

# Cholesterol

## Highlights

### Total Cholesterol Goals

A blood test is used to measure cholesterol levels. A person's total cholesterol count includes measurements of low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides. Standard total cholesterol goals for adults are:

- Less than 200 mg/dL is desirable
- Between 200 - 239 mg/dL is considered borderline
- Over 240 mg/dL is considered high

### Lifestyle Changes

The first step to improving cholesterol levels is through lifestyle changes (especially diet and exercise). Even when drug therapy is required, lifestyle changes are also necessary. These include:

- Eat a heart-healthy diet with plenty of fiber-rich fruits and vegetables. Avoid saturated fats (found mostly in animal products) and trans-fatty acids (found in fast foods and commercially baked products). Instead, choose unsaturated fats (particularly omega-3 fatty acids found in fish oils and canola).
- Exercise regularly. Studies have shown that regular aerobic exercise can help boost HDL ("good" cholesterol) levels.
- Quit smoking.
- No dietary supplements have been shown to improve cholesterol levels, and some can cause health risks. In 2007, the FDA issued a warning about red yeast rice products, many of which contain unauthorized use of prescription drugs.

### Drug Therapy

A person's LDL ("bad" cholesterol) level generally determines if drug therapy is required. Most cholesterol drugs are used to help lower LDL levels. Some drugs are also used to help raise HDL levels. Drugs used in cholesterol treatment include:

- Statins
- Nicotinic acid (niacin)
- Bile-acid binding resins
- Fibrates
- Ezetimibe

## **Cholesterol Screening and Treatment for Children**

In 2008, the American Academy of Pediatrics (AAP) recommended expanded screening and treatment of high cholesterol in children.

- The AAP now recommends cholesterol screening for children with risk factors beginning as early as age 2 and no later than age 10.
- The AAP also recommends statin drug treatment for children as young as age 8 who have high LDL levels.
- The issue of prescribing statin drugs to children is being hotly debated. Lifestyle modifications (diet, exercise) are still the recommended first treatment approach for children.

## **Introduction**

Lipids are the building blocks of the fats and fatty substances found in animals and plants. They are microscopic layered spheres of oil, which, in animals, are composed mainly of cholesterol, triglycerides, proteins (called lipoproteins), and phospholipids (molecules made up of phosphoric acid, fatty acids, and nitrogen). Lipids do not dissolve in water and are stored in the body to serve as sources of energy.

## **Cholesterol**

Cholesterol is present in all animal cells and in animal-based foods (not in plants). In spite of its bad press, cholesterol is an essential nutrient necessary for many functions, including:

- Repairing cell membranes
- Manufacturing vitamin D on the skin's surface
- Producing hormones, such as estrogen and testosterone
- Possibly helping cell connections in the brain that are important for learning and memory

Regardless of these benefits, when cholesterol levels rise in the blood, they can have dangerous consequences, depending on the type of cholesterol. Although the body acquires some cholesterol through diet, about two-thirds is manufactured in the liver, its production stimulated by saturated fat. Saturated fats are found in animal products, meat, and dairy products.

Saturated fats are found predominantly in animal products, such as meat and dairy products, and are strongly associated with higher cholesterol levels. Tropical oils -- such as palm, coconut, and cocoa butter -- are also high in saturated fats.

## **Triglycerides**

Triglycerides are composed of fatty acid molecules. They are the basic chemicals contained in fats in both animals and plants.

## **Lipoproteins**

Lipoproteins are protein spheres that transport cholesterol, triglyceride, or other lipid molecules through the bloodstream. Most of the information about the effects of cholesterol and triglyceride actually concerns lipoproteins.

Lipoproteins are categorized into five types according to size and density. They can be further defined by whether they carry cholesterol or triglycerides.

*Cholesterol-Carrying Lipoproteins.* These are the lipoproteins commonly referred to as cholesterol.

- Low density lipoproteins (LDL). (Often called "bad" cholesterol.)
- High-density lipoproteins (HDL), the smallest and most dense. (Often called "good" cholesterol.)

*Triglyceride-Carrying Lipoproteins.*

- Intermediate density lipoproteins (IDL). They tend to carry triglycerides.
- Very low density lipoproteins (VLDL). These tend to carry triglycerides.
- Chylomicrons (largest in size and lowest in density).

## **Effects of Lipoproteins and Triglycerides on Heart Disease**

*Low Density Lipoproteins (LDL), the "Bad" Cholesterol.* The main villain in the cholesterol story is low-density lipoprotein (LDL). The lowest incidence of heart disease is usually found among people with the lowest LDL levels. Lowering LDL is the primary goal of cholesterol drug and lifestyle therapy.

