major clinical outcomes in statin treatment trials (*Table 8*). Initial studies of statin therapy examined the impact on coronary artery disease progression and regression.⁴³ Subsequent large trials with statins demonstrated efficacy, safety, and favorable outcomes.⁹⁻¹³ These studies provide evidence that statin therapy reduces the risk of first-time (primary prevention) and recurrent (secondary prevention) coronary events and death from all causes. Several of the trials also suggest that statins are capable of reducing ischemic stroke risk by approximately one-third in patients with evidence of CHD.^{44,45}

The Scandinavian Simvastatin Survival Study Group (4S) provided the first evidence that lipid-lowering therapy reduces all-cause mortality in subjects with a history of CHD.⁹ This study also demonstrated reduction in coronary death, coronary events, and stroke. In the Cholesterol and Recurrent Events (CARE) study, a secondary prevention trial with pravastatin in men and women with normal cholesterol, risk of coronary death and stroke were both significantly reduced.¹¹ The Long-term Intervention with Pravastatin in Ischemic Disease study (LIPID) proved a reduction in mortality, coronary events, and stroke in men and women with evidence of CHD and a wide range of cholesterol levels.¹² The West of Scotland Coronary Prevention Study (WOSCOPS) tested the effectiveness of statins in primary prevention of CHD.¹⁰ Risk of coronary death was decreased with pravastatin in hypercholesterolemic men with no clinical evidence of CHD. The AFCAPS/TexCAPS study with lovastatin showed significantly reduced risk for first coronary events in men and women without CHD and normal to mildly elevated LDL and low HDL cholesterol levels.¹³

There are also clinical benefits of the statins that may be explained by activities beyond the actual lipid-lowering action, including promotion of atherosclerotic plaque stability, improvement of endothelial dysfunction, and reversal of coagulation and platelet abnormalities.⁴³ Current evidence indicates that the beneficial action of statins occurs rapidly and may provide important anti-ischemic effects as early as one month after starting therapy.⁴³ Most recently, possible statin benefits outside of the cardiovascular system have been identified; statin therapy was associated with increased bone mineral density and reduced risk of fractures in several observational studies.⁴⁶⁻⁴⁹

Adverse Effects

The statins are generally well tolerated. Mild, transient gastrointestinal disturbances, rash, and headache are more common side effects.^{42,50} An increase in plasma aminotransferase activities to more than three times normal occurs in 1% to 2% of patients, but symptomatic hepatitis is rare.⁵⁰ Myopathy with increases in serum creatine kinase (CK) have been reported with all of the statins, and rarely, rhabdomyolysis and myoglobinuria leading to renal failure have occurred.⁵¹ Hepatic or renal dysfunction, electrolyte disturbances, infections, major trauma, and hypoxia may increase the risk of myotoxicity.^{50,51} Patients are also at significantly higher risk for myotoxicity with combined treatment of a statin and niacin or fibrates.^{42,52}

The risk of both hepatotoxicity and myotoxicity is dose related, and this risk may increase when medications that inhibit statin metabolism are concomitantly prescribed (*Table 9*).⁵⁰⁻⁵² Lovastatin, simvastatin, atorvastatin, and cerivastatin are all metabolized by CYP3A4, and serum concentrations can be increased by concurrent use of CYP3A4 inhibitors, such as erythromycin, cyclosporin, itraconazole, nefazodone, and protease inhibitors.^{42,50,52} Atorvastatin and cerivastatin appear to be less affected by inhibitors of CYP3A4.⁵⁰ Fluvastatin is metabolized by CYP2C9, and may interact with other medications metabolized by this isozyme.⁴² Pravastatin is metabolized by sulfation, and serves as a useful option if cytochrome P450 drug interactions are a concern.^{42,52}

Indications

Statins are useful in treating most of the major types of hyperlipidemia.⁵² All of the agents effectively decrease LDL levels, and are approved for this use by the U.S. Food and Drug Administration (*Table 10*). Although all statins decrease triglyceride levels to some degree and have a minimal effect on raising HDL, the labeled indications vary. Atorvastatin is the most effective statin at reducing LDL levels; however, unlike the more extensively studied agents, it has not been proved to reduce total mortality.

