CHOLESTEROL

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 a white, powdery substance that is found 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.

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 the "bad" cholesterol.)
- High-density lipoproteins (HDL), the smallest and most dense. (Referred to as the "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).

Lipoprotein(a). Lipoprotein(a), or lp(a), has a size and density somewhere between LDL and HDL. The molecules carry a protein that may interfere with the body's ability to dissolve blood clots. Lipoprotein(a) is being investigated as a possible marker or cause of heart disease.

Remnant Lipoproteins. Remnant lipoproteins are byproducts of chylomicrons, very low-density lipoproteins (VLDL), or both. Some research indicates that high levels may be an important risk factor for coronary artery disease, particularly in patients who have otherwise normal cholesterol levels.

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 canola and fish oils).
- 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
- Ezetimbe

Cholesterol and Triglycerides Goals

Reducing LDL and total cholesterol levels, while at the same time boosting HDL 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.

In 2004, the National Cholesterol Education Program updated its clinical practice guidelines. The new recommendations set lower 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, the new guidelines emphasize lower LDL levels and earlier treatment for people with coronary artery disease, or other forms of atherosclerosis, and diabetes.

In 2007, the American Heart Association established general LDL goals for children that take into account these fluctuations. The association's 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).

Although current guidelines as described in the table 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)

Complications

Atherosclerosis

As many as half of these deaths were probably due to unhealthy cholesterol and lipid levels. Strong evidence points to LDL as the villain and HDL as a hero in the process. The role of other lipids, notably triglycerides, is not entirely clear.

Unhealthy cholesterol, particularly low-density lipoprotein (LDL), forms a fatty substance called plaque, which builds up on the arterial walls. Smaller plaques remain soft, but

The following chart summarizes all goals.

Cholesterol Goals for Adults			
Total Cholesterol Goals	**LDL Goals**	**HDL Goals**	**Triglyceride Goals**
Less than 200 mg/dL is desirable. Between 200 and 239 is borderline. Over 240 is high.	*70 mg/dL* is considered a reasonable 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.) *Below 100 mg/dL* 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; 70 mg/dL is an optimal goal for these individuals. *130 mg/dL* or below for people with two or more risk factors; 100 mg/dL is an optimal goal. *160 mg/dL* or below for people at less risk (one or zero risk factors); 130 mg/dL is an optimal goal. *Anything above 160 mg/dL* is high, with levels above 190 being very high. LDL levels over 190 require medication even with no other cardiac risk factors present.	Levels above 40 mg/dL are desirable; levels above 60 mg/dL are optimal.	Below 150 mg/dL is normal. 150 - 199 is borderline high. 200 - 499 is high. Over 500 is very high.
*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.			

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.

The effects of cholesterol on the heart may involve more than just the arteries. There is some evidence that unhealthy levels may affect the heart muscles and increase the risk for heart failure. High cholesterol levels may even reduce the protection that aspirin provides for people with heart disease.

Lipoprotein(a). Studies are finding an elevated risk for angina and first heart attacks in people with elevated levels of lipoprotein(a), also known as or lp(a). This lipoprotein falls somewhere between HDL and LDL in density and may have some properties that increase the risk for blood clots. Some experts suggest, however, that high levels of lp(a) may merely be *markers* of late-stage atherosclerosis, not a cause. Because concentrations of lipoprotein(a) are usually inherited, they do not respond to dietary or lifestyle changes. At this time, few experts recommend drug treatments to reduce lp(a) levels. Older women, but not men, appear to be at greater risk for high lp(a) levels and their consequences.

Coronary Artery Disease and High Cholesterol

Coronary artery disease, commonly known as heart disease, is the leading cause of death in the U.S. and was responsible for nearly 500,000 deaths in 2003.

On an encouraging note, mortality rates associated with coronary artery disease have declined dramatically during the past 30 years. Some experts estimate that about 30% of the decline is due to better cholesterol management and statin drugs.

