A Harvard Medical School Special Health Report

Managing Your Cholesterol

In this report:

Why "good" cholesterol is good (and "bad" cholesterol is bad)

Calculating your heart attack risk

Making sense of the new guidelines

Do you need advanced testing?

SPECIAL BONUS SECTION
Lifestyle changes to improve your cholesterol levels

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LATE BREAKING NEWS

Editor's note: ***Since this report went to press in 2014, there have been two noteworthy updates regarding cholesterol-lowering medications as well as a final ruling on the use of cholesterol-raising trans fats in America's food supply. Following are the details of these developments.***

Two novel cholesterol-lowering drugs approved

In the summer of 2015, the FDA approved two new drugs, alirocumab (Praluent) and evolocumab (Repatha). They belong to a novel category of cholesterol-lowering drugs called PCSK9 inhibitors, which we had previously described in this report as experimental drugs.

PCSK9 is a protein that targets a certain class of receptors on the liver. These receptors remove low-density lipoprotein (LDL, or "bad" cholesterol) from the blood as it passes through the liver. PCSK9 reduces the number of LDL receptors in the liver, resulting in higher levels of LDL in the blood. By hampering PCSK9's ability to work, the PCSK9 inhibitors allow more LDL receptors to remain in the liver. With more receptors available to sweep away LDL, a person's blood levels of LDL plummet.

Three trials in *The New England Journal of Medicine* (NEJM) demonstrated the LDL-lowering ability of these new drugs, which are given by injection under the skin. In all three trials, all of the participants took one of the standard cholesterol-lowering drugs, known as statins. In addition, half were given a PCSK9 inhibitor (either evolocumab or alirocumab) by injection every two to four weeks; the other half got a dummy injection (placebo). After a year, LDL levels were 60% lower in the PCSK9-inhibitor groups. In those treated with evolocumab, the average LDL after one year of treatment was 48 milligrams per deciliter (mg/dL), the lowest LDL ever seen in the experimental arm of a cholesterol-lowering trial. Some participants' LDL levels even fell below 25 mg/dL. Over all, people taking the PCSK9 inhibitors were 50% less likely to have had a heart attack or stroke or develop heart failure over the course of the one-year trials.

Both alirocumab and evolocumab are approved for people who are already taking the maximum tolerated dose of a statin and either have known heart disease (a previous heart attack or stroke) or a genetic condition that causes very high LDL levels, called familial hypercholesterolemia (see page 15). Evolocumab is also approved for people who have a very rare form of the disease called homozygous familial hypercholesterolemia. This is a condition associated with exceedingly high levels of LDL cholesterol and a high risk of heart disease.

The most common side effects of the drugs included reactions at the injection site, such as redness, swelling, itching, and pain. Less commonly, some people developed symptoms resembling flu or a cold, and some experienced cognitive problems, such as mental confusion or trouble paying attention.

The new drugs are estimated to cost around $14,600 per year, although the actual out-of-pocket cost will depend on a person's insurance coverage. Statins—most of which are available as generics—cost as little as $4 per month through discount programs at large chain stores. So if you can control your LDL cholesterol level with diet alone or diet plus a statin, these approaches will be much more cost-effective than using a PCSK9 inhibitor. Also,

you will avoid the need for an injection every two to four weeks. The PCSK9 inhibitors should be reserved for people in whom diet plus a statin has not been effective and for people who cannot tolerate statins because of side effects. People with familial hypercholesterolemia should receive a PCSK9 inhibitor as primary therapy.

From these powerful new drugs we will learn more about how low LDL cholesterol levels should be maintained for optimal health.

Study suggests the benefit of a combo drug

Another *NEJM* study clarified the potential benefits of a combination drug for preventing heart attacks and strokes. The IMPROVE-IT study included more than 18,000 people who were recovering from heart attacks. Half took a statin drug called simvastatin, and half took Vytorin—a combination of simvastatin and ezetimibe (see page 42). After six years, LDL levels in the Vytorin group dropped to an average of 54 mg/dL, and 32.7% of those taking Vytorin had experienced a stroke or repeat heart attack. Those who took simvastatin alone had a higher average LDL level (70 mg/dL), and 34.7% of them had had another heart attack or a stroke. Rates of side effects were similar in both groups. (The retail price of Vytorin is about $200 per month.)