Dosing and Monitoring

Specific dosing and monitoring guidelines for the statins are provided in *Table 11*. Higher than usual starting doses are sometimes used if the patient needs an LDL reduction beyond what the recommended starting dose can achieve. As most endogenous cholesterol production occurs at night, single doses of these agents should be administered in the evening.⁵² A new 0.8 mg dosage of cerivastatin was recently approved by the FDA for marketing. The recommended usual starting dose for cerivastatin will remain 0.4 mg, but patients that do not achieve desired cholesterol levels can be titrated up to the 0.8 mg strength. An extended-release fluvastatin 80 mg (Lescol XL[®]) is now being studied with improved efficacy over the regular-release product.

Patients should be reevaluated after each dosage adjustment or therapeutic intervention. Repeat lipid analysis can be obtained as soon as 4 weeks after initiation or changes in therapy.^{2,3} Liver function tests (i.e., transaminases) should be monitored at baseline and then periodically during therapy.⁴² The symptoms of hepatitis induced by statins, including fatigue, sluggishness, anorexia, and weight loss, resemble those of an influenza-like syndrome.⁵² Because CK levels will not rise with myotoxicity until muscle pain starts, there is no benefit from periodic testing in asymptomatic patients.⁴² Although serious adverse effects are rare, patients should be told to discontinue their medication and consult their physician for any unexplained muscle aches or symptoms of hepatotoxicity.

Cost and Cost-Effectiveness

Although the statins are the most expensive lipid-lowering medicines, their use is extremely cost-effective for treating hyperlipidemia in high-risk patients compared with many other routine medical interventions (*Table 11*).^{53,54} Atorvastatin, when compared with simvastatin, lovastatin, and fluvastatin was found to be the most cost-effective choice to achieve NCEP goals.⁵⁵ This statin cost-effectiveness analysis did not include pravastatin or cerivastatin. Cerivastatin is one of the least expensive agents for dyslipidemia, although cost is certainly not the only determinant of cost-effectiveness. Primary prevention with a statin may not be cost-effective for younger men and women with few risk factors when compared with primary prevention in older age patients and secondary prevention.⁵⁶ This supports the concept of the NCEP recommendations that lipid-lowering therapy should be targeted to patients who have CHD or elevated risk for CHD.^{2,3}

NIACIN

Niacin effectively decreases LDL and triglyceride levels and, more than any other drug, increases HDL cholesterol (*Table 10*). In the Coronary Drug Project study, niacin proved to decrease myocardial infarction and 15-year mortality rates in men with CHD.⁷ It is widely available as an over-the-counter product and is one of the least expensive medications for the management of dyslipidemia. Despite these advantages, niacin has several notable disadvantages, mostly relating to poor tolerability and toxic effects.^{17,57-59} Approximately 40% of patients discontinue niacin due to adverse effects.⁵⁷

Adverse Effects

The predominant side effects of niacin are secondary to prostaglandin-mediated vasodilation, particularly skin flushing and pruritus.⁵⁸ Other side effects include nausea, vomiting, abdominal pain, headache, glucose intolerance, hyperuricemia, exacerbation of peptic ulcer disease, and acanthosis nigricans.^{50,57,58} Elevated liver transaminases and hepatitis have been reported with niacin, and occur more frequently than in patients taking statins, especially at doses of more than 2000 mg of niacin daily.⁵² Extended-release niacin has been reported to cause liver dysfunction more commonly than regular-release niacin, but at usual doses of no greater than 2000 mg this is less of a concern.^{50,52,57-59} The extended-release formulations are also more likely to produce gastrointestinal side effects, but they are generally better tolerated than regular-release niacin because they minimize cutaneous flushing.^{7,57,58} Caution is required in administering a statin concomitantly with niacin because the combination is associated with an increased incidence of rhabdomyolysis.^{42,50}