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. One study reported that men with total cholesterol levels higher than 240 mg/dL had a risk nearly two to four times that of men whose cholesterol was below 200 mg/dL. On average, every time a person's cholesterol level drops by a point, the risk of heart disease drops by 2%.

Low Density Lipoproteins (LDL), the "Bad" Cholesterol

The primary villain in the cholesterol story is low-density lipoprotein (LDL). In a major study, the lowest incidence in heart disease was 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.

- When LDL collects on arterial walls these oxidants are released from the wall membranes.
- Oxidants are missing an electron and tend to bind with other molecules in the body, a process called *oxidation*.
- When the oxidation process modifies LDL, it signals the immune system that a harmful molecule has appeared.

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

- White blood cells and other factors gather and form a fatty substance called plaque. (Of interest in this process is an enzyme called lipoprotein-associated phospholipase A2, which binds to oxidized LDL. Studies report that this enzyme may play a major role in the release of plaque-forming inflammatory factors.)
- Other immune factors also cause inflammation and injure the *endothelium,* the layer of cells that line blood vessels.
- Immune factors that increase the risk for blood clots are also mobilized.
- Oxidized LDL plays another dangerous role by reducing levels of nitric oxide, a chemical that helps relax the blood vessels and allow blood to flow freely.

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

HDL helps keep arteries open and reduces the risk for heart attack. High levels of high HDL (above 60 mg/dL) may be nearly as important for the heart as low levels of LDL. HDL levels below 40 mg/dL are considered to be harmful. In one study, for each 4 mg/dL decline in HDL levels there was a 10% increase in coronary artery disease.

Triglycerides

Triglycerides are major troublemakers for the heart. They appear to interact with HDL cholesterol in such a way that HDL levels fall as triglyceride levels rise. Low HDL is known to be harmful to the heart.

The harmful imbalance of high triglycerides with low HDL levels is also associated with obesity (particularly around the abdomen), insulin resistance, and diabetes. Insulin is a hormone essential for regulating the storage and use of glucose (sugar) and amino acids (proteins) in the body. Insulin resistance occurs when there are normal levels of insulin but the body cannot use it. Insulin resistance increases the risk for developing type 2 diabetes, and it is also associated with metabolic syndrome. Both of these conditions increase the risk for heart disease.

Some evidence also suggests that high triglycerides pose other dangers, regardless of cholesterol levels. Triglycerides,

for example, may be responsible for 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.

Stroke and High Cholesterol

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 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.

Alzheimer's Disease and High Cholesterol

Evidence points to high cholesterol levels, along with high blood pressure and a family history of the disease, as independent risk factors for AD. A major research target for common factors between cholesterol levels and AD has been apolipoprotein E (ApoE). ApoE plays a role in the movement and distribution of cholesterol for repairing nerve cells during development and after injury. People who carry a variant of this gene (ApoE4) are at significantly higher risk for AD.

High cholesterol may pose a risk for Alzheimer's regardless of this genetic factor, however. Some studies report that cholesterol is important within the brain for cell communication and memory.

Risk Factors

About half of all American adults have total cholesterol levels over 200 mg/dL. Twenty-five percent of these people have unhealthy levels. Total cholesterol levels have been declining over the last several decades, at least among middle-aged and older adults. This decline may be partly due to the increased use of statins and other lipid-lowering medications. However, total cholesterol levels are getting higher among younger adults (ages 25 – 34 years). The major risk factor for these high rates may be the Western lifestyle. The typical high-fat/low-fiber American diet coupled with sedentary habits is largely responsible for this unfortunate trend.

Risk by Gender

Men. Heart disease is the major cause of death in men. On average, men develop coronary artery disease 10 - 15 years earlier than women do and have a greater risk for dying of heart disease at a younger age.

Women. Coronary artery disease is also the number one killer of women. Women ages 20 - 34, and those beyond menopause (around age 55), have higher cholesterol levels than men. Some evidence suggests that lower HDL levels may be a more significant risk in women than in men, especially when combined with high-triglyceride levels.

