Heart disease continues to be the leading cause of death for both men and women in the United States. According to the Centers for Disease Control and Prevention (CDC), one of every four deaths is from heart disease. The primary risk factors for CVD are high blood pressure, elevated cholesterol levels, and smoking. Other lifestyle factors such as obesity, a sedentary lifestyle, poor diet, and excessive alcohol intake also may increase risk. Elevated cholesterol levels have been shown to double the risk of heart attacks. The CDC estimates that less than one-half of people with high cholesterol levels get treatment for the condition, putting these individuals at an even greater risk of a cardiovascular event.¹

Cholesterol is a waxy, fatlike substance the body uses to make hormones, vitamin D, and other critical enzymes. The body needs some cholesterol to function properly and can make most of the cholesterol it needs, but cholesterol also comes from animal foods in the diet. Cholesterol is carried through the body in packages called lipoproteins, which help transport fats. The two most important lipoproteins related to heart health are LDL and HDL. LDL cholesterol is linked to CVD because it can build up in the arteries, blocking the passage of blood and leading to a heart attack or stroke. HDL cholesterol works against LDL cholesterol to clear it from the body by returning it to the liver. For a low risk of heart disease, it’s recommended to have a low LDL level and a high HDL level. In the United States, approximately 32% of the population has an elevated LDL level.² ³ Having high cholesterol produces no symptoms, so a blood test is required to diagnose the condition. It’s recommended that cholesterol be checked every five years. Ideal cholesterol levels are: total, less than 200 mg/dL; LDL, less than 100 mg/dL; and HDL, 40 to 60 mg/dL and higher.⁴

The American Heart Association (AHA) has created guidelines to help physicians reduce the risk of heart attacks in their patients. An important part of heart attack prevention as determined by these guidelines is the close management of cholesterol levels along with the use of medications to lower levels if needed.⁵ Of those patients taking cholesterol-lowering medications, 93% are prescribed a statin, making statins one of the most widely used medications in the United States. It’s estimated that 32 million Americans take a statin medication.⁶ According to data from the National Health and Nutrition Examination Survey, the use of statin medications increased from 20% in 2003 to 28% in 2012.⁷
With the increasing rates of statin medication use, it’s important for RDs to be informed about their use as well as any potential side effects or food-drug interactions. RDs can help counsel patients taking statin medications to make lifestyle changes to further lower their risk of heart attack and stroke. Dietitians also may suggest alternative therapies for patients unable to tolerate the side effects of statins.

This continuing education course examines the history of the use of statin medications, as well as the role RDs play in the management of patients with hyperlipidemia. It addresses food-drug interactions, medication side effects, and complementary therapies to help manage patients at risk of heart attack or stroke.

**History of Cholesterol**

Since cholesterol was discovered in 1758, researchers who studied it have been awarded 13 Nobel Prizes, making it one of the most important research topics for more than a century. French scientist François-Paul-Lyon Poulletier de la Salle first discovered cholesterol when isolating it from gallstones. In 1816, another French scientist, Michel-Eugène Cheyruel, observed the lipidlike characteristics of this substance and named it “cholesterine.” In 1913, Nicolaï Anitschkow, a Russian scientist, fed pure cholesterol to rabbits, which caused the development of severe atherosclerosis in the aorta. This study was the first to link cholesterol to the development of heart disease, but Anitschkow’s findings weren’t widely accepted at the time. It wasn’t until the 1940s that research into the cholesterol and heart disease connection began to emerge. By the 1950s and 1960s, strong clinical evidence emerged about the connection between high blood cholesterol and heart disease. John Gofman, PhD, a researcher at the University of California at Berkeley, was the first to use a centrifuge to separate plasma lipoproteins. He also identified that heart attacks were more common when the blood contained greater amounts of LDL and less common when HDL levels were elevated.

In the mid-1940s, President Franklin D. Roosevelt died from heart disease, which already had become the leading cause of death among Americans. After President Roosevelt’s death, the government initiated a large-scale research study on cardiovascular health, conducted by the National Heart, Lung, and Blood Institute, previously known as the National Heart Institute. The study, which took place in Framingham, Massachusetts due to its proximity to Harvard Medical School and the participation of several local physicians, became known as the Framingham Heart Study. Data from the study allowed researchers to develop criteria for identifying heart failure as well as risk factors that lead to heart attacks, such as elevated cholesterol and blood pressure. In 1977, data from the Framingham study identified a connection between elevated LDL levels and heart disease risk, as well as the protective benefit of high levels of HDL. The Framingham Heart Study continues and is already on its third group of participants after 65 years of collecting data on heart disease.