Low-density lipoprotein (LDL) transports about 75% of the blood's cholesterol to the body's cells. It is normally harmless. However, if it is exposed to a process called oxidation, LDL can penetrate and interact dangerously with the walls of the artery, producing a harmful inflammatory response. Oxidation is a natural process in the body that occurs from chemical combinations with unstable molecules. These molecules are known as oxygen-free radicals or oxidants.

In response to oxidized LDL, the body releases various immune factors aimed at protecting the damaged arterial walls. Unfortunately, in excessive quantities they cause inflammation and promote further injury to the areas they target.

*High Density Lipoproteins (HDL), the "Good" Cholesterol.* High density lipoprotein (HDL) appears to benefit the body in two ways:

- It removes cholesterol from the walls of the arteries and returns it to the liver for disposal from the body.

- It helps prevent oxidation of LDL. HDL actually appears to have its own antioxidant properties.
- It might fight inflammation.

HDL helps keep arteries open and reduces the risk for heart attack. High levels of HDL (above 60 mg/dL) may be nearly as protective for the heart as low levels of LDL. HDL levels below 40 mg/dL are associated with an increased risk of heart disease.

*Triglycerides.* Triglycerides interact with HDL cholesterol in such a way that HDL levels fall as triglyceride levels rise. High triglycerides may pose other dangers, regardless of cholesterol levels. For example, they may be associated with blood clots that form and block the arteries. High triglyceride levels are also associated with the inflammatory response -- the harmful effect of an overactive immune system that can cause considerable damage to cells and tissues, including the arteries.

### Cholesterol and Triglycerides Goals

Total cholesterol count includes measurements of LDL, HDL, and triglycerides. The following chart summarizes all lipid goals for adults.

Cholesterol Goals for Adults			
Total Cholesterol Goals	LDL Goals	HDL Goals	Triglyceride Goals
Less than 200 mg/dL is desirable.	<p><i>70 mg/dL</i> is considered an important goal for very high-risk patients (recent heart attack; current active or unstable cardiovascular or cerebrovascular disease; or two multiple risk factors as defined above.)</p> <p><i>Below 100 mg/dL</i> is optimal for everyone. It should be the goal for high-risk people, including those with existing heart disease, diabetes, or two or more risk factors for heart disease; <i>70 mg/dL</i> is an optimal goal for these individuals.</p> <p><i>130 mg/dL</i> or below for people with two or more risk factors; <i>100 mg/dL</i> is an optimal goal.</p> <p><i>160 mg/dL or below</i> for people at less risk (one or zero risk factors); <i>130 mg/dL</i> is an</p>	Levels above 40 mg/dL are desirable; levels above 60 mg/dL are optimal.	Below 150 mg/dL is normal.
Between 200 and 239 is borderline.			150 - 199 is borderline high.
Over 240 is high.			200 - 499 is high.
			Over 500 is very high.

	<p>optimal goal.</p> <p><i>Anything above 160mg/dL is high, with levels above 190 being very high. LDL levels over 190 require medication even with no other cardiac risk factors present.</i></p>		
<p>*Risk factors for heart disease include a family history of early heart problems before age 55 for men (before age 65 for women), smoking, high blood pressure, diabetes, being older (over 45 for men and 55 for women), and having HDL levels below 35 mg/dL. People with two or more of these risk factors may have a 10-year risk of heart attack that exceeds 20%, and may therefore need to aim for LDL levels of 100 mg/dL or below.</p>			

*Cholesterol Goals for Children.* In 2007, the American Heart Association established general LDL goals for children. LDL goals are 190 mg/dL or less for children with no additional heart disease risk factors and 160 mg/dL or less for children with additional risk factors (such as family history of high cholesterol, heart disease, and diabetes).

## **Risk Factors**

Unhealthy cholesterol levels (low HDL, high LDL, and high triglycerides) increase the risk for heart disease and heart attack. Some risk factors for cholesterol can be controlled (diet, exercise, weight) while others cannot (age, gender, and family history).

## **Age and Gender**

From puberty on, men tend to have lower HDL (“good” cholesterol) levels than women. One reason is that the female sex hormone estrogen is associated with higher HDL levels. Because of this, premenopausal women generally have lower rates of heart disease than men. After menopause, as estrogen levels decline, women catch up in their rates of heart disease. Throughout the menopausal years, HDL levels decrease and LDL (“bad” cholesterol) and triglyceride levels increase. For men, LDL and triglyceride levels also rise as they age and the risks for heart disease increase as well. (There is some evidence that high triglyceride levels carry more risks for women than men.) Heart disease is the main cause of death for both men and women.

*Children and Adolescents.* Children who have abnormal cholesterol levels are at increased risk of developing heart disease later in life. However, it is difficult to distinguish “normal” cholesterol levels in children. Changes in cholesterol levels occur between the ages of 8 - 18, and vary between genders and population groups. Cholesterol levels tend to naturally rise sharply until puberty, decrease sharply, and then rise again.