Risk by Age

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.

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.

As in adults, the primary source of unhealthy cholesterol levels in children comes from diets high in unhealthy fats: Saturated fats (found mainly in animal and dairy products) and trans fatty acids (found in commercial food products).

Young and Middle-Aged Adults. The strongest evidence of unhealthy cholesterol levels and heart disease is in adults over age 45. However, while total cholesterol levels are decreasing among older adults, they are increasing in those ages 25 - 34 years. Research strongly suggests that the younger a person is when unhealthy cholesterol levels develop, the greater the chance for serious heart and blood vessel problems in the future. Young men without cholesterol problems have been found to have a higher life expectancy, by up to 8 years. Other studies have suggested similar risks from unhealthy cholesterol in young women as well.

Elderly Adults. About 85% of people who die from coronary artery disease are over the age of 65. Because high cholesterol is an important risk factor for heart disease, experts strongly recommend statin or other lipid-lowering therapy for elderly people with high cholesterol levels. Surveys indicate that total cholesterol levels have been declining in older people over the last few decades. Many experts believe this is due in part to increased use of statin drugs.

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. Although obesity does not appear to be strongly associated with overall cholesterol levels, obese individuals tend to have high triglyceride 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.

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. Some doctors suggest that patients with high cholesterol should be evaluated for thyroid function before they are given cholesterol-lowering drugs. Research is mixed on whether mild hypothyroidism (subclinical

hypothyroidism) is associated with unhealthy cholesterol levels. [For more information, see *In-Depth Report #38*: Hypothyroidism.]

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).

Some inherited disorders and genetic abnormalities have been identified:

- Familial hypercholesterolemia causes dangerous increases in cholesterol. It may be more common than previously thought. One European study reported familial hypercholesterolemia in 1 out of every 400 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. A very low-fat diet is essential and is an effective treatment for these individuals.
- Several studies have found a genetic mutation affecting neuropeptide Y in people with high total cholesterol and LDL levels. Neuropeptide Y is a compound in the brain that regulates appetite.
- Researchers have identified a gene called APOAV, which may help detect patients at risk for elevated levels of triglycerides.

Other Medical Conditions

Other medical conditions and risk factors strongly associated with unhealthy cholesterol levels include:

- Polycystic ovarian syndrome. Women with this disorder, particularly those who are obese, appear to be at increased risk for high triglyceride and low HDL levels. This risk may be due to higher levels of the male hormone testosterone in these women.
- Kidney disease
- Certain medications such as specific antiseizure drugs, corticosteroids, and isotretinoin (Accutane)

Symptoms

There are no warning signs for high LDL cholesterol levels. When symptoms finally occur, they usually take the form of angina or heart attack in response to the buildup of atherosclerotic plaque in the patient's arteries. This is definitely a condition where it pays to invest in preventive medicine before dangerous complications occur.

Diagnosis

Blood tests can easily measure both HDL and overall cholesterol levels. It is very difficult to measure LDL levels by themselves, but LDL levels can be reliably calculated by subtracting HDL and triglyceride levels from total cholesterol. The exact formula is:

LDL = TOTAL CHOLESTEROL - HDL - TRIGLYCERIDES/5.

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, experts 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.

Home Tests. Tests are available for home use and in public locations, such as shopping malls and pharmacies. For example, the CholesTrak Test can be taken at home with results in 10 minutes, but it measures only total cholesterol. The BioSafe Cholesterol Panel Test is also a home test, but it needs to be sent to a laboratory. This test, however, is very accurate and provides a full lipid profile.

Skin Test

A new type of test measures cholesterol levels in the skin. High skin levels may indicate an increased risk for atherosclerosis and serious heart disease.

