Medicines for Managing High Cholesterol: A Review

by Mary Jo Carden, R.Ph., Esq.

E.L.F. Publications, Inc. is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmaceutical education. This program has been approved for 1.5 contact hour (0.15 CEU).
Universal Program Numbers:
406-000-08-002-H01P & . 406-000-08-002-H01T
The expiration date for this program is 1/31/10.

Learning Objectives

Pharmacists:

After completing this lesson, pharmacists should be able to:

- Understand the clinical guidelines for treating high cholesterol.
- Describe approaches to medication therapy for managing high cholesterol.
- List the therapeutic categories for cholesterol medications.
- Explain how collaborative practice has improved cholesterol management.
- List several devices for measuring cholesterol in the pharmacy.
- Describe patient counseling tips to help with medication compliance and adherence.
-

Pharmacy Technicians:

After completing this lesson, pharmacy technicians should be able to:

- Describe medication therapy used to treat high cholesterol.
- List the therapeutic categories for cholesterol medications.
- List several devices for measuring cholesterol in the pharmacy.
- Describe patient medication compliance tools and devices that are available.

I. Introduction

Hypercholesterolemia or dyslipidemiais a generalized term for the presence of abnormal levels of cholesterol and/or triglycerides in the blood stream associated with an imbalance of lipoproteins. It is a condition that affects more than 106 million Americans age 20 and above, with the occurrence greater in women than in men (55 million compared to 50 million respectively). According to the National Heart, Lung, and Blood Institute and the National Center for Health Care Statistics, the measurement for high blood cholesterol is based on a total cholesterol fasting reading of 200 mg/dL or higher. The causes of high blood cholesterol include lack of proper exercise, high fat, low fiber diet, obesity, and genetic factors. In the United States, the incidence of high blood cholesterol occurs nearly equally in Whites, African Americans, and Latin Americans.

Hyperlipidemia can result in the development of atherosclerosis, a condition commonly known as clogging of the arteries and is currently the leading cause of cardiovascular death among men and women in the United States. Hypercholesterolemia can also result in other

conditions such as pancreatitis and non-alcoholic fatty liver disease. Despite the incidence of atherosclerosis in Americans, the overall incidence of cardiovascular deaths has declined in the past 50 years partly attributed to use of a variety of cholesterol-lowering agents.

The use of cholesterol-lowering agents is a controversial topic and scientific literature is replete with studies and information related to proper ways to lower cholesterol and reduce the cardiovascular risks. Individuals who have an initial finding of high blood cholesterol typically receive guidance to lose weight, modify unhealthy diets, smoking cessation, and increase exercise. If these interventions are unsuccessful, then individuals typically begin a medication regimen designed to help them reach their target range for appropriate cholesterol levels based on age, family history, and preexisting or concomitant medical conditions or other risk factors.

Pharmacists are an important health care professional in screening individuals for high cholesterol and providing recommendations for further intervention. During an individual's course of therapy, pharmacists help to monitor progress, provide education to ensure continued success with therapy, and provide the appropriate counseling and monitoring for medication therapy regimens. Pharmacists' interventions in the area of cholesterol management have proven to be very successful.

This article provides pharmacists and pharmacy technicians with an overview of current guidelines for the determination of a hypercholesterolemia diagnosis, current clinical guidelines, including diet, exercise, and other non-medication intervention, and an assessment of medications to lower cholesterol levels. The article will also review current research findings regarding the efficacy of certain medications compared to others. Finally, the article provides an overview of pharmacist medication management programs designed to improve patient compliance with management of hypercholesterolemia.

II. Overview of hypercholesterolemia and dyslipidemia

Lipids, including cholesterol and triglycerides, are important components of humans' blood stream. Cholesterol forms the structure of cellular membranes, synthesizes steroid hormones, and aids in the formation of bile acids. Triglycerides primarily serve to store energy in fat cells and to burn energy through the use of muscle tissue. Lipoproteins, a combination of lipids and proteins aid in the solubility of blood proteins in the bloodstream. Lipoproteins include:

- Chylomicrons, the largest lipoprotein with a triglyceride core. They are synthesized and secreted from the intestines and serve to transport exogenous cholesterol (ingested from food), fatty acids, and fat-soluble food throughout the blood stream.
- Low-density lipoprotein (LDL), a key contributor to atherosclerosis, is largely accountable for circulating cholesterol in the bloodstream. LDL is formed from the remnants of very low-density lipoprotein (VLDL) and intermediate-density lipoprotein(IDL). VLDL contains primarily triglycerides and is formed in the liver. IDL is formed from VLDL and contains triglycerides and cholesteryol ester. The liver metabolizes approximately one-half of the IDL found in the body and the other half becomes LDL. A final cholesterol reading measures both IDL and LDL components.
- High-density lipoprotein (HDL) assists in the return of lipoprotein and triglycerides to the liver for excretion, a process known as reverse cholesterol transport.