Indications

Niacin is particularly useful for patients with mixed cholesterol abnormalities. Although the extended-release niacin has been reported to be slightly less effective in lowering LDL levels and increasing HDL levels, it is often preferred over the regular-release formulations because of improved compliance and persistence secondary to improved tolerability.^{50,57} Niacin is not recommended for patients with diabetes, and should be used cautiously in patients with a history of peptic ulcer disease, hepatic dysfunction, alcohol abuse, and gout.^{50,59}

Dosing and Monitoring

To minimize the side effects of niacin, start the patient on a low dose and increase the dose in small increments periodically (*Table 11*). Liver function tests (i.e., transaminases) should be monitored at baseline and then periodically during therapy. Serum uric acid and fasting glucose should be tested at baseline and then 4 to 6 weeks after the niacin dosage is stabilized. Patients should be instructed to take 325 mg of aspirin 30 to 60 minutes before each dose of niacin to reduce the severity of flushing. To minimize flushing, have the patient take niacin at the end of a meal and not take it with alcohol or hot beverages. Pharmacists should refer patients who are self-medicating with niacin to their primary care provider so that appropriate monitoring can occur. Given that many niacin products are available over-the-counter, pharmacists have a potentially large role in ensuring appropriate use of this therapy. Patients should be counseled on how to manage symptoms associated with niacin's vasodilatory effects and to minimize gastrointestinal effects by administering doses with food.⁵⁹ Symptoms of hepatotoxicity should also be reviewed.

BILE ACID RESINS

Cholestyramine, colesevelam, and colestipol are the BARs currently available. Colesevelam (Welchol[®]) was approved in May 2000 by the U.S. Food and Drug Administration (FDA). These agents bind cholesterol and bile acids in the intestinal lumen and prevent their reabsorption, therefore causing the liver to increase its uptake of circulating LDL through an increase in LDL receptors.⁴² The BARs are moderately effective at lowering LDL levels, and slightly raise HDL (*Table 10*). Uncommonly, an increase in serum triglyceride values may be seen. The Lipid Research Clinics Coronary Primary Prevention Trial established that cholestyramine therapy significantly decreased coronary events.⁶ BARs are seldom used as initial therapy because success is often limited by poor patient tolerance.¹⁷ Approximately one-third of patients will not take the full prescribed dosage because of constipation or poor palatability.¹⁷

Adverse Effects

In addition to constipation, common gastrointestinal disturbances with BARs include nausea, indigestion, bloating, diarrhea, and flatulence.⁴² This class of medications is not recommended for use in patients with severe, chronic constipation or bowel disease. Intestinal absorption of the fat soluble vitamins (i.e., A, D, E, K) and numerous medications that include levothyroxine, warfarin, thiazide diuretics, and digoxin may be interfered with concomitant administration of BARs (*Table 9*).⁴² In spite of the undesirable side effect profile, the BARs have an excellent safety profile because they are not absorbed.^{2,3}

Indications

The principal indication for therapy with a BAR is to further reduce serum LDL concentrations in patients who are already receiving a statin.⁵² If they are used for monotherapy, they should be restricted to patients with hypercholesterolemia, but not hypertriglyceridemia.⁵²

Dosing and Monitoring

Gastrointestinal side effects may generally be minimized by increasing the dosage of the BAR slowly, along with increasing fluid intake and taking stool softeners (*Table 11*).^{42,52} Colesevelam and colestipol are available as tablet and cholestyramine and colestipol are available as powder formulations. Patients should be instructed to take the tablets with adequate fluids. The powder formulations can be mixed in cold liquids such as pulpy fruit juices to increase palatability.

Alternatively, they may be mixed with soft foods (i.e., apple sauce, non-fat yogurt, oatmeal), but not carbonated beverages. The total daily dose can be premixed and stored in the refrigerator (advise the patient to shake or stir well before each use). Other medications should be administered 2 hours before or 4 hours after the BAR.⁴²

FIBRATES

The fibric acid derivatives available in the United States include gemfibrozil (Lopid[®]) and fenofibrate (Tricor[®]). Fibrates are mainly used to treat hypertriglyceridemia and to increase HDL cholesterol (*Table 10*).^{2,3,50} Fenofibrate was recently FDA approved to reduce LDL levels, but the effects of fibrates on LDL can be variable.⁵⁰ The Helsinki Heart Study established that gemfibrozil therapy significantly decreased coronary events.⁸ The effects of fenofibrate on CHD have not been evaluated.