Screening Guidelines

General Screening Recommendations. Experts groups differ slightly on when screening should start, but the following are generally accepted recommendations:

- 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.
- Selective screening of children who are at risk for high cholesterol and heart disease or familial hypercholesterolemia, which is genetically elevated cholesterol. Risk factors include having parents with total cholesterol levels greater than 240 mg/dL, or having a parent or grandparent who had symptomatic heart disease at age 55 or younger for men and age 65 or younger for women. Obese children with waist circumference between the 75th - 90th percentile are also at increased risk for cardiovascular and metabolic disorders and may need testing.
- Patients already being treated for high cholesterol should be checked every 2 - 6 months.

Lifestyle Changes

Although most studies proving that lowering cholesterol saves lives are done using drug therapy, 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

Although there are many major dietary approaches for protecting health, experts 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 fresh 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 proteins, choose soy protein, poultry, and fish over meat. A 2006 study found that soy does not help improve cholesterol. However, experts still recommend it as a heart healthy food choice.
- 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.
- Some studies suggest that for the greatest heart protection, it is not the duration of a single aerobic exercise session that counts but the total daily amount of energy expended. However, other studies indicate that exercise duration (not frequency or intensity) is most important for raising HDL levels.
- 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 in people exposed to cigarette 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, garlic does not significantly reduce cholesterol, according to a 2007 *Archives of Internal Medicine* study. Researchers tested raw garlic and two types of garlic supplements in 192 patients with moderately high LDL levels. None of the forms of garlic had any effect on LDL levels. However, the researchers note that garlic may still help people with very high LDL levels, and it may contain other heart-protective properties.
- *Policosonol*. Policosanol is a nutritional supplement derived from sugar cane that has been promoted as having lipid-lowering benefits. In a randomized, placebo-controlled trial published in 2007 in the *Archives of Internal Medicine*, policosanol was no better than placebo in 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.

Treatment

In 2004, the National Cholesterol Education Program issued its latest recommendations for cholesterol control and management. These guidelines increase the number of Americans who should be taking LDL-lowering medication.

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 experts now focus on lowering LDL ("bad") cholesterol. Reducing LDL levels is particularly critical for patients with diabetes.

The doctor will start or consider medication, increase dosage of medication, or add new medication when:

- 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).

Risk factors for heart disease 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)

Statin therapy has been proven to decrease the incidence of major coronary events, the need for coronary revascularization procedures, and the incidence of stroke. These benefits seem to occur no matter what cholesterol level is present at the beginning of treatment and the reduction in risk continues for the most part at all lipid levels. Generally, this benefit is present for all age groups, both genders, and whether or not the patient has pre-existing vascular disease.

Recent studies have found that aggressive lipid lowering with high-dose or intensive statin therapy is more beneficial than standard statin therapy in patients with existing heart disease. Data from several trials suggest that intensive statin therapy produces greater reductions in LDL and C reactive protein (CRP) levels.

The hope has been that the more statins can lower LDL, the more effective they will be in slowing and even reversing the progression of atherosclerosis. However, to date statins have only been shown to slow the rate of atherosclerotic progression, and not reverse heart disease. Future studies will continue to investigate this issue. Many experts believe that the more that LDL is reduced through statin therapy, the greater the reduction in risk for heart disease, heart attack, and stroke

It is important to emphasize that cholesterol-lowering medications are used along with healthy lifestyle habits, not in place of them.

Choosing the Correct Lipid-Lowering Medication. Experts now 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. In 2007, the American Heart Association (AHA) issued a scientific statement addressing the use of cholesterol drugs in children and adolescents. The AHA recommends that overweight or obese children should undergo lifestyle modifications (diet, exercise) before trying drug therapy to lower high cholesterol levels.

For children and adolescents who have high-risk cholesterol imbalances -- and a family history of high cholesterol, heart attack, stroke, and diabetes -- the AHA now recommends statins as the first-line drug therapy.

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 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.