At about the same time the Framingham study was initiated, the connection between blood cholesterol and heart disease was being evaluated further via the epidemiologic studies of Ancel Keys, PhD, a researcher from the University of Minnesota. Keys began
his famous Seven Countries Study in the mid-1960s after a trip to Europe, where he noticed a potential connection between high-fat diets and heart attack rates. This observation led to further research to determine whether this connection was true across various populations and cultures. Before Keys’ Seven Countries study, atherosclerosis and cholesterol levels had been assessed only in animals that had been fed high-fat or high-cholesterol diets and hadn’t been observed in humans. Keys’ Seven Countries Study followed 15,000 men over 10 years and found that blood cholesterol levels were proportional to the incidence of heart attacks.¹⁴

Based on the collection of epidemiologic and animal studies, the connection between heart disease and elevated cholesterol levels is well defined. Because heart disease remains the primary cause of death in the United States, it’s no surprise that any medication that will effectively lower cholesterol levels, such as statins, is widely prescribed by physicians.

History of Statins
Cholesterol found in the blood comes from the diet or is synthesized by the liver. Once adequate amounts of cholesterol have been absorbed from dietary sources, the liver is supposed to stop producing cholesterol to prevent excess. An enzyme called HMG-CoA reductase, which aids in the conversion of HMG-CoA to mevalonate, controls the suppression of cholesterol production in the liver. Therefore, the ability to control this particular rate-limiting step in cholesterol production would reduce overall cholesterol levels in the body. Once this process was identified, scientists began to investigate various methods to help reduce the activity of HMG-CoA reductase, hoping to lower plasma cholesterol.¹⁵ The discovery of a medication to help control cholesterol became desirable as research continued to link elevated blood cholesterol levels to an increased risk of heart attacks.

Several attempts were made in the 1950s and ’60s to develop a medication to block the cholesterol pathway in the body. One of the first medications to be discovered was Triparanol, or MER/29. Although this medication did lower cholesterol levels, it was soon pulled from the market because it caused cataracts and led to a build-up of other sterols in the body.¹⁶ In 1955, the cholesterol-lowering properties of niacin were discovered, and a class of medications called fibrates was developed from niacin.¹⁷ The cholesterol-lowering ability of fibrates, however, was found to be minimal and not as effective as desired.

Researchers continued to work to identify a way to reduce the activity of HMG-CoA reductase to lower cholesterol levels. A compound called compactin, isolated from blue-green algae, was found to be successful at lowering cholesterol levels in patients with familial hypercholesterolemia. But development of this drug was stopped due to evidence that it caused lymphoma in dogs.¹⁸ After the demonstrated success of compactin, Merck Research Laboratories isolated another similar compound from a fungus called mevinolin; that compound would eventually be renamed lovastatin.¹⁹ Once lovastatin was tested in humans, it was shown to reduce LDL cholesterol levels significantly.²⁰ This led to multiple studies on the use of lovastatin to treat cholesterol
levels, all of which showed very promising results. By 1986, Merck sent a new drug application to the FDA, and lovastatin became the first commercial statin to hit the market. Since Merck received approval to produce lovastatin, statins have been tested in multiple clinical trials and consistently have been shown to lower LDL cholesterol levels and heart attack risk by approximately 30%. The long-term studies on statin medications show few adverse effects, and it's generally believed that the benefits significantly outweigh the potential risks of muscle pain or liver damage.

Today, statins are the most commonly prescribed medications in the United States, with sales topping $20 billion per year. Several statins are available on the market, sold under names such as Lipitor (atorvastatin), Zocor (simvastatin), Mevacor (lovastatin), Crestor (rosuvastatin), Lescol (fluvastatin), and Pravachol (pravastatin). Lipitor is the most commonly used statin in the United States.

**Practice Guidelines for the Use of Statins**

The AHA has developed guidelines to help determine who would most benefit from the use of statin medications to lower the risk of heart disease. The latest guidelines, updated in 2013, estimate that about one-third of adults would benefit from the use of statins to help reduce their risk of cardiovascular events. The guidelines outline four groups that would particularly benefit from statin therapy:

- patients who already have had a cardiovascular event;
- patients who have an LDL cholesterol level higher than 190 mg/dL;
- patients with diabetes who are older than age 40 and have an LDL level higher than 70 mg/dL; and
- patients older than 40 who have a 7.5% risk of having a heart attack in the next 10 years.