## **Genetic Factors and Family History**

Genetics play a major role in determining a person's blood cholesterol levels. (Children from families with a history of premature heart disease should be tested for cholesterol levels after

they are 2 years old.) Genes may influence whether a person has low HDL levels, high LDL levels, high triglycerides, or high levels of other lipoproteins, such as lipoprotein(a).

Inherited cholesterol disorders include:

- Familial hypercholesterolemia is a genetic disorder that causes high cholesterol levels, particularly LDL, and premature heart disease. It occurs in as many as 1 in 500 people.
- Familial lipoprotein lipase deficiency is a very rare disorder that causes depletion of lipoprotein lipase. This is an enzyme that appears to be important in the removal of lipoproteins that are rich in triglycerides. People who are deficient in it have high levels of cholesterol and fat in their blood.

## **Lifestyle Factors**

*Diet.* The primary dietary elements that lead to unhealthy cholesterol include saturated fats (found mainly in red meat, egg yolks, and high-fat dairy products) and trans fatty acids (found in fried foods and some commercial baked food products). Shellfish is also high in dietary cholesterol.

*Weight.* Being overweight or obese increases the risks for unhealthy cholesterol levels.

*Exercise.* Lack of exercise can contribute to weight gain, decreases in HDL levels, and increases in LDL and total cholesterol levels.

*Smoking.* Smoking reduces HDL cholesterol and promotes build-up of fatty deposits in the coronary arteries.

## **Obesity, Metabolic Syndrome, and Type 2 Diabetes**

In the U.S., obesity is at epidemic levels in all age groups. The effect of obesity on cholesterol levels is complex. Overweight individuals tend to have high triglyceride and LDL levels and low HDL levels. This combination is a risk factor for heart disease. Obesity also causes other effects (high blood pressure, increase in inflammation) that pose major risks to the heart.

Obesity is particularly dangerous when it is one of the components of the metabolic syndrome, formerly known as syndrome X. This syndrome consists of obesity marked by abdominal fat, unhealthy cholesterol levels, high blood pressure, and insulin resistance. Metabolic syndrome is a pre-diabetic condition that is significantly associated with heart disease and higher mortality rates from all causes. Many doctors recommend that patients with metabolic syndrome should be aggressively treated with high-dose statin therapy to lower LDL levels.

Obesity is also strongly associated with type 2 diabetes, which itself poses a significant risk for high cholesterol levels and heart disease.

Children who are overweight are at higher risk for high triglycerides and low HDL, which may be directly related to later unhealthy cholesterol levels. Childhood LDL levels and body-mass

index (BMI) are strongly associated with cardiovascular risk during adulthood. Overweight and obese children who have high cholesterol should also get tested for high blood pressure, diabetes, and other conditions associated with metabolic syndrome.

[For more information, see *In-Depth Report #60: Diabetes type 2.*]

## **Other Medical Conditions**

*High Blood Pressure.* High blood pressure (hypertension) contributes to the thickening of the heart's blood vessel walls, which can worsen atherosclerosis (accumulated deposits of cholesterol in the blood vessels.) High blood pressure, high cholesterol, and diabetes all work together to increase the risk for developing heart disease. [For more information, see *In-Depth Report #14: High blood pressure.*]

*Hypothyroidism.* Low thyroid levels (hypothyroidism) are associated with higher risk for high total and LDL cholesterol, and triglycerides. Treating the thyroid condition can significantly reduce cholesterol levels. Research is mixed on whether mild hypothyroidism (subclinical hypothyroidism) is associated with unhealthy cholesterol levels. [For more information, see *In-Depth Report #38: Hypothyroidism.*]

Hypothyroidism is a decreased activity of the thyroid gland which may affect all body functions. In this condition, the rate of metabolism slows, causing mental and physical sluggishness. The most severe form of hypothyroidism is myxedema, which is a medical emergency.

*Polycystic Ovarian Syndrome.* Women with this endocrine disorder may have increased risks for high triglyceride and low HDL levels. This risk may be due to the higher levels of the male hormone testosterone associated with this disease.

*Kidney Disease.* Kidney disease increases the risk of heart disease.

## **Other Risk Factors**

*Medications.* Certain medications such as specific antiseizure drugs, corticosteroids, and isotretinoin (Accutane) may increase lipid levels.

## **Complications**

### **Heart Disease**

Atherosclerosis is a common disorder of the arteries. Fat, cholesterol, and other substances collect in the walls of arteries. Larger accumulations are called atheromas or plaque and can damage artery walls and block blood flow. Severely restricted blood flow in the heart muscle leads to symptoms such as chest pain.

Unhealthy cholesterol, particularly low-density lipoprotein (LDL) cholesterol, forms a fatty substance called plaque, which builds up on the arterial walls of the heart. Smaller plaques remain soft, but older, larger plaques tend to develop fibrous caps with calcium deposits.