Classes of Medications

Statins

Statins are the most effective drugs for the treatment of high cholesterol, particularly in elevated LDL cholesterol, and may even prove important drugs for many people at risk for heart disease who have normal cholesterol levels. Statins inhibit the liver enzyme HMG-CoA reductase, which the body uses to manufacturer of cholesterol. These drugs effectively reduce the risk of major coronary events, including first and second heart attacks, in both adult women and men of any age with unhealthy cholesterol levels. Doctors estimate a 25 - 30% reduction in mortality rates when patients take statins after a heart attack. These drugs may also help improve outcomes in patients with heart disease who have had angioplasty.

Important studies have reported lower rates of heart attack, stroke, and mortality rates from all causes in statin users who were at high risk for heart disease, even if they had normal or low cholesterol levels. Benefits were similar in these people regardless of gender, age, or the presence of specific heart risk factors, such as diabetes or peripheral artery disease.

Brands. Statins are currently categorized into four groups:

- So-called natural statins, including lovastatin (Mevacor, generics), pravastatin (Pravachol), and simvastatin (Zocor, generics). These are the most studied statins and have proven effectiveness and good safety record.
- Synthetic statins include fluvastatin (Lescol) and atorvastatin (Lipitor). In 2007, Lipitor was approved for additional indications to reduce the risk of heart attacks, strokes, certain types of heart surgery, hospitalization for heart failure, and chest pain in patients with heart disease. Lipitor is also approved for children.
- Newer statins include rosuvastatin (Crestor), which was approved in 2003. In 2007, rosuvastatin received an additional approval for slowing atherosclerosis in patients with high cholesterol levels. Like all statin drugs, rosuvastatin can cause serious side effects; the risks are higher for Asian patients (see "Adverse Effects" section).
- Fixed-dose combination statins, which combine two drugs in one pill, first appeared on the market in 2004. Ezetimibe/simvastatin (Vytorin) combines two cholesterol medications that work in different ways. Simvastatin blocks cholesterol production in the liver, while ezetimibe (a non-statin cholesterol medication) blocks cholesterol absorption in the digestive tract. Despite the theoretical advantages of the combination, the ENHANCE study published in 2008 showed that while the combination produced mild LDL lowering than simvastatin alone, it was no better at slowing the progression of atherosclerosis. More research is needed. 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 are also available with niacin in fixed-dose combinations, such as lovastatin-niacin (Advicor) and simvastatin-niacin (Simcor).

Statins are generally administered once a day, typically in the evening because most cholesterol synthesis occurs between midnight and 3 a.m. (Atorvastatin and rosuvastatin, however, can be taken in the morning.) Statins are often

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

*Beneficial Effects on the Heart and Circulation.*Statins are particularly effective for lowering LDL levels. They also reduce triglycerides, apparently in direct proportion to their LDL-lowering effects. Statins also raise HDL levels, but to a lesser extent than other anti-cholesterol drugs. (The newer statins appear to produce more significant increases in HDL.) Evidence suggests that statins may offer other health benefits beyond lowering cholesterol:

- Statins may improve the function of the *endothelium* (the lining of blood vessels), thereby improving blood flow. (This benefit apparently does not extend to people with diabetes.)
- Statins appear to reduce inflammation in the arteries, which is now believed to be a major factor in blood vessel injury.
- Statins may help prevent blood clotting, a major factor in heart attacks.

Beneficial Effects Outside the Heart. Studies also suggest that the benefits of statins go beyond the heart. At this time, nearly all studies on the following conditions have used natural statins:

- Stroke. Statins may reduce the risk for *ischemic* stroke in high-risk patients with a wide range of cholesterol and lipid levels. (Ischemic strokes occur from blockage in the blood vessels that lead to the brain.)
- Diabetes. Statins may have a number of effects that are helpful for patients with diabetes by preventing cardiovascular events including coronary death, heart attack, and stroke.
- High Blood Pressure. In an important study, patients with high blood pressure and slightly high cholesterol levels had fewer heart attacks and strokes when they took the statin atorvastatin. The study was stopped early so all subjects could have the benefit of statins. An earlier study showed similar benefits with the statin simvastatin.
- Kidney Disease. Statins may protect against heart disease development in patients with mild kidney disorders. Some research suggests that statins may also help slow the progression of existing kidney disease.