Adverse Effects

The most common adverse effect associated with fibrate therapy is gastrointestinal intolerance, such as abdominal pain, nausea, vomiting, diarrhea, constipation, and dyspepsia.⁴² Neuromuscular (e.g, headache, dizziness, vertigo, arthralgias) and dermatologic reactions have also been reported.⁴² Fibrates increase biliary cholesterol concentrations and can cause gallstones.^{42,52} Monotherapy with a fibrate is rarely associated with myalgias or rhabdomyolysis.⁴² The incidence significantly increases with concomitant use of a statin.^{42,51} For this reason, extreme caution should be used when these agents are used together (*Table 9*).

Efficacy and Indications

The primary indications for fibrate therapy are serum triglyceride concentrations of more than 1000 mg/dL (or more than 400 mg/dL in higher risk patients) and low HDL concentrations.^{2,3,52}

DISCUSSION

Successful implementation of NCEP guidelines frequently requires multiple lipid-lowering medications because many patients with dyslipidemia have difficulty reaching treatment goals with monotherapy.¹⁷ If further reductions in LDL are required, combinations of medications should be used, which includes the use of poorly tolerated medications, such as niacin and the BARs.^{2,3} Poorly tolerated regimens decrease patient compliance and persistence, which ultimately affects the achievement LDL goal values.¹⁷ Pharmacists, through patient education, can improve medication adherence. Improved compliance, persistence, and outcomes have already been demonstrated with pharmacist-directed care of patients with dyslipidemia.²² For pharmacists interested in providing lipid management services, formal training and certification is available through the American Pharmaceutical Association's, "Pharmaceutical Care for Patients with Dyslipidemias" program (<http://www.aphanet.org/>). The National Association of Boards of Pharmacy also offers Dyslipidemia Disease State Management certification by examination (<http://www.nabp.net/>).

Although advances have been made in the prevention of CHD through lipid-lowering therapy, CHD remains the leading cause of death in the United States. Pharmacists have already influenced dyslipidemia disease state management. Several attributes of the pharmacy profession contribute to its success. Pharmacists are accessible to patients and physicians, motivated to expand patient care services, and have a unique knowledge of drug therapy. New point-of-care testing techniques

provide pharmacists with accurate objective data to reinforce their counseling and intervention activities relative to persistence and compliance with diet, exercise, and drug therapy. All pharmacists can contribute to improved lipid therapy outcomes with thorough knowledge of the cholesterol-lowering medications and current clinical guidelines.

Table 1. Risk Factors for CHD^{2,3}

<p>Positive Risk Factors (Add 1 risk factor)</p> <p>Age Men 45 years of age or older Women 55 years of age or older (or early menopause without estrogen replacement)</p> <p>Family history of premature cardiovascular disease in first-degree relatives Less than 55 years of age for male relatives Less than 65 years of age for female relatives</p> <p>Current smoker Hypertension (even if treated) Low HDL cholesterol level (less than 35 mg/dl) Diabetes mellitus</p>
<p>Negative Risk Factors (Subtract 1 risk factor)</p> <p>High HDL cholesterol level (60 mg/dl or greater)</p>

HDL = high-density lipoprotein; LDL = low-density lipoprotein

Table 2. Follow-up After Initial Screening of Patients without CHD^{2,3}

Total Cholesterol*	HDL*	Follow-up
Desirable (Less than 200 mg/dL)	Desirable HDL (35 mg/dL or greater)	Repeat testing within 5 years
	Low HDL (less than 35 mg/dL)	Perform fasting [†] lipid panel within 8 weeks
Borderline High (200-239 mg/dL)	Desirable HDL (53 mg/dL or greater) and fewer than 2 risk factors	Reevaluate risk status in 1-2 years
	Either a low HDL (less than 35 mg/dL) or 2 or more risk factors	Perform fasting [†] lipid panel within 8 weeks
High (240 mg/dL or greater)	-	Perform fasting [†] lipid panel within 8 weeks