Although the difference in cardiovascular events between the groups may seem small, some experts note that even a 2% reduction spread across the U.S. population would make a significant dent in deaths and disabilities caused by cardiovascular disease. Because the findings add to evidence that a lower LDL leads to fewer cardiovascular events, some experts believe the pendulum,might swing back to refocusing on LDL targets, as in previous cholesterol guidelines (see "Making sense of the new statin guidelines," page 24). Vytorin is a reasonable choice to lower LDL cholesterol in those people who have not responded well to a statin alone.

Trans fats: The long goodbye

In June 2015, the FDA finalized its determination that trans fats are no longer "generally recognized as safe" for use in foods (see page 29). That means any food company wanting to use partially hydrogenated oils—the main source of harmful trans fats—must get the FDA's approval to do so. Companies have until 2018 to stop using partially hydrogenated oils or to petition the FDA for approval. Trans fats raise the LDL cholesterol level, and in this way they increase the risk of heart disease. Previously they were commonly found in margarines and other foods containing partially hydrogenated oils.

About 85% of trans fat has already been removed from the U.S. food supply. But until 2018, it still makes sense to keep checking food labels for the words "partially hydrogenated" or "hydrogenated fat," so that you can avoid these harmful fats.

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Dear Reader,

For years, cholesterol numbers dominated discussions about heart health and disease. The amount of "bad" cholesterol in a person's bloodstream largely determined whether he or she needed treatment, what medications to take, and even what target level to reach. Those numbers were etched in doctors' minds by guidelines from the National Heart, Lung, and Blood Institute, which largely directed when and how doctors treated high cholesterol between 2004 and 2013.

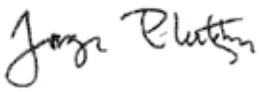
In late 2013, however, new national guidelines from the American Heart Association and American College of Cardiology shifted the focus somewhat, recommending that treatment be based not on cholesterol numbers alone, but on an individual's overall risk for having a heart attack or stroke or for developing some other form of cardiovascular disease. People with high cholesterol are still advised to take cholesterol-lowering statin drugs—but so are some people with "normal" cholesterol levels who are at high risk for heart disease.

The new guidelines have generated heated debate among doctors and cholesterol experts. Some worry that applying the guidelines will unnecessarily increase the number of Americans on statins—and that the calculator used to help doctors determine treatment overestimates cardiovascular risk, again resulting in some people unnecessarily taking statins. On the other hand, some experts feel aspects of the guidelines are not aggressive enough, given their abandonment of specific target cholesterol levels.

This report will help you make sense of the new guidelines and figure out how, or if, they apply to you. It covers the basics about cholesterol: what it is, what it does in the body, how it is measured and treated, and how to work with your doctor to lower your risk of cardiovascular disease—the No. 1 killer of Americans. While the treatment section covers medications—mainly statins—it also focuses on lifestyle choices that are important weapons in the fight against heart disease.

High cholesterol is not a disease. It is a risk factor for heart disease, and you can do something about it. This report will help you make informed decisions.

Sincerely,



Jorge Plutzky, M.D.
Medical Editor

Cholesterol: Good, bad, and indifferent

If you held an ounce of cholesterol in your hand, you would see a whitish-yellow waxy powder that resembles very fine scrapings from a candle. That waxy consistency is no accident, for cholesterol is a type of fat—or what doctors and researchers call a lipid. Though cholesterol tends to have a bad reputation—with its name linked to heart attacks, strokes, and other types of cardiovascular disease—cholesterol and other lipids are as necessary for humans and other animals as water or air.

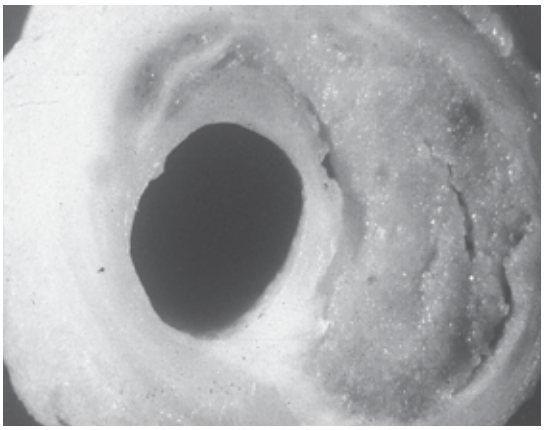
Cholesterol is the main component of cell membranes and other structures, a kind of building block for body tissues. Certain glands use it to produce corticosteroids and hormones, including testosterone and estrogen. The liver uses it to help make the bile acids we need to digest and absorb fats. Cholesterol is also an important precursor to vitamin D.