Adverse Effects. Statins tend to be better tolerated than other cholesterol-lowering drugs. In many studies the side effects reported were nearly the same as those taking placebo. 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 has involved 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 2005, the FDA issued a public health advisory for rosuvastatin (Crestor), noting that this drug, like other statins, increased the risk for myopathy and rhabdomyolysis. The risks were greatest at the highest dose level (40 mg). The FDA advises that patients should not start therapy at a higher dose. In addition, the FDA reported the results of a post-marketing study that found that people of Asian heritage had twice the blood levels of the drug as Caucasians who had taken the same dose. Because of this difference in drug metabolism, the FDA advises that Asian Americans should start treatment at the lowest rosuvastatin dose (5 mg). 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.

Statins can also affect the liver, particularly at higher doses, so patients should have periodic liver function tests. (However, abnormal test results do not necessarily indicate an increased risk for liver disease.) 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.

Nicotinic Acid (Niacin)

Brands. Nicotinic acid is the active compound found in niacin, or vitamin B3. It is the first choice for patients with low HDL levels. Brands include Niacor, Nicolar, 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 is given in much higher doses and is available only by prescription. 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, nicotinic acid 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 nicotinic acid. 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 nicotinic acid. 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 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 nicotinic acid 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 nicotinic acid because it elevates uric acid.

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.

When used in combination with dietary control, LDL levels are reduced by 15 - 20%. Combinations with nicotinic acid are even more effective, with reductions of 40 - 60% observed.

Brands. Cholestyramine (Questran, Questran Light) is commonly used in a powder that is dissolved in liquid. Colesevelam (Welchol) is available in tablet form.

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.

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.

Fish Oil

Omega 3 fattay acids in fish oil (Lovaza, over the counter) can lower triglyceride levels.

Side Effects. Side effects include burping and a a fishy taste. LDL levels may increase in some patients.

Ezetimibe

Ezetimibe (Zetia) blocks absorption of cholesterol that comes from food. Ezetimibe is usually prescribed alone or in combination with a statin. Ezetimbe 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.

In 2004, the FDA approved Vytorin, which combines ezetimbe and the statin simvastatin into a single pill. Vytorin should not be used along with fibrate drugs.

In 2008, the results of a small study of patients with familial hypercholesterolemia, (an inherited form of high cholesterol), indicated that the combination of ezetimbe and simvastatin (marketed as Vytorin) showed no benefit over simvastatin alone (marketed as Zocor) in reducing the rate of atherosclerosis progression. The American College of Cardiology advises patients that the results of this trial are still very preliminary. More studies need to be conducted before any changes in clinical recommendations can be made. If you have concerns about Vytorin, discuss them with your doctor. Patients who take Vytorin should not stop using this drug without talking to their doctors.

Investigational Therapies

CETP Inhibitors. Cholesteryl ester transfer protein (CETP) inhibitors, such as the experimental drug torcetrapib, are

a new drug class that is being investigated for its effect on raising HDL ("good" cholesterol) levels while lowering LDL ("bad") cholesterol levels. Torcetrapib was the most widely studied of these drugs. However, in December 2006, the drug's manufacturer abruptly stopped late-stage clinical trials after discovering that torcetrapib significantly increased blood pressure and risk of death.

Several studies published in 2007 in the *New England Journal of Medicine* revealed that while torcetrapib does greatly boost HDL levels (by 61% in one study) and lower LDL, it has no effect on arterial plaque. It is still not clear whether the failure of trocetrapib is specific to this drug or the entire CETP drug class. Given the current findings, it is also unclear whether research will continue on other CETP drugs.