A. Overview of the role of formation and metabolism of lipoproteins

1. Formation

Lipoproteins forms from consumption of food in the diet, known as the exogenous pathway, and based upon the regular metabolic cycle primarily through the liver, known as the endogenous pathway.

a. Overview of the exogenous pathway

Ingestion of food causes intestinal cells to absorb fatty acids and cholesterol, esterifies them, and incorporates them into the core of the chylomicrons with a triglyceride rich core. Chylomicrons are then secreted into plasma where the triglycerides are eventually released as free fatty acids and used by fat tissues for energy storage and muscles for energy release. Some components of the chylomicrons are also transferred to HDL, taken up by the liver and then degraded to deliver daily cholesterol dietary cholesterol requirements.

b. Overview of the endogenous pathway

The liver secretes VLDL, rich in triglycerides, to the plasma that is used by fat tissues to store energy and muscles to release energy. Part of the remaining VLDL remnants (IDLs) is degraded by the liver and the remainder becomes LDL, which primarily contains cholesteryl ester. Certain individuals who experience dyslipidemia because of this pathway carry identifiable genetic disorders. Others experience metabolic disorders caused by diet, lack of exercise, medications, or preexisting conditions which causes the endogenous pathway to malfunction leading to dyslipidemia.

B. Physiological causes of dyslipidemia

Dyslipidemia occurs because of genetic or acquired defects in the catabolism and metabolism of lipoproteins. The major defects and the impact are listed below.

1. Lipoprotein assembly

a. Familial hypertriglyceridemia (FHTG) and familial combined hyperlipidemia (FCHL) are caused by defects in the secretion of VLDL from the liver. FHTG is caused by an overproduction of triglycerides with a normal number of VLDL particles resulting in increased triglyceride levels, but generally not associated with high cholesterol levels. FCHL is caused by an increased amount of a protein called apolipoprotein B that helps carry VLDL and LDL to cells resulting in an increased level of cholesterol and triglycerides in the cells. In both of these conditions, symptoms are generally noticeable in adolescence or early adulthood and last a lifetime. These individuals are also at greater risk than the general population for cardiovascular disease that occurs before age 50.

b. Metabolic syndrome, a condition often caused by obesity and a diet high in fats, is related to a number of conditions, including Type 2 diabetes and insulin resistance, and also results in an increased level of triglyceride production because of unknown defects in the lipoprotein assembly process. Metabolic syndrome is also a component of high triglyceride levels in individuals with FCHL.

2. Lipoprotein catabolism defects

a. Lipoprotein lipase (LPL) is an enzyme synthesized in fat and muscle tissue and then transported to the surface of cells to act on triglyceride rich lipoproteins, including chylomicrons and VLDL. This process then produces fatty acids that are used by muscles for energy or are stored in fat cells for energy reserves. Rare genetic causes of LPL deficiency result in hyperlipidemia that presents in neonates or infants. More often, LPL deficiencies are caused by acquired causes,

such as untreated diabetes or uremia caused by kidney failure resulting in hyperlipidemia. High triglyceride levels occur when acquired LPL is accompanied by excessive input of VLDL or when untreated diabetes is present in individuals with FHTG or FCHL.

b. Remnant catabolism genetic defects occur in some individuals with a genetically identified mutation. This genetic impairment inhibits the uptake of VLDL and chylomicrons in the liver thus resulting in low LDL levels. While these individuals might have normal to low cholesterol levels, if a person acquires or has a genetic defect related to LPL, then the amount of VLDL might be excessive resulting in hyperlipidemia levels. Also, the high levels of the remnants of VLDL and chylomicrons that contain approximately equal amounts of cholesterol and triglycerides often result in hypercholesterolemia and hypertriglyceridemia.

c. Defects on cell surfaces caused by either natural causes or dietary issue often result in the inability of cells to properly absorb LDL to allow cholesterol release necessary for membranes, bile production, and hormone synthesis. This defect also causes increased levels of internal cellular cholesterol because the cholesterol is not properly released from the cell through the regular catabolic process.

   A high level of dietary cholesterol delivered to the liver by chylomicron receptors can also result in LDL catabolism defects by suppressing LDL receptors and impair removal of LDL from the plasma. Diets high in saturated fats can reduce LDL receptor activity and increase LDL production. Hypothyroidism may also cause LDL receptor-mediated cholesterol removal.

3. HDL function and regulation

   Typically, the goal of HDL regulation is to achieve greater, not lower levels, as is the case with LDL. Reductions in HDL levels can be caused by genetic disorders caused by an apolipoprotein structural mutation. (Apolipoprotein A-1 is critical for the production and metabolism of HDL.) Other enzymatic deficiencies associated with the production and metabolism of HDL also causes lower levels.

   Exogenous factors associated with decreases in HDL levels include cigarette smoking; obesity, particularly in the mid-section; male gender; lack of exercise; low-fat diets, hypertriglyceridemia, uremia, and medications, including androgens, progestin's, and antihypertensive agents. Low HDL commonly occurs in cases where individuals have extremely elevated triglyceride levels, such as in metabolic syndrome.