The AHA provides a risk calculator with which physicians can determine each individual’s 10-year risk of CVD. The calculator allows the physician to enter demographic data such as gender, age, and ethnicity, as well as basic medical information such as current cholesterol levels and blood pressure. The risk estimator then provides a risk percentage and recommendations for statin usage if the patient is at high risk. The guidelines also suggest ideal dosages of each statin medication and approximately how much each statin would lower LDL cholesterol levels. The AHA no longer recommends specific cholesterol target levels for patients receiving statin treatment, but instead recommends that physicians prescribe the maximum dosage tolerated for those at risk of cardiovascular events, as identifying target levels may lead to undertreating patients at risk. These guidelines are meant to direct physicians on the treatment of those at risk of cardiovascular events and to lower the incidence of heart attacks in the United States.

Statins are considered safe, with the benefits outweighing potential adverse effects. Over time, with more research on the use of these medications, some concern has been raised about possible adverse effects for a small percentage of users. In 2012, the FDA released a consumer safety information bulletin on the use of statins; issues of
concern included the possibility of liver failure, reports of memory loss and cognitive impairment, an increased risk of elevated blood sugar, and the potential for muscle damage or myopathy.27

Muscle pain is the most commonly reported side effect of statin use, affecting approximately 10% to 25% of people taking the medication.28 It’s unclear why a certain percentage of the population is affected by statins in this way, but several hypotheses are being investigated, including genetic variances and mitochondrial dysfunction caused by statins.29,30 Another theory is that cholesterol is a critical component of cell membranes, including muscle cells, and the reduction of cholesterol levels may make cells unstable and less fluid.31 Muscle pain also was thought to be caused by coenzyme Q10 (CoQ10) depletion, as statins block the metabolic pathway that creates CoQ10. But research hasn’t found that CoQ10 is depleted in muscle tissue, and studies evaluating supplementation with CoQ10 haven’t shown consistent improvement in muscle pain.32 Although the exact cause of statin-related myopathy is unknown, it’s believed to be dose related. It’s more common in female patients, those with a smaller body frame, individuals of Asian ethnicity, and older patients.33 A more serious adverse effect of statin use is rhabdomyolysis, a severe form of muscle damage that also affects kidney function. However, meta-analysis data don’t indicate that rhabdomyolysis is a common side effect.34

Cognitive problems also have been identified as potential side effects of statin use. There are several case reports of patients who experienced memory loss while taking statins, which generally improved after the discontinuation of the medication.35 The research, however, is mixed on the connection between cognitive impairment and statin use. A 2008 study by Cramer and colleagues, published in *Neurology*, followed participants taking statins over five years, with cognitive evaluations conducted every 12 to 15 months. Those who took statins during the study period were half as likely to develop dementia as were those who didn’t take statins. Further investigation is needed to determine whether statins are possibly protective against or contribute to the development of cognitive issues. The exact cause of statin-related side effects remains unknown, although the primary theories are related to changes in cholesterol metabolism via HMG-CoA reductase and its end products.

**Dietary Considerations**

Identification and management of food-drug interactions is a critical part of the RD’s role. Although statins have few significant food-drug interactions, there are a few foods that may influence the efficacy of the treatment and therefore should be discussed with patients taking statins.

Certain statins should be taken with food, while others should be taken on an empty stomach to increase bioavailability. Specifically, lovastatin should be taken with food for increased absorption of the medication, whereas rosuvastatin absorption is significantly decreased if taken on a full stomach and therefore should be taken on an empty stomach. The efficacy of other statin medications, such as simvastatin, pravastatin, and fluvastatin, doesn’t seem to be influenced by a full or empty stomach.36
Dietary fiber generally is recommended to help lower cholesterol. But there have been several studies showing that various types of dietary fiber or high-fiber foods can interfere with the absorption of statin medications. A 2011 study found that mice given oat bran in addition to atorvastatin showed no significant change in LDL levels when compared with mice given either oat bran or atorvastatin alone. It’s believed that bran inhibits intestinal absorption of the medication. Similar results have been seen with pectin and oat bran with lovastatin. Richter and colleagues found that LDL cholesterol levels increased while patients on lovastatin were consuming additional fiber, whereas levels decreased after the fiber was stopped. A different type of fiber, psyllium, was found to improve the efficacy of lovastatin in a study by Agrawal and colleagues in 2007. Thirty-six subjects were given lovastatin alone, psyllium alone, or a combination of psyllium and lovastatin for four weeks. The psyllium plus lovastatin group showed a significant decrease in LDL, total cholesterol, and triglyceride levels, demonstrating an additive effect. A similar result was found in another study using simvastatin and psyllium in combination to lower LDL cholesterol.