*Need not be fasting

[†]9-12 hours post-prandial

Table 3. Initial Classification of Cholesterol and Triglyceride Levels^{*2,3}

Classification	Total (mg/dL)[†]	LDL (mg/dL)[†]	HDL (mg/dL)[†]	Triglycerides (mg/dL)[†]
Low	-	-	Less than 35	-
Desirable	Less than 200	Less than 130	-	Less than 200
Borderline	200 to 239	130-159	-	200 to 400
High	240 or greater	160 or greater	60 or greater	400 to 1,000
Very High	-	Greater than 220	-	Greater than 1,000

LDL = low-density lipoprotein; HDL = high-density lipoprotein

*Clinical decisions should generally be made based on 2 fasting lipid profiles, between 1 and 8 weeks apart.

[†]To convert cholesterol values from mg/dL to mmol/L, multiply by 0.026

Table 4. Treatment Decisions Based on LDL Levels and Risk Factors^{2,3}

Risk Stratification	Diet Initiation (LDL mg/dL)[*]	Drug Initiation (LDL mg/dL)[*]	Goal (LDL mg/dL)[*]
Without CHD [†] & with fewer than 2 risk factors	160 or greater	190 or greater	Less than 160
Without CHD [†] & with 2 or more risk factors	130 or greater	160 or greater	Less than 130
With CHD [†]	Greater than 100	Greater than 130	100 or less

*To convert values for cholesterol to mmol/L, multiply by 0.026

[†]CHD applies to established coronary heart disease & other clinical atherosclerotic disease

Table 5. NCEP Guidelines for Hypertriglyceridemia^{2,3}

Triglyceride Value	Intervention
Desirable (Less than 200 mg/dL)	Normal value
Borderline (200 to 400 mg/dL)	<ul style="list-style-type: none">• Primary treatment is lifestyle modification: weight control, low-fat, low-cholesterol diet, regular exercise, smoking cessation, alcohol restriction• Medications may be considered in patients with established CHD, family history of premature CHD, concomitant total cholesterol of 240 mg/dL or greater and HDL less than 35 mg/dL, genetic form of hypertriglyceridemia, or multiple risk factors for CHD
High (400 to 1,000 mg/dL)	<ul style="list-style-type: none">• Treatment as above and emphasis on controlling causes of secondary hypertriglyceridemia (e.g., diabetes)• Medication is recommended by some authorities, and should be started if the patient has a history of acute pancreatitis
Very High (Greater than 1,000 mg/dL)	<ul style="list-style-type: none">• Vigorous triglyceride-lowering efforts because of increased risk of pancreatitis• Treat secondary causes of hypertriglyceridemia (e.g., diabetes)• Institute very low-fat diet, restrict alcohol• Medication is recommended by some authorities, and should be started if the patient has a history of acute pancreatitis or triglyceride level of less than 1,000 mg/dL is not achieved

Adapted from Safeer RS, Lacivita CL. Choosing drug therapy for patients with hyperlipidemia. *Am Fam Physician.* 2000;61:3371-82.