   Increased levels of HDL are associated with aerobic exercise, female gender, high fat diets, alcohol use, and certain medications including estrogen, fibrates, and nicotinic acid.

4. Role of hepatic lipase in dyslipidemia

   Increased levels of hepatic lipase, an enzyme involved in the metabolism of LDL and HDL, often lead to an increase in LDL and a decrease in HDL levels. Males, individuals with excessive abdominal fat, and individuals with metabolic syndrome often experience increases in hepatic lipase.

II. Diagnosis and management of dyslipidemia

High cholesterol and other issues associated with dyslipidemia do not manifest outright signs or symptoms. Certain individuals are at greater risk for developing high cholesterol and other conditions including: individuals who smoke, individuals who are obese or overweight

individuals who have high blood pressure, individuals with hypertension, diabetics, individuals who have a family history of heart disease, primarily a parent or sibling, and individuals who primarily consume a high fat diet.

Given the prevalence of dyslipidemia in the United States, the Agency for Health Care Research and Quality (AHRQ), a sub agency of the United States Department of Health and Human Services released the following screening guidelines in 2001:

- Lipid screenings should consist of a measurement of total blood cholesterol, LDL, and HDL levels. The agency concluded that measurement of triglyceride levels is inconclusive to determine risk associated with cardiovascular disease.
- Routine screening of men 35 years and older and women age 45 and older. Recommend treatment for individuals at increased risk of cardiovascular disease.
- Routine screening of younger men age 20-35 and women age 20-45 with known risk factors for cardiovascular disease. Makes no recommendation for or against routine screening of younger individuals not at risk for cardiovascular disease.

In 2004, the National Cholesterol Education Programs (NCEP) updated guidelines first released in 2001for the diagnosis and treatment of adult patients with high cholesterol. These recommendations include the levels of lipoprotein levels and total cholesterol that trigger the need for treatment and management. These recommendations vary by age, gender, and presence of other cardiovascular conditions, type 2 diabetes, or metabolic syndrome. Lipoprotein levels should be collected through a blood test following a 9-12 hour fast. The following represents current recommendations for readings:

- LDL levels, which mark the primary target for whether to treat or not treat (all readings in mg/dL)
  Less than 100 - optimal
  100-129 - near optimal/above optimal
  130-159 - borderline high
  160-189 - high
  Greater than or equal to 190 - high
- Total cholesterol levels in general (all readings in mg/dL)
  Less than 200 - desirable
  200-239 - borderline high
  Greater than or equal to 240 - high
- HDL levels (in mg/dL)
  Less than 40 - low
  Greater than or equal to 60 - high and ideal.

Upon confirmation of increased cholesterol readings, individuals should be assessed for the risks or presence of cardiovascular heart disease (CHD), including carotid artery disease, peripheral arterial disease, and abdominal aortic aneurysm. Then, individuals with a confirmed high or borderline high LDL reading should be further evaluated for other risk factors that would dictate the need for treatment: history of cigarette smoking; history of active hypertension (greater than 140/90 mmHG) or current medication treatment for hypertension; HDL cholesterol reading of less than or equal to 40 mg/dL; family history of CHD in a first degree relative (male relative55 years of age or younger; female relative 65 years of age or younger); and all men age 45 and older and all women age 55 and older. A treatment plan with the goals of cholesterol management therapy is developed based on a combination of the presence or absence of risk factors and then ten-year calculated CHD risk using the Framingham Tables that estimate risk. (Table 1 provides the Framingham Risk tables for males and females: Then, overall goals of

LDL management, including options for lifestyle changes, medication therapy, or both are assessed using Table 2 below. Lifestyle changes include weight management, increase physical activity, decrease daily intake of saturated fat, and increase intake of soluble fiber and plant sterols. Lifestyle changes should be implemented for three months and then individual should be evaluated for success. Medication therapy is then added if LDL goals not met through lifestyle changes or risk factors necessitate therapy. Pharmacists often play an integral role in developing and managing the treatment plans of individuals with high cholesterol.

III. Medication therapy options for treatment of cholesterol

Six classes of prescription medications currently exist for the treatment and management of increased cholesterol: statins (also known as HMG CoA reductase inhibitors); bile acid sequestrants; nicotinic acid; fibric acids and a new class of medications that inhibits intestinal absorption of cholesterol. Medication therapy is selected for an individual based upon his or her lipid profile and existing conditions.

Use of hormone replacement therapy in postmenopausal women had also previously been used to reduce cholesterol levels and the overall incidence of CHD. However, a recent study shows that women with high cholesterol should be treated with cholesterol lowering medications rather than hormone replacement therapy.