The long-term result is *atherosclerosis*, commonly called hardening of the arteries. The heart is endangered in two ways by this process:

- Eventually these calcified and inelastic arteries become narrower (a condition known as stenosis). As this process continues, blood flow slows and prevents sufficient oxygen-rich blood from reaching the heart. This condition leads to angina (chest pain) and, in severe cases, to heart attack.
- Smaller unstable plaques may rupture, triggering the formation blood clots on their surface. The blood clots block the arteries and are important causes of heart attack.

This process is accelerated and enhanced by other risk factors, including high blood pressure, smoking, obesity, diabetes, and a sedentary lifestyle. When more than one of these risk factors is present, the risk is compounded.

*Coronary Artery Disease.* The end result of atherosclerosis is coronary artery disease. Coronary artery disease, commonly known as heart disease, is the leading cause of death in the U.S.

Studies consistently report a higher risk for death from heart disease with high total cholesterol levels (200 mg/dL and higher). The higher the cholesterol, the greater the risk. On average, every time a person's total cholesterol level drops by a point, the risk of heart disease drops by 2%. [For more information, see *In-Depth Reports* #03: Coronary artery disease.]

### **Peripheral Artery Disease**

Peripheral artery disease (PAD) is caused by the buildup of plaque in the feet, legs, hands, and arms. It most often occurs in the legs. PAD is associated with atherosclerosis. The risk for PAD increases by 5 - 10% with every 10 mg/dL increase in total cholesterol levels. Lower levels of HDL and high triglyceride levels also increase the risk for PAD. [For more information, see *In-Depth Report* #102: Peripheral artery disease.]

### **Stroke**

Having adequate levels of HDL may be the most important lipid-related factor for preventing *ischemic* stroke, a type of stroke caused by blockage of the carotid arteries that carry blood to the brain. HDL may even reduce the risk for *hemorrhagic* stroke, a less common type of stroke caused by bleeding in the brain that is associated with low overall cholesterol levels.

The build-up of plaque in the internal carotid artery may lead to narrowing and irregularity of the artery's lumen, preventing proper blood flow to the brain. More commonly, as the narrowing worsens, pieces of plaque in the internal carotid artery can break free, travel to the brain, and



block blood vessels that supply blood to the brain. This leads to stroke, with possible paralysis or other deficits.

The effects of high total cholesterol and LDL levels on ischemic stroke are less clear. Some research suggests that the risk for ischemic stroke increases when total cholesterol is above 280 mg/dL. Other studies suggest that high cholesterol poses a risk for stroke only when specific proteins associated with inflammation are present. [For more information, see *In-Depth Report #45: Stroke.*]

## **Symptoms**

There are no warning signs for high LDL and other unhealthy cholesterol levels. When symptoms finally occur, they usually take the form of angina (chest pain) or heart attack in response to the buildup of atherosclerotic plaque in the heart arteries.

Atherosclerosis is a disease of the arteries in which fatty material is deposited in the vessel wall, resulting in narrowing and eventual impairment of blood flow. Severely restricted blood flow in the arteries to the heart muscle leads to symptoms such as chest pain. Atherosclerosis shows no symptoms until a complication occurs.

## **Diagnosis**

Blood tests can easily measure cholesterol levels. A blood test for cholesterol should include the entire lipoprotein profile: LDL, total cholesterol, HDL, and triglycerides. It is very difficult to measure LDL levels by themselves, but LDL levels can be reliably calculated using total cholesterol and HDL levels.

To obtain a reliable cholesterol reading, doctors advise:

- Avoid strenuous exercise for 24 hours before the test.
- Do not eat or drink anything but water for 12 hours beforehand.
- If the test results are abnormal, a second test should be performed between 1 week and 2 months after the first test.

## **Screening Guidelines**

Periodic cholesterol testing is recommended in all adults, but the major national guidelines differ on the age to start testing.

- Recommended starting ages are between 20 - 35 for men and 20 - 45 for women.
- Adults with normal cholesterol levels do not need to have the test repeated for 5 years unless changes occur in lifestyle (including weight gain and diet).
- Adults with a history of elevated cholesterol, diabetes, kidney problems, heart disease, and other conditions require more frequent testing.

Screening with a fasting lipid profile is recommended for children who:

- Have risk factors such as a family history of high cholesterol, and history of heart attacks before age 55 for men and before age 65 for women. Screening should begin as early as age 2 and no later than age 10.
- Are obese (above 85th percentile for weight) or who have diabetes. If the child's cholesterol level tests normal, retesting is recommended in 3 - 5 years.

Patients already being treated for high cholesterol should be checked every 2 - 6 months.

## **Treatment**

Lifestyle changes (such as diet, weight control, exercise, and smoking cessation) are the first line of defense for treating unhealthy cholesterol levels. If levels still remain high, drug treatment is an effective next step. However, while statins have been shown to slow the rate of atherosclerotic progression, they have not yet been shown to reverse heart disease.