Table 6. Effects of Selected Drugs on Serum Lipids

Drug	Lipid Effects	Comments
Alcohol ³⁵	Increased TG Increased HDL	
Alpha ₁ -blockers ³⁶	Decreased LDL (slight) Decreased TG (5%-15%) Increased HDL (5%-15%)	Beneficial effects
Amiodarone ^{35,36}	Increased TG	
Anabolic steroids ^{35,36}	Increased LDL Decreased HDL	
Beta-blockers, non-ISA ³⁶	Increased TG (20%-50%) Decreased HDL (13%-15%)	Beta ₁ -selective agents have less effect on HDL
Beta-blockers, ISA ³⁶	Increased HDL (9%)	Beneficial effects
Corticosteroids ³⁶	Increased LDL Increased TG Increased HDL	
Cyclosporine ^{35,36}	Increased LDL	
Estrogen therapy (PEPI) ³⁷	Decreased LDL (10%) Increased TG (15%) Increased HDL (9%)	Oral CEE alone
Isotretinoin ^{35,36}	Increased LDL Increase TG (significant) Decreased HDL	
Metformin ³⁶	Decreased LDL Increased TG	Beneficial effects
Oral contraceptives ³⁶	Increased LDL Increased TG Decreased HDL	Effects mild and variable; depends on progestin:estrogen ratio
Progestins ³⁶	Increased HDL (15%-14%)	Related to androgenic activity
Protease inhibitors ³⁸	Increased TC Increased TG	
Thiazide diuretics ³⁶	Increased LDL (25%) Increased TG (15%)	Effect is often transient

CEE = conjugated equine estrogen; HDL = high-density lipoprotein; ISA = intrinsic sympathomimetic activity;
LDL = low-density lipoprotein; TC = total cholesterol; TG = triglycerides

Table 7. NCEP Diet Recommendations^{2,3}

Nutrient	Step I (% of total CALORIES)	Step II (% of total CALORIES)
Total Fat (9 CALORIES per gram of fat)	30% or less	30% or less
• Saturated Fat (e.g., coconut, palm, butter, lard, shortening, animal fat, dairy fat)	8% to 10%	Less than 7%
• Polyunsaturated Fat (e.g., safflower, sunflower, corn, cottonseed, & soybean oils)	10% or less	10% or less
• Monounsaturated Fat (e.g., canola, olive, & peanut oils)	15% or less	15% or less
Cholesterol	Less than 300 mg/day (4 or fewer egg yolks/week)	Less than 200 mg/day (2 or fewer eggs yolks/week)

Table 8. Outcomes of Major Studies with Statins

Trial	Description	Outcome
Secondary Prevention (patients with CHD)		
Scandinavian Simvastatin Survival Study (4S) ⁹	Simvastatin 10-40 mg/day n = 4,444; 5.0 years TC 212-310 mg/dL	30% decreased mortality 42% decreased coronary death 30% decreased stroke
Cholesterol and Recurrent Events (CARE) Study ¹¹	Pravastatin n = 4,159; 5.0 years TC greater than 240 mg/dL	8% decreased mortality (NS) 19% decrease coronary death 31% decreased stroke
Long-term Intervention with Pravastatin Ischaemic Disease (LIPID) Study ¹²	Pravastatin 40 mg/day n = 9,014; 6.1 years TC 155-271 mg/dL	22% decreased mortality 24% decreased coronary death 19% decreased stroke
Primary Prevention (patients without documented CHD)		
West of Scotland Coronary Prevention Study ¹⁰ (WOSCOPS)	Pravastatin 40 mg/day n = 6,595 (men only); 4.9 years TC 272 mg/dL average	22% decreased mortality (NS) 33% decreased coronary death 11% decreased stroke (NS)
Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) ¹³	Lovastatin 20-40 mg/day n = 6,605; 5.2 years LDL 130-190 mg/dL HDL less than 50mg/dL	36% decreased coronary death

HDL = high-density lipoprotein; LDL = low-density lipoprotein; NS = not significant; TC = total cholesterol