Statin medications

Statins provide the most powerful LDL-lowering affect of all existing options for treatment of high cholesterol. The mechanism of action occurs through inhibition of HMG CoA reductase, an enzyme that controls the early stages of catabolism and metabolism of LDL production and assists in lowering the level in the blood. Statins also increase hepatic metabolism of cholesterol, specifically the particulates of LDL. As a result of the success of statins in lowering LDL levels between 20-60%, these are currently the most prescribed class of medications for treating high cholesterol. In general statins have also been shown to lower triglyceride levels and show modest increases in HDL levels.

The following statins are available in the United States:

- Lovastatin and pravastatin are both generically available and therefore use of these agent might reduce costs for patients and provide effective reduction of LDL, generally 30%.
- Simvastatin, also generically available, is generally recommended for individuals who require LDL reductions of more than 30%, have heart disease or diabetes, or acute coronary syndrome without an elevated LDL.
- Lipitor® (atorvastin, Pfizer, Inc.) is indicated for use in individuals with a history of myocardial infarction with highly elevated LDL levels. Use is generally recommended for a period of two years and then consider change to simvastatin. Despite this recommendation, Lipitor remains a market force in the statin market but has lost some ground in the past two because of the reported efficacy of the lower-cost generic alternatives.
- Crestor® (rosuvsastatin calcium, AstraZeneca)has a relatively small market share because of controversial information published soon after its FDA approval in 2003. A 2005 study compared Crestor to Lipitor, simvastatin, and pravastatin, and found a three-fold increase in the potential for side effects with Crestor compared to the other three products.

Statins are given in the evening, either at dinnertime or at bedtime because the body produces more cholesterol during the overnight hours. Maximum effectiveness generally occurs within 4-6 weeks of therapy at which time LDLs are re-tested and the need for further therapy evaluated. Recommended dosages vary by product.

Side effects include mild to moderate gastrointestinal effects, including upset stomach, gas, constipation, and abdominal cramping. An increase in liver enzyme production represents a more serious concern with the use of statins. Patients should receive regular blood test to detect elevated liver enzyme levels and patients with substantial elevations should not use statins.

Renal failure caused by muscle weakness and deterioration have occurred with the use of statins. Symptoms include muscle soreness, pain and weakness, and urine discoloration because of increased release of creatinine. Individuals with these symptoms should be monitored for kidney failure. Furthermore, individuals that have a history of hypothyroidism or renal insufficiency should use statins with caution and the products are contraindicated for pregnant or nursing women.

Recently, the actual efficacy of statins in preventing heart disease has been called into question by a review of several scientific analyses conducted in the past 10 years. One analysis conducted in 2003 reviewed the results of three randomized controlled studies suggesting that the 3-5 year potential for MI or stroke prevention is only 1.4% or 1 in 71 people. This analysis further suggests that while statins provide some protection against MI or stroke, the death rate was approximately equal for individuals not taking statins compared to those prescribed statins. This does not suggest that patients should not be given statins, particularly for those individuals with other conditions that increase risk of cardiovascular death. However, treatment should be closely evaluated in individuals who might experience some of the more serious side effects associated with statin use.

Bile acid sequestrants

For purposes of this analysis, prescribing information for Colestid® (colestipol hydrochloride for oral suspension, Pfizer, Inc.) is used. These agents in this class work in a similar manner but exceptions with different medications are noted.

Cholesterol in the blood is a precursor of bile acids that are secreted in bile from the liver and the gall bladder into the intestines. Bileacid sequestrants work to bind bile acids in the intestines that are excreted in the feces. This process partially removes the bile acids from enterohepatic circulation and thus prevents reabsorption in the liver. The fecal loss of the bile acid binding agents also results in an increased oxidation of cholesterol to bile acids, causing an increased amount of available LDL receptors, increased uptake of hepatic LDL, leading to an increased clearance of LDL thus decreasing blood levels. LDL reductions of 10-20% are generally more modest compared to the statins. Therapy with these agents typically does notusually result in a change to triglyceride levels.

Three bile acid sequestrants products are marketed: cholestyramine, colestipol, and WelChol™ (colesevelam, Daiichi Sankyo, Inc.). All of these products are available as either a tablet or a powder. Use of these products have typically been proven safe after nearly 30 years of use. However, in addition to the more modest reductions in LDL levels compared to statins, the products also contain some other drawbacks, including inconvenient administration, gastrointestinal side effects, and contradictions when used concomitantly with certain other medications. Powered forms of the product must be mixed with water and are generally taken once or twice daily (in rare case three times a day might be required.) Multiple tablets must be taken with large amounts of water to avoid gastrointestinal side effects such as nausea, bloating,

or gas. The products are not effective against lowering triglyceride levels and therefore, combination therapy with statins is often necessary.

These products also bind other prescription medications, including tetracycline, furosemide, penicillin G, hydrochlorothiazide, and gemfibrozil and decrease their absorption. To avoid potential interactions, other medications should be taken 1 hour before or 4-6 hours after these agents.