Reducing LDL ("bad" cholesterol) and total cholesterol levels, while at the same time boosting HDL ("good" cholesterol) levels, can prevent heart attacks and death in all people (with or without heart disease). Reducing LDL is the primary goal of most cholesterol therapy. Cholesterol-lowering medications are used along with healthy lifestyle habits, not in place of them. Lowering cholesterol levels with lifestyle changes and drug treatment has been shown to decrease the risk of heart attacks and other complications of atherosclerosis.

The National Cholesterol Education Program's (NCEP) clinical practice guidelines set treatment goals for LDL levels based on a patient's risk factors for heart disease. The risk factors include:

- Having a first-degree female relative diagnosed with heart disease before age 65 or a first-degree male relative diagnosed before age 55
- Being male and over age 45 or female and over age 55
- Cigarette smoking
- Diabetes
- High blood pressure
- Metabolic syndrome (risk factors associated with obesity such as low HDL levels and high triglycerides)

Two or more of these risk factors increases by 20% the chance of having a heart attack within 10 years.

The LDL cholesterol level is one of the most important factors in determining whether a patient needs cholesterol therapy and whether the treatment is working properly. In particular, guidelines emphasize lower LDL levels and earlier treatment for people with coronary artery disease, or other forms of atherosclerosis, and diabetes. (For a table of Cholesterol Goals for Adults, see the "Introduction" of this report.)

Although current cholesterol goals are extremely useful for most patients, sometimes results of the testing are difficult to interpret and make it difficult for doctors to decide on the appropriate treatment. This is especially true for patients whose test results show:

- Low LDL levels (which are protective) but also low HDL or high triglycerides (which are harmful)
- High total cholesterol levels (which are harmful) but also high HDL levels (which are protective)

*Starting Medications.* Even modest lowering of high cholesterol levels, whether through drug therapy or lifestyle changes, reduces the risk of disability and death from heart disease. Most drug treatment now focuses on lowering LDL ("bad") cholesterol. A doctor will start or consider medication, increase dosage of medication, or add new medication when a patient's:

- LDL cholesterol is 190 mg/dL or higher.
- LDL cholesterol is 160 mg/dL or higher AND patient has one risk factor for heart disease.
- LDL cholesterol is 130 mg/dL or higher AND patient has either diabetes or two other risk factors for heart disease.
- LDL cholesterol is 100 mg/dL or higher AND patient has heart disease. (If patient has diabetes, even without heart disease, medication may be considered for an LDL cholesterol of 100 mg/dL.)
- LDL cholesterol is greater than 70 mg/dL AND patient has had a recent heart attack or has known heart disease along with diabetes, current cigarette smoking, poorly controlled high blood pressure, or the metabolic syndrome (high triglycerides, low HDL, and obesity).

Statin therapy has been proven to decrease the incidence of major coronary events, the need for coronary revascularization procedures, and the incidence of stroke. Studies are also evaluating the use of statins for preventing heart disease in patients who have high C-reactive protein (CRP) levels but who are otherwise healthy and have normal LDL cholesterol. CRP is a protein that helps measure inflammation in the body, with increased CRP levels indicating more inflammation. Researchers are studying whether this inflammation is a risk factor for heart disease, even in otherwise healthy people with normal cholesterol levels.

*Choosing the Correct Lipid-Lowering Medication.* Doctors recommend that drug treatments be tailored for raising or lowering specific lipids, depending on the patient's blood lipid picture:

- Statins are now the standard drugs for most people who require LDL-lowering therapy. Bile-acid binding resins or niacin may be considered. If LDL goals are not achieved, combinations of a statin with a bile-acid resin or niacin should be considered.
- Fibrates or niacin are beneficial for people who need to lower triglycerides and increase HDL.

*Considerations for Children and Adolescents.* Lifestyle modifications (diet, exercise) are the first course of action for treating children who have unhealthy cholesterol levels or who are at risk for

them. In 2008, the American Academy of Pediatrics (AAP) recommended prescribing statin drugs for children age 8 and older who have elevated LDL levels of 190 mg/dL or over. The AAP also recommended statins for children with LDL 160 mg/dL if there is a family history of heart disease or other risk factors.

For children with diabetes, cholesterol drug treatment is recommended when LDL levels are 130 mg/dL. The goal is to lower LDL levels to less than 160 mg/dL or even 110 mg/dL for children with strong risk factors. However, the issue of prescribing statins to children is being hotly debated within the medical community.

*Considerations for People with Diabetes.* At this time, statins are recommended as the best drugs for improving cholesterol and lipid levels in people with diabetes. Studies suggest that they can reduce the risk for adverse heart events in people with diabetes, even if patients' cholesterol levels are normal or if their diabetes is mild. Fibrates may also be useful for some people with type 2 diabetes. Niacin (nicotinic acid) has the best effect on the cholesterol profile of people with diabetes, but it also increases blood sugar levels and can be difficult to tolerate.