Table 9. Selected Drug Interactions with Lipid-lowering Drugs

Precipitant Drug	Object Drug	Comments
Inhibitors of CYP 3A4 ^{42,50,51} Clarithromycin, erythromycin, cyclosporine, HIV-protease inhibitors, itraconazole, ketoconazole, nefazodone	Lovastatin, simvastatin, atorvastatin, cerivastatin	Increased statin serum concentration Increased risk of severe myopathy or rhabdomyolysis
Inducers of CYP 3A4 ^{42,50} Barbiturates, carbamazepine, rifampin	Lovastatin, simvastatin, atorvastatin, cerivastatin	Decreased statin serum concentration
Inhibitors of CYP 2C9 ⁴² Cimetidine, omeprazole	Fluvastatin	Increased statin serum concentration
Inducers of CYP 2C9 ⁴² Rifampin	Fluvastatin	Decreased fluvastatin serum concentration
Myotoxic Drugs ⁵¹ Fibrates, cyclosporine, erythromycin, verapamil, itraconazole, nefazodone Niacin, ^{42,50}	Statins	Increased risk of severe myopathy or rhabdomyolysis. The risk of myopathy with niacin is less than that of the fibrates. ⁵⁰ Incidence of myotoxicity with lovastatin plus gemfibrozil is 5% and with cyclosporin is ~30% ⁵¹
Statins and Fibrates ⁴²	Warfarin	Increased hypoprothrombinemic response to warfarin
Bile Acid Binding Resins ^{42,52}	Digoxin, levothyroxine, warfarin, thiazide diuretics, vitamins A,D,E,K, statins, and many others	Decreased absorption of object drugs Take 2 hours before or 4 hours after resin

Table 10. Efficacy of Lipid-lowering Agents

Drug	Changes in Lipid Values		
	Decreased LDL	Increased HDL	Decreased Triglycerides
Statins			
Atorvastatin (Lipitor [®])	39%-60%	6%	19%-37%
Cerivastatin (Baycol [®])	34%	7%	16%
Lovastatin (Mevacor [®])	24%-40%	7%-10%	10%-19%
Fluvastatin (Lescol [®])	25%-34%	NA	12%-23%
Pravastatin (Pravastatin [®])	22%-34%	7%-12%	15%-24%
Simvastatin (Zocor [®])	38%-47%	8%	15%-24%
Niacin			
Niacin, extended-release (Niaspan [®])	5%-14%	18%-22%	21%-28%
Niacin, regular-release ^{2,3}	20%-30%	35%-55%	20%-35%
Bile Acid Binding Resins			
Cholestyramine (Questran [®])	20	5	NA
Colestipol (Colestid [®])	20	5	NA
Fibrates			
Gemfibrozil (Lopid [®])	10	11	35%
Fenofibrate (Tricor [®])	10-20	7-15	25%-45%

Information based on data in package inserts

Table 11. Dosing, Monitoring, and Cost of Lipid-lowering Agents

Drug	Dosage	Monitoring	Cost/ Month ⁵³
Atorvastatin (Lipitor [®])	Start: 10 mg daily at bedtime Max: 80 mg daily	Check lipid profile for response at 4 weeks. Check ALT/AST at baseline & 12 weeks after starting or at dosage increase, then every 6 months. Discontinue if ALT or AST greater than 3 times normal range or if myopathy or myositis occurs	\$56- \$210
Cerivastatin (Baycol [®])	Start: 0.4 mg daily at bedtime If CrCl is less than 60 mL/min, start at	Check lipid profile for response at 4 weeks. Check ALT/AST at baseline, 6 & 12 weeks after starting or dosage increase,	\$43

	0.2 mg daily dose. Max: 0.4 mg daily	then every 6 months. Discontinue if ALT or AST greater than 3 times normal range or if myopathy or myositis occurs	
Fluvastatin (Lescol [®])	Start: 20 mg daily at bedtime Max: 80 mg divided in 2 daily doses	Check lipid profile for response at 4 weeks. Check ALT/AST at baseline & 12 weeks after starting or dosage increase, then every 6 months. Discontinue if ALT or AST greater than 3 times normal range or if myopathy or myositis occurs	\$38-\$80
Lovastatin (Mevacor [®])	Start: 20 mg daily with evening meal Max: 80 mg daily If CrCl is less than 30 mL/min, maximum daily dose is 20 mg	Check lipid profile for response at 4 weeks. Check ALT/AST at baseline & 12 weeks after starting or dosage increase, then every 6 months. Discontinue if ALT or AST greater than 3 times normal range or if myopathy or myositis occurs	\$74-\$251
Pravastatin (Pravachol [®])	Start: 10 mg daily at bedtime Max: 40 mg daily If hepatic or renal dysfunction, maximum daily dose is 10 mg.	Check lipid profile for response at 4 weeks. Check ALT/AST at baseline & 12 weeks after starting or dosage increase, then every 6 months. Discontinue if ALT or AST greater than 3 times normal range or if myopathy or myositis occurs	\$70-\$112
Simvastatin (Zocor [®])	Start: 20 mg daily at bedtime Max: 80 mg daily If patient is elderly or has severe renal insufficiency, maximum daily dose is 5 mg. If given in combination with fibrates or niacin, maximum daily dose is 10 mg.	Check lipid profile for response at 4 weeks. Check ALT/AST at baseline & every 6 months for the first year; repeat after dosage increases. ALT/AST every 3 months for patients taking 80 mg/day. Discontinue if ALT or AST greater than 3 times normal range or if myopathy or myositis occurs Closely monitor patients with severe renal insufficiency.	\$114
Niacin			
Nonprescription, Regular-release Niacin ⁵⁹	Start: 50-100 mg twice daily for the first week; double dosage every week to	Check lipid profile for response at 4 weeks. Check ALT/AST, uric acid, and fasting glucose at baseline and 4-6 weeks after	~\$5-\$15