Nicotinic acid (niacin)

Niacin is a water-soluble B vitamin that lowers total cholesterol, lowers LDL levels, lowers triglyceride levels, and raises HDL levels. Treatment generally results in LDL decreases of 10-20%, triglyceride decreases of 20-50%, and HDL increases of 15-35%.

Niacin is available in immediate release, timed release, and extended release forms, with the immediate release form recommended to begin therapy. Forms of nicotinic acid are also available over-the-counter as non-FDA approved food supplements, but if used in dosage levels necessary to lower cholesterol, self-medication is not recommended. Dosages typically begin at 1.5-3 grams daily for immediate release forms and 1.5-2 grams for other forms.

Side effects range from moderate to severe and often potentially result in discontinuation of therapy. In the beginning of therapy, patients often experience flushing that tends to diminish over time. Flushing occurs less frequently when using extended release forms, however, patients must be warned that if non-prescription niacin food supplements marketed as extended release agents are used improperly, liver failure might occur. This rationale supports exclusive use of prescription agents, such as Niaspan® (niacin extended release tablets, Abbott Laboratories) for cholesterol management. Niaspan has not been shown to cause liver failure based on empirical data but no clinical studies have been performed. Patients with a history of liver disease, other hepatic insufficiency, or excessive alcohol use should to use niacin products. Individual's liver function should be closely monitored during therapy and reports of muscle pain or weakness should warrant closer examination of liver function.

Other side effects and contraindications also require close monitoring. Individuals who take antihypertensive agents should be closely monitored when because niacin potentially increases the antihypertensive effects of some medications, including nitrates, calcium channel blockers, and beta adrenergic agents, resulting in the potential for postural hypotension. Empirical research suggests that concomitant use with aspirin could reduce the metabolic clearance of niacin resulting in increased potential for side effects, although no clinical studies confirm this finding. Individuals with diabetes should use niacin with caution because it has been shown to exacerbate glucose intolerance. Individuals with gout might experience elevations in uric acid. Finally, individuals who require anticoagulation therapy should be monitored closely because niacin has been shown to have a small but statistically significant dose related increase in prothrombin time.

Other side effects include gastrointestinal disorders such as nausea, vomiting, and gas. While these symptoms are generally mild, patients with peptic ulcer disorders might require discontinuation of medications.

Fibrates (gemfibrozil, colfibrate, fenofibrate)

Fibrates are used primarily to decrease triglyceride levels and VLDL in some patients and secondarily to increase HDL levels in others with specific types of hyperlipidemia. (Prescribing information for gemfibrozil is used in this article as an example of fibrates. Gemfibrozil has been shown to be more effective than colfibrate in reducing the incidence of coronary death than colfibrate.)

Patients who present a risk of pancreatitis with triglyceride levels of greater than 2000 mg/dL, elevated VLDL, and chylomicrons respond best to fibrates. Individuals at risk for coronary heart disease, with all of the following symptoms should consider fibrates as a treatment option: low HDL levels, elevated LDLs, and elevated triglycerides that have not responded to other therapy.

Typically fibrates are administered twice daily in the morning and the evening 30 minutes prior to a meal.

Use of fibrates presents a number of potential contraindications and therefore use should be limited to patients meeting all the requirements for use. Individuals with renal or hepatic insufficiency or a history of gall bladder disease should not use fibrates. When used in individuals who take anticoagulation therapy, the dosage of the anticoagulant should be reduced to ensure appropriate prothrombin time and levels of the anticoagulant closely monitored. Use with statins may increase muscle weakness and deterioration and has been shown to increase serum creatinine levels, leading to a greater risk of acute renal failure or death. Individuals should be monitored for renal insufficiency and other symptoms associated with decreases in renal function.

Other frequently sited adverse events that are less severe than those stated above include gastrointestinal issues, including stomach upset, nausea, diarrhea, and abdominal pain. Some individuals taking fibrates present with acute appendicitis that has been correlated with use of the drug.

Ezetimibe

Ezetimibe is a new chemical entity with a unique mechanism of action. Merck/Schering Plough currently markets two brand name products that contain this chemical: Zetia® (ezetimibe) and Vytorin® (ezetimibe/simvastatin). Ezetimibe inhibits total cholesterol in the blood by reducing the absorption of cholesterol by the small intestine leading to a decrease in the amount of cholesterol delivered to the liver. Ezetimibe has been effective in lowering total cholesterol, LDL, apolipoprotein B, and triglycerides as well as increase HDL. Use in combination with a statin or use of the combination product Vytorin has helped to enhance the effects of the product. Use of ezetimibe in combination with fenofibrate has also shown to improve lipid profiles for certain individuals who have hyperlipidemia associated with a mixture of reasons. Studies have not determined the impact of morbidity and mortality associated with cardiovascular disease when ezetimibe is used alone or in combination with other products.