Grapefruit juice interacts with many drugs, as it modifies the body’s metabolism of certain medications. Grapefruit contains furanocoumarins and flavonoids that can interfere with the efficacy of statin medications. A study by Lilja and colleagues investigated the effect of grapefruit juice on the metabolism of simvastatin. Ten participants drank 200 mL of grapefruit juice or 200 mL of water over three days. On the third day a single dose of simvastatin was administered to both the experimental and control groups. Plasma levels of simvastatin were measured over 24 hours. Researchers found that those who drank the grapefruit juice had significantly higher levels of plasma simvastatin than did those who were given only water. Lilja and colleagues also evaluated the effect of grapefruit juice on the use of atorvastatin and pravastatin. They discovered that grapefruit juice had no effect on pravastatin, but increased absorption of atorvastatin. Due to the effect grapefruit juice may have on the medications, it’s generally recommended that patients taking statins avoid grapefruit or grapefruit juice.

Only a few studies have evaluated the interaction between alcohol intake and statin medications. A study by Smit and colleagues assessed the effect of alcohol consumption on a single dose of fluvastatin. For participants who consumed alcohol with the medication, there was a significantly shorter medication half-life than there was for those who didn’t consume alcohol. But overall, there was no significant difference in the lipid profile of any of the participants, regardless of alcohol consumption. Smit and colleagues also conducted a longer study to evaluate alcohol intake and the efficacy of statins over six weeks and found similar results, with no significant impact of alcohol consumption on the efficacy of the medication. There have been no studies on specific types of alcohol, such as wine, and their effect on statin medications.

Overall, with the exception of grapefruit juice, there are few food-drug interactions with statin medications. It’s important to recommend that patients read the medication labels closely and follow all instructions related to the specific statin they’ve been prescribed.
Alternatives to Statins

Due to side effects, some patients may not be able to tolerate statin medications and thus remain at high risk of CVD. For these patients, there are some alternatives to statin medications that may help lower cholesterol as well as heart attack risk. These include therapeutic diets, omega-3 fats, and plant sterols and stanols.

Lifestyle changes have been tried as a complementary treatment to statin therapy. Unfortunately, most studies on dietary modification have shown little effect on cholesterol levels. Schaefer and Brousseau found only a 5% reduction in LDL levels after nine weeks following the AHA Step 2 diet. But that reduction of LDL also resulted in a reduction in HDL and therefore didn’t improve lipid ratios or lower the risk of heart attacks. The only diet that has shown any significant improvements in lipid levels, according to current research, is the diet created by Dean Ornish, MD, a very strict, low-fat, low-cholesterol, vegetarian diet. The Ornish diet restricts fat to 7% of calories, limits dietary cholesterol to 12 mg per day, and excludes all oils, even monounsaturated oils. The diet also includes an exercise and stress reduction component. After a year on the Ornish diet, 48 patients had an average of 37% reduction in LDL cholesterol. Adherence to the diet also resulted in a decrease in coronary artery lesions. There’s ongoing larger-scale research on Ornish’s findings to see whether the results can be replicated. The main criticisms of the Ornish diet are that adherence is nearly impossible for most people and that the diet may be too high in carbohydrates, possibly leading to elevated triglyceride levels.

Exercise has been shown to play a role in helping modify LDL to HDL ratios by raising HDL levels. A 1991 study by Wood and colleagues investigated the effect of a low-calorie diet alone or a low-calorie diet paired with exercise over one year in overweight, sedentary participants. Those who exercised and followed a lower-calorie diet had significantly increased HDL levels than did those who only followed the diet without any increased exercise. Stefanick and colleagues completed another similar study using the Step 2 diet (which was then endorsed by both the AHA and the National Cholesterol Education Program) in addition to exercise and found a significant reduction in LDL levels for those participants in the diet plus exercise group. Based on these two studies, it’s important to encourage exercise in any patient with elevated cholesterol levels.