In fact, cholesterol is so important that your liver and intestines make an additional supply beyond the "dietary" cholesterol you consume in food. Though many people fret about the cholesterol in their food, only 20% to 25% of the cholesterol in your bloodstream actually comes directly from this source. Your body makes the other 75% to 80% from such raw materials as fats, sugars, and proteins. If you're an adult who eats only 200 to 300 milligrams (mg) of cholesterol a day (one egg yolk has about 200 mg), your body will make an additional 800 mg a day, most of it in the liver.

So why is cholesterol a concern? The problem isn't having cholesterol in your bloodstream—it's having too much, especially too much of the wrong kind. When that happens, it can accumulate in the walls of blood vessels, where it can cause trouble (see Figure 1, below left).

This chapter drills down into the biology of cholesterol. It may provide more detail than you want to know; if so, feel free to skip ahead to sections on treatment, testing, and the new guidelines. But you may find yourself coming back here to understand some important issues—for example, why HDL cholesterol is considered "good" or why high triglycerides can be a problem.

Figure 1: Inside a cholesterol-filled artery



What goes in doesn't all come out. Years of eating foods rich in saturated and trans fat and easily digested carbohydrates contributes to the development of cholesterol-laden plaque in the arteries that nourish the heart and other parts of the body. These deposits narrow arteries and slow blood flow through them. When plaque breaks apart, it can cause a heart attack or stroke.

Cholesterol's various forms

Since cholesterol is a fat, it can't travel alone in the bloodstream. It would end up as useless globs (imagine bacon fat floating in a pot of water). To get around this problem, the body packages cholesterol and other lipids into minuscule protein-covered particles that mix easily with blood. These tiny particles, called lipoproteins (lipid plus protein), move cholesterol and other fats throughout the body.

Cholesterol and other lipids circulate in the bloodstream in several different forms. Of these, the one that gets the most attention is low-density lipoprotein—better known as LDL, or "bad" cholesterol. But lipoproteins come in a range of shapes and sizes,

and each type has its own tasks. They also morph from one form into another. These are the five main types:

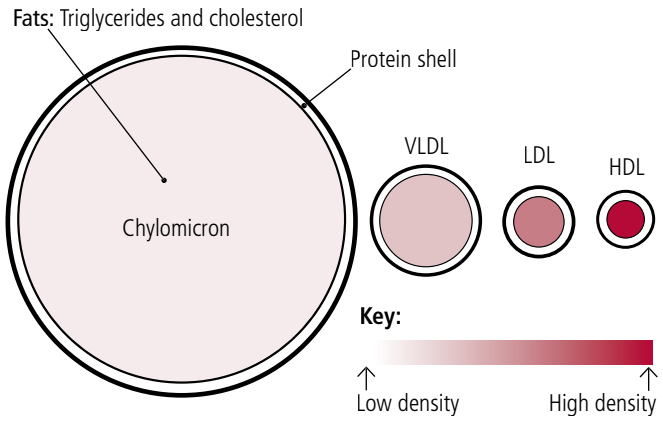
- **Chylomicrons** are very large particles that mainly carry triglycerides (fatty acids from your food). They are made in the digestive system and so are influenced by what you eat.
- **Very-low-density lipoprotein (VLDL)** particles also carry triglycerides to tissues. But they are made by the liver. As the body's cells extract fatty acids from VLDLs, the particles turn into intermediate-density lipoproteins, and, with further extraction, into LDL particles.
- **Intermediate-density lipoprotein (IDL)** particles form as VLDLs give up their fatty acids. Some are removed rapidly by the liver, and some are changed into low-density lipoproteins.
- **Low-density lipoprotein (LDL)** particles are even richer in pure cholesterol, since most of the triglycerides they carried are gone. LDL is known as "bad" cholesterol because it delivers cholesterol to tissues and is strongly associated with the buildup of artery-clogging plaque.
- **High-density lipoprotein (HDL)** particles are called "good" cholesterol because they remove cholesterol from circulation and from artery walls and return it to the liver for excretion.

fast fact | Cholesterol levels are measured in terms of milligrams per deciliter (mg/dL), or thousandths of a gram per each tenth of a liter. A value of 240 mg/dL is the equivalent of dissolving about a pinch of cholesterol—about a third of an ounce—in a gallon of water.