Plasmapheresis and Familial Hypercholesterolemia. Plasmapheresis is a blood-filtering procedure that is used to dramatically reduce triglycerides and may also be used to remove LDL. The procedure may be beneficial for patients with severe hereditary forms of high cholesterol who do not respond to other therapies. Studies suggest, for example, that plasmapheresis is particularly useful for patients with familial hypercholesterolemia. The process takes about 3 hours. If not performed regularly, its benefits last only about 2 weeks. People using this procedure are still advised to maintain a healthy diet and continue to take any prescribed medications to control cholesterol.

Resources

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

References

AHA; ACC; National Heart, Lung, and Blood Institute, Smith SC Jr, Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update endorsed by the National Heart, Lung, and Blood Institute. *J Am Coll Cardiol*. 2006 May 16;47(10):2130-9.

Armitage J. The safety of statins in clinical practice. Lancet. 2007 Nov 24;370(9601):1781-90. Barter P, Gotto AM, LaRosa JC, Maroni J, Szarek M, Grundy SM, et al. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. *N Engl J Med*. 2007 Sep 27;357(13):1301-10.

Crouse JR 3rd, Raichlen JS, Riley WA, Evans GW, Palmer MK, O'Leary DH, et al. Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: The METEOR Trial. *JAMA*. 2007 Mar 25; [Epub ahead of print]

Deedwania P, Barter P, Carmena R, Fruchart JC, Grundy SM, Haffner S, et al. Reduction of low-density lipoprotein cholesterol in patients with coronary heart disease and metabolic syndrome: analysis of the Treating to New Targets study. *Lancet*. 2006 Sep 9;368(9539):919-28.

Ford I, Murray H, Packard CJ, Shepherd J, Macfarlane PW, Cobbe S. Long-term follow-up of the West of Scotland Coronary Prevention Study. *N Engl J Med*. 2007 Oct 11;357(15):1477-86.

Gaziano M, Manson JE, Ridker PM. Primary and secondary prevention of coronary heart disease. In: Libby P, Bonow RO, Mann DL, Braunwald E, Zipes DP, eds. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine,* 8th ed. Saunders; 2007;chap 45.

Jolliffe CJ, Janssen I. Distribution of lipoproteins by age and gender in adolescents. *Circulation*. 2006 Sep 5;114(10):1056-62. Epub 2006 Aug 28.

Kastelein JJ, van Leuven SI, Burgess L, Evans GW, Kuivenhoven JA, Barter PJ, et al. Effect of torcetrapib on carotid atherosclerosis in familial hypercholesterolemia. *N Engl J Med*. 2007 Mar 26; [Epub ahead of print]

Kodama S, Tanaka S, Saito K, Shu M, Sone Y, Onitake F, et al. Effect of aerobic exercise training on serum levels of high-density lipoprotein cholesterol: a meta-analysis. *Arch Intern Med*. 2007 May 28;167(10):999-1008.

McCrindle BW, Urbina EM, Dennison BA, Jacobson MS, Steinberger J, Rocchini AP, et al. Drug therapy of high-risk lipid abnormalities in children and adolescents. A scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Disease in the Young, With the Council on Cardiovascular Nursing. *Circulation.* 2007 Mar 21; [Epub ahead of print]

Nissen SE, Tardif JC, Nicholls SJ, Revkin JH, Shear CL, Duggan WT, et al. Effect of torcetrapib on the progression of coronary atherosclerosis. *N Engl J Med*. 2007 Mar 26; [Epub ahead of print]

Park MK. Dyslipidemia and Other Cardiovascular Risk Factors. In: *Pediatric Cardiology for Practitioners*, 5th ed. Mosby; 2008:chap 33.

Thavendiranathan P, Bagai A, Brookhart MA, Choudhry NK. Primary prevention of cardiovascular diseases with statin therapy: a meta-analysis of randomized controlled trials. *Arch Intern Med*. 2006 Nov 27;166(21):2307-13.

US Preventive Services Task Force. Screening for lipid disorders in children: US Preventive Services Task Force recommendation statement. *Pediatrics*. 2007 Jul;120(1): e215-9.

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