## **Medications**

### **Statins**

Statins are the most effective drugs for the treatment of high cholesterol, particularly for lowering LDL levels. They also have modest effects in lowering triglycerides and increasing HDL levels. Statins inhibit the liver enzyme HMG-CoA reductase, which the body uses to manufacture cholesterol. These drugs effectively reduce the risk of major coronary events, including first and second heart attacks and stroke, in adults with unhealthy cholesterol levels.

*Brands.* Statins approved in the U.S. include:

- Lovastatin (Mevacor)
- Pravastatin (Pravachol)
- Simvastatin (Zocor)
- Fluvastatin (Lescol)
- Atorvastatin (Lipitor)
- Rosuvastatin (Crestor)

Statins may also be prescribed as fixed-dose combination drugs, which combine two drugs in one pill:

- Ezetimibe/simvastatin (Vytorin) combines two cholesterol medications that work in different ways.
- Amlodipine/atorvastatin (Caduet) is a dual-therapy medication that combines the antihypertensive calcium channel blocker amlodipine with atorvastatin. It is used to treat simultaneously high blood pressure and high cholesterol.

Statins may be prescribed along with other cholesterol-lowering drugs, such as bile acid-binding resins, nicotinic acid (niacin), and fibrates.

*Side Effects.* Statins tend to be better tolerated than other cholesterol-lowering drugs. Side effects may include gastrointestinal discomfort, headaches, skin rashes, muscle aches, sexual dysfunction, drowsiness, dizziness, nausea, constipation, and peripheral neuropathy (numbness or tingling in the hands and feet).

The primary safety concern with statins is an uncommon condition called myopathy, in which a patient may experience muscle pains and certain lab tests may be elevated. A specific myopathy, called rhabdomyolysis, can lead to kidney failure, but fortunately its occurrence is very rare. The risk for myopathy/rhabdomyolysis is highest at higher doses and in older people (over 65 years), those with hyperthyroidism, and those with renal insufficiency (kidney disease). Both statins and fibrates carry a risk for myopathy. The combination of the two drugs increases this side effect. Some people who use a statin-fibrate combination withdraw from the regimen because of muscle discomfort.

In general, all statin therapy should start at a lower dose and be raised incrementally until healthy cholesterol levels are maintained. Patients should immediately tell their doctor about any unusual muscle discomfort or weakness, fever, nausea or vomiting, or darkening of urine color. Rosuvastatin (Crestor), may be associated with increased risk for myopathy and rhabdomyolysis, especially when given at the highest dose level (40 mg). The FDA advises that patients should not start therapy at a higher dose. In addition, people of Asian heritage appear to metabolize the drug differently and should start treatment at the lowest rosuvastatin dose (5 mg).

Statins can also affect the liver, particularly at higher doses, so patients should have periodic liver function tests. Anyone with liver problems and women who are pregnant or breastfeeding should not use statins. High doses of statins increase the risk for kidney failure, particularly for patients with other existing risk factors (diabetes, hypertension, atherosclerosis, history of heart failure).

*Interactions with Drugs and Food.* Statins may have some adverse interactions with other drugs, including other cholesterol-lowering medications. Among the drugs that increase the risk for adverse effects are cyclosporine, macrolide antibiotics, and certain antifungals. Patients should tell their doctors about any other medications they are taking. Grapefruit juice and Seville oranges may increase statin potency.

## **Niacin (Nicotinic Acid)**

*Brands.* Nicotinic acid is the active compound found in niacin, or vitamin B3. It is a particularly helpful choice for patients with low HDL levels. Brands include Niacor, Nicolinar, and Slo-Niacin. An extended-release form (Niaspan), administered at bedtime, may have fewer side effects, including headaches and flushing, than rapidly-acting niacin drugs. Although niacin is available over the counter, the active form used for cholesterol treatment is given in much higher doses. It is important to take this medication under a doctor's direction in order to ensure its safety and effectiveness.

*Benefits.* When used in high doses, niacin has the following benefits:

- Raises HDL levels higher than other anti-cholesterol drugs
- Reduces triglyceride levels very effectively
- Lowers LDL-cholesterol and lipoprotein(a)
- Costs less than other anti-cholesterol drugs

Combinations with other drugs, particularly statins, may add significant benefits.

*Side Effects.* Many patients do not like the side effects of the rapidly-absorbed form of niacin. About a quarter of patients who use rapid-acting forms of nicotinic acid stop taking them. The most common side effects are flushing of the face and neck, itching, headache, blurred vision, and dizziness. They usually occur 5 minutes to hours after taking the drug and can last for minutes to, uncommonly, hours. The body may eventually become tolerant to these effects, so they may diminish in time.