Other lipoproteins also exist, including alpha-lipoprotein, beta-lipoprotein, lipoprotein(a), and pre-beta-lipoprotein.

As the names of the main lipoproteins suggest, they have different densities. Chylomicrons and VLDL particles are the largest, fluffiest, and least dense. HDL particles are the smallest and most dense (see Figure 2, below left). Density isn't solely a matter of size, but also of the ratio of fat to protein in each particle. The higher the ratio—meaning the higher the fat content—the lower the particle density. Even among particles of a certain type, such as LDL, particle size and density can vary. Some data suggest that smaller, denser LDL particles are more dangerous than larger, fluffier ones (see "LDL particle size," page 5).

Figure 2: The particles story



Lipoproteins—four kinds of which are shown in this diagram—circulate in the bloodstream. They carry and deliver cholesterol, triglycerides, and other substances to cells and tissues. The largest and lowest-density particle is the chylomicron, which contains mostly triglycerides. The smallest and densest particle is high-density lipoprotein (HDL, right), which contains less cholesterol and more protein and dense lipids.

From food to cholesterol

When you eat, your intestines absorb nutrients from your food. Intestinal enzymes dismantle fats into their component fatty acids. These are then reassembled into new triglyceride molecules, and packaged—along with a small amount of cholesterol—into chylomicrons. At the same time, carbohydrates and proteins that are absorbed from the intestine pass to the liver. The liver converts some of these nutrients to triglyceride molecules, packages them with cholesterol and proteins called apolipoproteins, and releases the resulting VLDL particles into the bloodstream (see Figure 3, page 4).

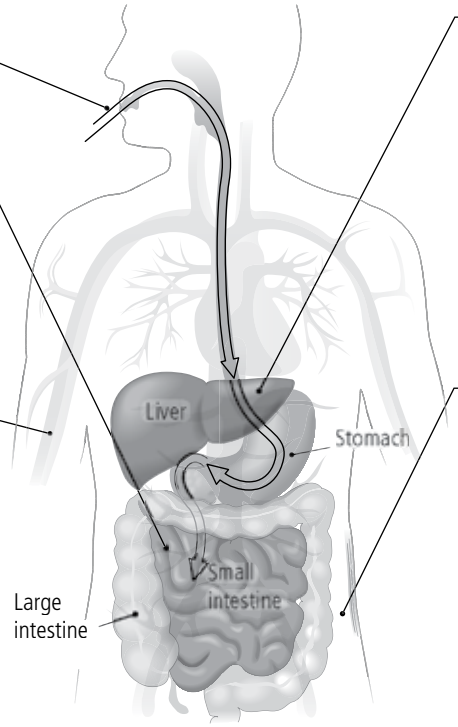
After you eat a meal or snack, the amount of triglyceride-rich particles in the blood increases for several hours. As chylomicrons and VLDLs course through the bloodstream, they temporarily stick to the walls of blood vessels in tissue that needs energy or in fatty tissue that stores energy. Specific enzymes

Figure 3: Cholesterol's path through the body

Eating. The food you eat contains fats, carbohydrates, and proteins.

Digesting. Your intestine breaks down some of these nutrients. It takes fats and reassembles them into triglyceride molecules, and then adds a small amount of cholesterol and repackages them into chylomicrons. It sends carbohydrates and proteins to the liver for processing.

The particles. Chylomicrons and VLDLs course around the bloodstream, sometimes sticking to blood vessels or fatty tissue, which take their triglycerides into the cells. The resulting particles are known as remnant particles (if from chylomicrons) or IDLs (if from VLDLs). As the IDLs circulate in the bloodstream and undergo further changes, they become LDLs.



The liver. Here, some carbohydrates and proteins get changed into triglyceride molecules, and then put together with apolipoproteins and cholesterol. This combination results in VLDL particles, which the liver then sends into the bloodstream.

Storing energy. Some of the fats from these particles are not immediately used by cells, but are stored inside cells for later use.

come along and transfer triglyceride molecules from chylomicrons or VLDLs into the body's tissues. As this happens, the particles' protective protein coats are rearranged and reconfigured. This gives them a new "address label" that can be read by the liver or other tissues that take up lipoproteins.