Zetia is generally administered as a 10 mg dose once daily and can be taken with or without food. Likewise, Vytorin, the combination of ezetimibe/simvastatin, is also doses one time daily with dosages ranging from 10 mg/10 mg to 10 mg/80 mg.

To date, ezetimibe has been shown to be very safe with a limited number of contraindications with other medications. Specifically, the product should be used cautiously with cyclosporine, particularly patients with renal insufficiency, because of the risk of increased concentrations of both medications.

The drug should not be used if an individual experiences hypersensitivity to the product. Individuals with existing hepatic insufficiency should not use ezetimibe. When using Vytorin or using ezetimibe in combination with another statin, the cautions against use in individuals with elevated liver enzymes, pregnancy, and lactation, should be followed.

Side effects were similar to the statin products, including muscle pain, weakness, and other gastrointestinal effects. Individuals receiving a combination of ezetimibe and a statin were more likely to experience these adverse effects.

IV. The Role of the Pharmacist in Managing Patients with High Cholesterol

Lipid disorders generally do not manifest symptoms and therefore, individuals should be encouraged to be tested by pharmacists. Research has shown that most of the adult population in the United States is at risk for lipid disorders and the potential for the cardiovascular disorders and therefore screening is critical.

Pharmacists' interventions have been shown to positively impact the outcomes associated proactive lipid management. In 2000, the American Pharmacists Association Foundation published the results of Project ImPACT detailing the outcomes associated with pharmacists' care in hyperlipidemia. Twenty-six pharmacies, including chain and independent community, home health and clinics, participated to examine the behaviors and medication compliance rates for 397 individuals over a period of 24.6 months. Overall the study found that medication compliance rates were 93.6% and 90.1% with 62.5% of patients achieving the NCEP goals.

In this study, pharmacists received referrals from prescribers of individuals newly diagnosed with dyslipidemia or patients who self-referred. Pharmacists collected the appropriate patient information to determine the risks associated with cardiovascular disease. Pharmacists then determined fasting lipid levels using a proprietary device using a finger stick. Results were then logged and patients then received monthly follow-up visits for a period of three months and then quarterly thereafter. Initial visits totaled 20-30 minutes and then subsequent visits totaled 10-30 minutes. Pharmacists tracked progress associated with compliance, CAD risks, NCEP goals, and cholesterol test results. When pharmacists made recommendations to prescribers suggesting modification or changes in patient medication regimens, these changes were accepted 76.6% of the time.

Pharmacists who submitted payments to third party plans for counseling services received a 53% payment rate. Some plans paid only for the lipid profile and others paid for counseling, while some paid for both. Two sites successfully secured contracts to provide these services to individuals in a health plan.

The process used by Project imPACT can be replicated by other pharmacies. Research continues to evolve regarding cholesterol management using medications. Health plans and Medicare Part D plans will scrutinize this literature and possibly seek to provide incentives to both patients and health care professionals who can meet therapeutic goals, including for cholesterol management. The pharmacist as a health care professional with regular access to the public can play a crucial role in this area.

V. Summary

Dyslipidemia continues to be a major public health issue in the United States and other developed nations. Management of the condition generally includes a combination of lifestyle changes and medication. Individuals must be consistently monitored to ensure that they are meeting the goals of therapy and for common side effects associated with medications for lipid management. Pharmacists should understand the impact of the medication on the patient as well as the potential costs associated with the medication. Recently, effective medications for cholesterol management have been approved in generic form. Pharmacists should ensure that they educate themselves about new medications and not simply rely on direct-to-consumer advertising as a primary form of education. By arming themselves with the most current clinical evidence, generic approvals for cholesterol-lowering medications, and the risks and benefits of newer medications, pharmacists can help patients achieve their goals and manage therapy properly.

References available on request.

Table 1

Estimate of 10-Year Risk for Men
Framingham Point Scores by Age Group

Age	Points
20-34	-9
35-39	-4
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	11
70-74	12
75-79	13

Framingham Point Scores by Age Group and Total Cholesterol

Total Cholesterol	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	0
200-239	7	5	3	1	0
240-279	9	6	4	2	1
280+	11	8	5	3	1

Framingham Point Scores by Age and Smoking Status

	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

Framingham Point Scores by HDL Level

HDL	Points
60+	-1
50-59	0
40-49	1
<40	2

Framingham Point Scores by Systolic Blood Pressure and Treatment Status

Systolic BP	If Untreated	If Treated
<120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
160+	2	3

10-Year Risk by Total Framingham Point Scores

Point Total	10-Year Risk
< 0	< 1%
0	1%
1	1%
2	1%
3	1%
4	1%
5	2%
6	2%
7	3%
8	4%
9	5%
10	6%
11	8%
12	10%
13	12%
14	16%
15	20%
16	25%
17 or more	≥30%

Estimate of 10-Year Risk for Women
Framingham Point Scores by Age Group

Age	Points
20-34	-7
35-39	-3
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	12
70-74	14
75-79	16