The following may reduce flushing and itching:

- Starting with low doses taken at mealtime and gradually working up to the prescribed dose.
- Taking low-dose aspirin about 30 minutes before taking niacin. This may help prevent flushing.
- Avoiding hot drinks.
- Choosing an extended release form. (Even with this form, it is wise to gradually increase the bedtime dose over time and take a low-dose aspirin a half-hour beforehand.)

Stomach problems are common. Other side effects include dry skin and mucous membranes and darkening of the skin.

About 30% of patients who take niacin experience elevated levels in blood sugar (glucose), which can be a problem for people with diabetes. Niacin's effects on HDL and triglycerides, however, are especially suited for the lipid imbalances that are common in diabetes. Some studies report that people with diabetes who use niacin have little trouble with blood sugar control.

*Potentially Serious Complications.* About 3 - 5% of people taking niacin develop liver problems, which usually resolve after the medication is discontinued. The extended form (Niaspan) appears to be safe for the liver, but people with chronic liver disease should not use any form of nicotinic acid. People with gout should also avoid niacin because it elevates uric acid.

## **Fibrates**

*Brands.* Fibrates (sometimes called fibric acid derivatives) break down the particles that make triglycerides. Gemfibrozil (Lopid, generic) is the standard fibrate. It is usually taken twice a day, 30 minutes before breakfast and before the evening meal. Other fibrates include fenofibrate

(Tricor) and bezafibrate (Bezalip). They may be more effective in lowering cholesterol than gemfibrozil.

*Benefits.* Fibrates have the following effects on cholesterol, lipids, and other factors:

- They are good choices for many patients who need to lower triglyceride levels and increase HDL but who cannot take other drugs used for these purposes, such as nicotinic acid.
- Fibrates can produce modest reductions in LDL levels, although not as effectively as statins or other drugs. LDL may actually increase in patients with very high triglycerides who take these drugs. (The newer fibrates are much more effective in lowering LDL than gemfibrozil.)
- Fibrates may lower the risk of heart attack.

*Side Effects.* Side effects may include gastrointestinal discomfort, aching muscles, sensitivity to sunlight, and skin rashes. Fibrates have been known to cause gallstones, so people with gallbladder problems should not use these drugs.

The drugs may cause abnormal heart rhythms and can affect the liver and kidney.

*Drug Interactions.* Fibrates interact with a number of drugs and substances, including warfarin, some oral drugs used for diabetes, certain antibiotics, and grapefruit juice.

### **Bile-Acid Binding Resins**

Bile-acid binding resins work, as their name suggests, by binding to bile in the digestive tract. This reduces cholesterol in the following way:

- Bile is made in the liver and is used as one of the body's primary manufacturing components.
- Once the resins bind to bile in the digestive tract, the bile is excreted in feces.
- As the resins eliminate bile from the body, the liver takes more cholesterol from the bloodstream in order to produce more bile.
- As cholesterol is taken out of the bloodstream, LDL levels drop.

*Brands.* Cholestyramine (Questran, Questran Light) is commonly used in a powder that is dissolved in liquid. Colesevelam (Welchol) is available in tablet form. Colestipol (Colestid) is another type of resin drug.

*Side Effects.* None of these drugs poses major risks. Most, however, cause constipation, heartburn, gas, and other gastrointestinal problems, side effects that many people cannot tolerate. Colesevelam, a newer resin, appears to have significantly fewer of these side effects.

Bile-acting drugs may contribute to calcium loss and therefore increase the risk for osteoporosis. Over time, deficiencies of vitamins A, D, E, and K may occur, and vitamin supplements may be necessary.

Bile acid binders can also elevate triglyceride levels. Rarely, toxic effects on the liver have been reported. Patients with liver disorders should be monitored.

Bile-acid binding resins may also interfere with the absorption of other medications, including digoxin (Lanoxin), thyroid replacement hormones, warfarin, beta-blocker drugs, and a number of medications used to treat low blood sugar. In order to prevent drug interactions, other drugs should be taken 1 hour before or 4 - 6 hours after taking the bile acid-binding resins.

### **Ezetimibe**

Ezetimibe (Zetia) blocks absorption of cholesterol that comes from food. Ezetimibe is usually prescribed alone or in combination with a statin. Ezetimibe is also used in combination with fenofibrate (Tricor) for reduction of total cholesterol and LDL in patients with mixed hyperglycemia (high LDL levels, high triglycerides, low HDL levels) whose cholesterol has not been adequately controlled through diet alone.

Vytorin, is a combination of ezetimibe and the statin simvastatin into a single fixed dose pill. An important study found that combination does not protect arteries better than a statin alone. As a result, most doctors now recommend reserving ezetimibe for use as an add-on drug when statins do not achieve adequate LDL lowering. Vytorin should not be used along with fibrate drugs.