The creation of LDL

As chylomicrons and VLDLs give up their triglyceride (fatty acid) cargo, they become smaller and denser. Eventually, all that remains is the packaging material—the protein and cholesterol—and a fraction of the original triglyceride. These particles, called intermediate-density lipoproteins (IDLs), keep circulating and undergo further modification of their lipid and protein content. Over time, IDLs becomes LDLs. (The liver filters some chylomicron remnants from the system and recycles their components.)

LDL particles deliver cholesterol to virtually all the cells in the body. When there are more LDL particles in circulation than your body can use, your liver absorbs as many as it can to make bile acids or new lipoproteins. But if the liver can't clear all of the LDL from the blood, some of it can wind up in the wrong places—typically in blood vessels. The more LDL in the bloodstream, the more LDL and cholesterol end up in artery walls.

Recent research, however, suggests that LDL can vary somewhat in size and density, with the larger, less dense particles being less prone to lodging in artery walls (see "LDL particle size," page 5).

The role of HDL

In the simplest telling of the cholesterol story, HDL (the so-called good cholesterol) fights LDL (bad cholesterol). Like knights in shining armor, HDL particles patrol the blood vessels, snatching cholesterol from circulating LDL particles and from the dangerous, gooey plaque that lines artery walls. The knights of the HDL then carry their fatty cargo to the liver for recycling or disposal (see Figure 4, page 5). In this role, HDL protects against heart attack, stroke, and atherosclerosis.

The *real* story isn't quite so simple, of course. HDL is a much more complex substance than experts once believed. Instead of a single kind of particle, HDL is a

LDL particle size

When it comes to heart disease, not all LDL particles are created equal. Not everyone with high LDL develops heart disease, and some people with "normal" LDL do. One possible explanation has to do with the size and density of LDL particles. Smaller, denser LDL has an easier time getting into artery walls, where it can become oxidized, leading to the sequence of events that results in atherosclerosis. By contrast, larger, fluffier LDL particles are more like beach balls bouncing off the artery walls rather than getting stuck there. Therefore, larger, less dense LDL particles are believed to be less dangerous.

Several companies now offer so-called advanced lipoprotein testing (see "Ask the doctor: Advanced lipoprotein testing," page 22). This is a more detailed version of the standard lipid test. Advanced lipoprotein testing measures the amount of LDL and other lipid particles as well as their size and the number of particles in each size category. Is advanced testing necessary? For most people, the short answer is no. The non-HDL calculation from a standard lipid test (see "Non-HDL cholesterol," at right) can provide some of the same information.

family of different particles. Although they all contain lipids, cholesterol, and proteins called apolipoproteins, some types are spherical, while others are doughnut-shaped. Some types of HDL are great at plucking cholesterol from LDL and artery walls. Some can ease inflammation in artery walls, stimulate production of nitric oxide (a molecule that helps artery walls relax), and help prevent blood clots from forming inside arteries—all of which help ward off heart disease. Some types of HDL protect LDL from being chemically altered by oxygen, a change that makes LDL extra harmful. Under some circumstances, though, they can do just the opposite. To further complicate matters, other types of HDL don't remove cholesterol from artery walls. And some even transfer cholesterol the wrong way—into LDL and cells!

If your HDL level is on the low side, there are a number of ways to raise it—from regular exercise to medications (see "Fibrates" and "Niacin" on page 43, and "Medications: Statins" on page 38). But it's not clear whether HDL-boosting drugs actually reduce your risk of having a heart attack or stroke.

Non-HDL cholesterol

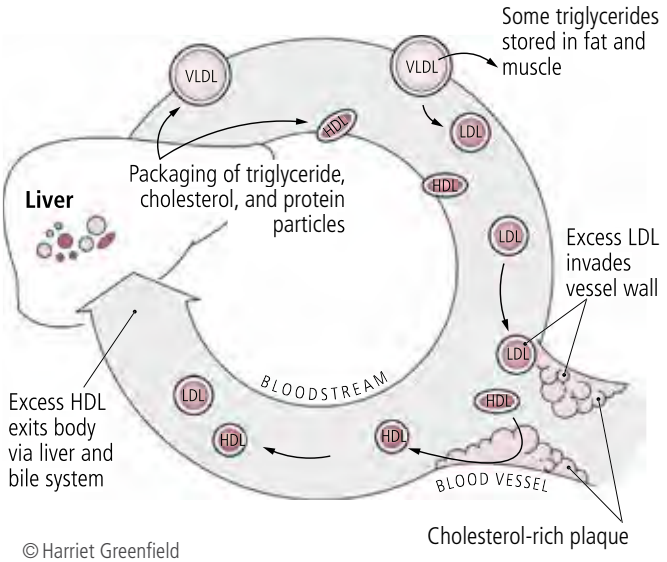
Non-HDL cholesterol refers to all cholesterol other than HDL—that is, the sum of your LDL, VLDL, and IDL cholesterol levels. Until recently, non-HDL cholesterol was used to guide treatment decisions.