Framingham Point Scores by Age Group and Total Cholesterol

Total Cholesterol	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	1
200-239	8	6	4	2	1
240-279	11	8	5	3	2
280+	13	10	7	4	2

Framingham Point Scores by Age and Smoking Status

	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

Framingham Point Scores by HDL Level

HDL	Points
60+	-1
50-59	0
40-49	1
<40	2

Framingham Point Scores by Systolic Blood Pressure and Treatment Status

Systolic BP	If Untreated	If Treated
<120	0	0
120-129	1	3
130-139	2	4
140-159	3	5
160+	4	6

10-Year Risk by Total Framingham Point Scores

Point Total	10-Year Risk
< 9	< 1%
9	1%
10	1%
11	1%
12	1%
13	2%
14	2%
15	3%
16	4%
17	5%
18	6%
19	8%
20	11%
21	14%
22	17%
23	22%
24	27%
25 or more	≥30%

From the National Cholesterol Education Program website: http://www.nhlbi.nih.gov/guidelines/cholesterol/risk_tbl.htm

Table 2

STEP 1: Determine lipoprotein levels - obtain complete lipoprotein profile after 9- to 12-hour fast.

ATP III Classification of LDL, Total, and HDL Cholesterol (mg/dL)

- **LDL Cholesterol - Primary Target of Therapy**

<100	Optimal
100-129	Near Optimal/Above Optimal
130-159	Borderline High
160-189	High
≥190	Very high

- **Total Cholesterol**

<200	Desirable
200-239	Borderline High
≥240	High

- **HDL Cholesterol**

<40	Low
≥60	High

STEP 2: Identify presence of clinical atherosclerotic disease that confers high risk for coronary heart disease (CHD) events (CHD risk equivalent):

- Clinical CHD
- Symptomatic carotid artery disease
- Peripheral arterial disease
- Abdominal aortic aneurysm.

STEP 3: Determine presence of major risk factors (other than LDL):

Major Risk Factors (Exclusive of LDL Cholesterol) That Modify LDL Goals

- Cigarette smoking
- Hypertension (BP ≥140/90 mmHg or on antihypertensive medication)
- Low HDL cholesterol (<40 mg/dl)*
- Family history of premature CHD (CHD in male first degree relative <55 years; CHD in female first degree relative <65 years)
- Age (men ≥45 years; women ≥55 years)

* HDL cholesterol ≥60 mg/dL counts as a "negative" risk factor; its presence removes one risk factor from the total count.
Note: in ATP III, diabetes is regarded as a CHD risk equivalent.

STEP 4: If 2+ risk factors (other than LDL) are present without CHD or CHD risk equivalent, assess 10-year (short-term) CHD risk (see Framingham tables).

Three levels of 10-year risk:

- >20% -- CHD risk equivalent
- 10-20%
- <10%

STEP 5: Determine risk category:

- Establish LDL goal of therapy
- Determine need for therapeutic lifestyle changes (TLC)
- Determine level for drug consideration

LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories.

Risk Category	LDL Goal	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (TLC)	LDL Level at Which to Consider Drug Therapy
CHD or CHD Risk Equivalents (10-year risk >20%)	<100 mg/dL	≥100 mg/dL	≥130 mg/dL (100-129 mg/dL: drug optional)*
2+ Risk Factors (10-year risk ≤20%)	<130 mg/dL	≥130 mg/dL	10-year risk 10-20%: ≥ 130 mg/dL 10-year risk <10%: ≥ 160 mg/dL
0-1 Risk Factor**	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)

** Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.*

*** Almost all people with 0-1 risk factor have a 10-year risk <10%, thus 10-year risk assessment in people with 0-1 risk factor is not necessary.*

STEP 6: Initiate therapeutic lifestyle changes (TLC) if LDL is above goal.

TLC Features

- TLC Diet:
  - Saturated fat <7% of calories, cholesterol <200 mg/day
  - Consider increased viscous (soluble) fiber (10-25 g/day) and plant stanols/sterols (2g/day) as therapeutic options to enhance LDL lowering
- Weight management
- Increased physical activity

STEP 7: Consider adding drug therapy if LDL exceeds levels shown in Step 5 table:

- Consider drug simultaneously with TLC for CHD and CHD equivalents
- Consider adding drug to TLC after 3 months for other risk categories.