### **Lovaza**

Lovaza is a prescription form of omega-3 fish oil, which may be prescribed to help lower triglyceride levels. Side effects include burping and a fishy taste. LDL levels may increase in some patients.

## **Lifestyle Changes**

The absolute mandate for improving cholesterol levels is to first make changes in lifestyle (both diet and exercise). Even when drugs are used, healthy diet and physical activity are critical companions.

### **Heart-Healthy Diets**

There are many major dietary approaches for protecting health, such as the Mediterranean diet, which emphasizes fruits, vegetables, and healthy types of fats. Doctors generally agree on the following recommendations for heart protection:

- Choose fiber-rich food (whole grains, legumes, and nuts) as the main source of carbohydrates, along with a high intake of fruits and vegetables. Walnuts in particular



have cholesterol-lowering properties and are a good source of antioxidants and alpha-linolenic acid.

- Avoid saturated fats (found mostly in animal products) and trans fatty acids (found in hydrogenated fats and many commercial products and fast foods). Choose unsaturated fats (particularly omega-3 fatty acids found in vegetable and fish oils). For dairy products, choose low fat over high fat.
- For proteins, choose soy protein, poultry, and fish over meat. Studies have found that soy does not help improve cholesterol. However, it is still a heart healthy food choice.
- Fish is particularly heart protective. People who don't or won't eat fish can take a daily fish oil supplement. Omega-3 fatty acid fish oil supplements contain docosahexaenoic (DHA) and eicosapentaenoic (EPA) acids, which have significant benefits for the heart, particularly for lowering triglyceride levels. Fish oil supplements are also available in prescription form (Lovaza).
- Controlling weight, quitting smoking, and exercising are essential companions of any diet program.

After embarking on any heart healthy diet, it generally takes an average of 3 - 6 months before any noticeable reduction in cholesterol occurs. However, some people see improved levels in as few as 4 weeks. An intensive program may be necessary to achieve significant improvements in cholesterol levels and to reduce heart risk factors.

[For more information, see *In-Depth Report #43: Heart-healthy diet.*]

## **Exercise**

Inactivity is one of the four major risk factors for coronary artery disease, on par with smoking, unhealthy cholesterol, and high blood pressure. In fact, studies suggest that people who change their diet in order to control cholesterol only achieve a lower risk for heart disease when they also follow a regular aerobic exercise program.

- People with an active lifestyle have a 45% lower risk of developing heart disease than sedentary people. Physically active people tend to have higher HDL (“good” cholesterol) levels. Research suggests that regular aerobic exercise can help increase HDL levels. Even moderate exercise reduces the risk of heart attack and stroke.
- Resistance (weight) training offers a complementary benefit to aerobics.

## **Quitting Smoking**

Cigarette smoking lowers HDL and is directly responsible for about 20% of all deaths from heart disease. The importance of breaking this habit cannot be emphasized enough. Once a person quits smoking, HDL cholesterol levels rise within weeks or months to levels that are equal to their nonsmoking peers. Passive smoking also reduces HDL levels and increases the risk of heart disease in people exposed to second-hand smoke.

## Alcohol

A number of studies have found heart protection from moderate intake of alcohol (one or two glasses a day). Moderate amounts of alcohol help raise HDL levels. Although red wine is most often cited for healthful properties, any type of alcoholic beverage appears to have similar benefit. Pregnant women, anyone who cannot drink moderately, and people with liver disease should not drink at all.

## Herbs and Supplements

Manufacturers of herbal remedies and dietary supplements do not need FDA approval to sell their products. Just like a drug, herbs and supplements can affect the body's chemistry, and therefore have the potential to produce side effects that may be harmful. There have been a number of reported cases of serious and even lethal side effects from herbal products. Always check with your doctor before using any herbal remedies or dietary supplements.

The following natural remedies are of interest for cholesterol control:

- *Garlic*. Contrary to popular belief, neither raw garlic nor garlic supplements significantly reduce LDL cholesterol levels.
- *Policosanol*. Policosanol is a nutritional supplement derived from sugar cane that has been promoted as having lipid-lowering benefits. However, rigorous research has not shown that policosanol has any effect on reducing LDL levels.
- *Red Yeast Rice*. Red yeast rice is used in traditional Chinese medicine. The FDA warns that many red yeast rice dietary supplement products sold as treatments for high cholesterol contain prescription drugs that can cause serious health problems.

## Resources

- [www.nhlbi.nih.gov/about/ncep](http://www.nhlbi.nih.gov/about/ncep) -- National Cholesterol Education Program
- [www.nhlbi.nih.gov](http://www.nhlbi.nih.gov) -- National Heart, Lung, and Blood Institute
- [www.acc.org](http://www.acc.org) -- American College of Cardiology
- [www.americanheart.org](http://www.americanheart.org) -- American Heart Association
- [www.eatright.org](http://www.eatright.org) -- American Dietetic Association