	1,000-1,500 mg/day, in 2 or 3 divided doses; if response inadequate, increase dosage slowly to daily maximum of 3,000 mg Max: 3000 mg daily	the dosage is stabilized. Repeat ALT/AST every 12 weeks thereafter for the first year, then every 6-12 months. Discontinue if ALT or AST greater than 3 times normal range or if myopathy or myositis occurs	
Extended-Release Niacin (Niaspan [®])	Start: 500 mg daily for 4 weeks, then 1,000 mg daily for 4 weeks; if response inadequate, increase daily dose by 500 mg every 4 weeks, to daily maximum of 2,000 mg Max: 2000 mg daily	Check lipid profile for response at 4 weeks. Check ALT/AST, uric acid, and fasting glucose at baseline and 4-6 weeks after the dosage is stabilized. ⁵⁹ Repeat ALT/AST every 12 weeks thereafter for the first year, then every 6-12 months. ⁵⁹ Discontinue if ALT or AST greater than 3 times normal range or if myopathy or myositis occurs	\$16-\$56
Bile Acid Binding Resins			
Cholestyramine (Questran [®])	Start: 4 g daily in 2 or 3 divided doses; increase at 4 week intervals as tolerated Max: 24 g daily	Check lipid profile for response at 4 weeks. Monitor for constipation If constipation occurs, increase fluid and fiber intake, consider stool softener (or laxative).	\$55-\$332
Colesevelam (Welchol [®])	Start: 3.75 g (6 tablets) daily in 1 or 2 doses with meals With statins: 2.5-3.75 g (4-6 tablets) daily Max: 4.375 g (7 tablets) daily	Check lipid profile for response at 4 weeks. Monitor concurrent drugs with narrow therapeutic index, monitor concurrent sustained-release verapamil	-
Colestipol (Colestid [®])	Start: 5 g daily in 2 or 3 divided doses; increase at 4 week intervals as tolerated Max: 30 g daily	Check lipid profile for response at 4 weeks. Monitor for constipation If constipation occurs, increase fluid and fiber intake, consider stool softener (or laxative).	\$49-\$293
Fibrates			
Gemfibrozil (Lopid [®])	Start: 600 mg twice daily, 30 minutes before morning and evening meals Max: 600 mg twice daily	Check lipid profile for response at 4 weeks. Check ALT/AST at baseline and periodically during first year of therapy.	\$84

Fenofibrate (Tricor [®])	Start: 67 mg daily taken with main meal; increase at 4 week intervals as tolerated Max: 201 mg daily	Check lipid profile for response at 4 weeks. Check ALT/AST at baseline and periodically during first year of therapy.	\$23-\$68
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CrCl = creatinine clearance; ALT = alanine transaminase; AST = aspartate aminotransferase

Estimated cost to the pharmacist based on average wholesale prices (rounded to the nearest dollar) for one month of therapy at starting and maximum dosages, in Red Book. Montvale, N.J.: Medical Economics Data, 2000.

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