Omega-3 fatty acids have been identified as cardioprotective in that fish intake has been shown to reduce heart attack risk in multiple studies. Omega-3s are believed to have an antiarrhythmic effect that may be protective against heart disease. The anti-inflammatory properties also may lower heart attack risk. Although omega-3 fats may be protective against CVD, they haven’t been shown to lower LDL cholesterol levels. Omega-3 fatty acids may not be an alternative to statin treatment but have shown promise in helping reduce cardiovascular risk and triglyceride levels when used in conjunction with statins. A 2001 study found that patients who received simvastatin in addition to an omega-3 supplement for 24 weeks showed a 20% to 30% reduction in serum triglyceride levels when compared with those who received the simvastatin alone. One review of research on omega-3 supplements and triglyceride levels found
that approximately 1 g per day of omega-3s from fish is needed to lower cholesterol levels, and as little as 0.21 g EPA and 0.12 g DHA from supplements significantly lowered triglyceride levels. Therefore, omega-3 supplements or an increased intake of omega-3s from food such as fish can be safely recommended to patients on statin medications.

Plants contain small quantities of a compound called phytosterols that are chemically similar in structure to cholesterol. Ingesting large quantities of phytosterols blocks dietary cholesterol absorption in the digestive system, decreasing the amount of cholesterol that enters the blood. A 2008 review of the studies on plant sterols found that they decreased LDL levels by an average by 0.31 mmol/L across all studies when compared with a placebo. The reviewers found that reductions in LDL were greater when the sterols were consumed in fat-based spreads such as mayonnaise and salad dressing. Plant sterols need to be taken consistently to help lower serum cholesterol levels. There are several products on the market, including margarine and dairy-based beverages that contain sterols, available at most grocery stores.

Although there are no lifestyle or dietary modifications that lower cholesterol as significantly as do statin medications, exercise, omega-3 fats, and phytosterols may help reduce cholesterol levels and can be recommended as complementary therapies.

**Bottom Line**

Statin medications, due to their overall efficacy and safety profile, will continue to be used as primary forms of prevention for those at risk of CVD due to elevated cholesterol levels. RDs can assist patients using statin therapy in making beneficial lifestyle changes, suggest alternative therapies that may work in conjunction with statin medications, and identify any potential side effects of the medications.

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**References**


Quiz

1. What are the primary risk factors for CVD?
   A. Sedentary lifestyle and a high-fat diet
   B. High blood pressure, elevated cholesterol levels, and smoking
   C. Alcohol intake, eating red meat, and smoking
   D. Obesity, high cholesterol, and alcohol intake

2. What does cholesterol do in the body?
   A. Makes hormones and enzymes
   B. Clogs arteries
   C. Helps metabolize fats
   D. Increases metabolism

3. Approximately what percent of the US population has elevated LDL cholesterol?
   A. 16%
   B. 32%
   C. 44%
   D. 69%

4. What is the American Heart Association’s (AHA) target level for LDL cholesterol for patients on statins?
   A. Below 200 mg/dL
   B. Above 150 mg/dL
   C. Below 100 mg/dL
   D. It doesn’t have a target level for patients on statins.

5. What study played a critical role in connecting heart attack risk and elevated cholesterol?
   A. The Framingham Study
   B. National Health and Nutrition Examination Survey
   C. Anitschkow’s 1960s rabbit study
   D. The AHA Step 2 diet study

6. How do statins work?
   A. They block cholesterol absorption from the diet.
   B. They remove cholesterol from the arteries.
   C. They interfere with the HMG-CoA reductase pathway.
   D. They prevent the conversion of dietary fat to cholesterol.
7. Statins generally lower heart attack risk by what percent?
   A. 5%
   B. 10%
   C. 30%
   D. 50%

8. What's the most common side effect of statin use?
   A. Muscle pain
   B. Memory loss
   C. Liver failure
   D. Stomach upset

9. What's the drug-nutrient interaction between dietary fiber and statins?
   A. Fiber lowers cholesterol, but has no effect on statins.
   B. Fiber and statins work together synergistically to lower cholesterol.
   C. Fiber can reduce absorption of statin medications, reducing efficacy.
   D. Fiber has no effect on cholesterol or on statin medications.

10. How do omega-3 fats help lower heart attack risk?
    A. By lowering cholesterol levels
    B. By preventing absorption of cholesterol from the diet
    C. By lowering inflammation levels
    D. By unclogging blocked arteries