Drugs Affecting Lipoprotein Metabolism

Drug Class	Agents and Daily Doses	Lipid/Lipoprotein Effects	Side Effects	Contraindications
HMG CoA reductase inhibitors (statins)	Lovastatin (20-80 mg), Pravastatin (20-40 mg), Simvastatin (20-80 mg), Fluvastatin (20-80 mg), Atorvastatin (10-80 mg), Cerivastatin (0.4-0.8 mg)	LDL-C ↓18-55% HDL-C ↑5-15% TG ↓ 7-30%	Myopathy Increased liver enzymes	Absolute: □ Active or chronic liver disease Relative: □ Concomitant use of certain drugs*
Bile acid Sequestrants	Cholestyramine (4-16 g) Colestipol (5-20 g) Colesevelam (2.6-3.8 g)	LDL-C ↓15-30% HDL-C ↑3-5% TG No change or increase	Gastrointestinal distress Constipation Decreased absorption of other drugs	Absolute: □ dysbeta-lipoproteinemia □ TG >400 mg/dL Relative: □ TG >200 mg/dL
Nicotinic acid	Immediate release (crystalline) nicotinic acid (1.5-3 gm), extended release nicotinic acid (Niaspan ®) (1-2 g), sustained release nicotinic acid (1-2 g)	LDL-C ↓5-25% HDL-C ↑15-35% TG ↓20-50%	Flushing Hyperglycemia Hyperuricemia (or gout) Upper GI distress Hepatotoxicity	Absolute: □ Chronic liver disease □ Severe gout Relative: □ Diabetes □ Hyperuricemia □ Peptic ulcer disease
Fibric acids	Gemfibrozil (600 mg BID) Fenofibrate (200 mg) Clofibrate (1000 mg BID)	LDL-C ↓5-20% (may be increased in patients with high TG) HDL-C ↑10-20% TG ↓20-50%	Dyspepsia Gallstones Myopathy	Absolute: □ Severe renal disease □ Severe hepatic disease

* Cyclosporine, macrolide antibiotics, various anti-fungal agents, and cytochrome P-450 inhibitors (fibrates and niacin should be used with appropriate caution).

STEP 8: Identify metabolic syndrome and treat, if present, after 3 months of TLC.

Clinical Identification of the Metabolic Syndrome - Any 3 of the Following:

Risk Factor	Defining Level
Abdominal obesity* Men Women	Waist circumference** >102 cm (>40 in) >88 cm (>35 in)
Triglycerides	≥150 mg/dL
HDL cholesterol Men Women	<40 mg/dl <50 mg/dl
blood pressure	≥130/≥85 mmHg
Fasting glucose	≥110 mg/dL

** Overweight and obesity are associated with insulin resistance and the metabolic syndrome. However, the presence of abdominal obesity is more highly correlated with the metabolic risk factors than is an elevated body mass index (BMI). Therefore, the simple measure of waist circumference is recommended to identify the body weight component of the metabolic syndrome.*

*** Some male patients can develop multiple metabolic risk factors when the waist circumference is only marginally increased, e.g., 94-102 cm (37-39 in). Such patients may have a strong genetic contribution to insulin resistance. They should benefit from changes in life habits, similarly to men with categorical increases in waist circumference.*

Treatment of the metabolic syndrome

- Treat underlying causes (overweight/obesity and physical inactivity):
  - Intensify weight management
  - Increase physical activity
- Treat lipid and non-lipid risk factors if they persist despite these lifestyle therapies:
  - Treat hypertension
  - Use aspirin for CHD patients to reduce prothrombotic state
  - Treat elevated triglycerides and/or low HDL (as shown in Step 9 below)

STEP 9: Treat elevated triglycerides.

ATP III Classification of Serum Triglycerides (mg/dL)

< 150	Normal
150-199	Borderline high
200-499	High
≥500	Very high

Treatment of elevated triglycerides (≥150 mg/dL)

- Primary aim of therapy is to reach LDL goal.
- Intensify weight management.
- Increase physical activity.
- If triglycerides are ≥200 mg/dL after LDL goal is reached, set secondary goal for non-HDL cholesterol (total - HDL) 30 mg/dL higher than LDL goal.

Comparison of LDL Cholesterol and Non-HDL Cholesterol Goals for Three Risk Categories

Risk Category	LDL Goal (mg/dL)	Non-HDL Goal (mg/dL)
CHD and CHD Risk Equivalent (10-year risk for CHD >20%)	<100	<130
Multiple (2+) Risk Factors and 10-year risk ≤20%	<130	<160
0-1 Risk Factor	<160	<190

If triglycerides 200-499 mg/dL after LDL goal is reached, consider adding drug if needed to reach non-HDL goal:

- intensify therapy with LDL-lowering drug, or
- add nicotinic acid or fibrate to further lower VLDL.

If triglycerides ≥500 mg/dL, first lower triglycerides to prevent pancreatitis:

- very low-fat diet (≤15% of calories from fat)
- weight management and physical activity
- fibrate or nicotinic acid
- when triglycerides <500 mg/dL, turn to LDL-lowering therapy.

Treatment of low HDL cholesterol (<40 mg/dL)

- First reach LDL goal, then:
- Intensify weight management and increase physical activity.
- If triglycerides 200-499 mg/dL, achieve non-HDL goal.
- If triglycerides <200 mg/dL (isolated low HDL) in CHD or CHD equivalent, consider nicotinic acid or fibrate.

From NIH Publication No. 01-3305, May 2001
http://www.nhlbi.nih.gov/guidelines/cholesterol/atglance.htm#Step1