You can find your non-HDL level by subtracting your HDL cholesterol value from your total cholesterol reading. If you have normal LDL but high triglycerides, experts recommend using your non-HDL levels as an additional guide in assessing possible treatments.

Triglycerides

A triglyceride molecule consists of three fatty acid chains linked to a backbone called glycerol. The amount of triglycerides in the bloodstream rises and falls throughout the day. After a meal, there can be so many triglyceride particles in the bloodstream that they give the blood a milky tint. Within a few hours, they're mostly cleared out.

Figure 4: Give and take: Cholesterol in the bloodstream



The liver releases fat-laden VLDLs into the bloodstream. VLDLs send some of their fatty triglycerides into the body's muscles and fat tissues, and the VLDLs become cholesterol-rich LDLs. The body needs LDLs for many functions, but often there are more LDLs than the body needs. If so, they are deposited in the lining of blood vessels in the form of cholesterol-rich plaque, which can cause heart disease. HDLs are the garbage collectors, scooping up the cholesterol and carrying it back to the liver for disposal.

Triglycerides are typically considered a risk factor for cardiovascular disease, but they are so influenced by other factors that their value as an independent risk factor is still debated. People with higher triglyceride levels often have excess body fat, especially around the abdomen. People with type 2 diabetes, prediabetes, and insulin resistance (meaning their cells don't respond to insulin's signal to "absorb sugar now") also tend to have high triglycerides. Having high triglycerides and low HDL puts you at particularly high risk for heart disease.

Whether or not high triglycerides alone contribute to heart disease, a very high triglyceride level can lead to pancreatitis (an inflammation of the pancreas) and other disorders. Doctors usually recommend treatment when the triglyceride level rises above 500 mg/dL.

Cholesterol and heart disease

In the late 1800s, a German doctor named Rudolf Virchow discovered that the coronary arteries of people who had died of heart attacks were often clogged with cholesterol-filled plaque. But it wasn't until the middle of the 20th century that cholesterol's link to heart disease began filtering into the scientific literature and public consciousness. Some of the most important early data came from the Seven Countries Study, a pioneering comparison of different populations around the world, which was the first study to link higher cholesterol in the bloodstream and increased death rates from heart disease. Around the same time, the landmark Framingham Heart Study began following the long-term cardiovascular health of more than 5,000 men and women in a single town in Massachusetts. In 1966, early results from Framingham showed that study participants whose total blood cholesterol levels topped 240 mg/dL were more likely to develop heart disease than those with lower cholesterol levels, all other factors being equal. Figure 5 (page 8) shows how excess cholesterol can cause trouble.

The role of diet

News that cholesterol in the bloodstream was linked to heart disease prompted an all-out war on cholesterol in food. From the 1960s on, we were advised to stay away from foods rich in cholesterol, like eggs, dairy foods, and some types of seafood. And for some people, that's wise advice, as cholesterol in the diet has a substantial impact on their cholesterol levels.

For many people, however, dietary cholesterol has little effect. The trouble is there's no easy way to tell if you are a "responder" or a "nonresponder" to dietary cholesterol. One gauge is to have your cholesterol checked after staying away from eggs for a month or so, then eat an egg a day for a few weeks and have your cholesterol checked again.

But the most important dietary change most people can make to lower cholesterol is to consume a diet rich in fruits, vegetables, fish, and whole grains. (For more information, see the Special Section, "Lifestyle changes to improve your lipid levels," page 28.) These foods physically help remove cholesterol from the bloodstream. In addition, the more of these you eat, the fewer foods you generally consume that are high in saturated fats, trans fats, and highly refined carbohydrates, all three of which boost cholesterol levels.

This doesn't work for everyone, however. Some people are genetically predisposed to having high blood cholesterol regardless of the amount of cholesterol and type of fat they eat (see "Genetic risks," page 13). In other cases, cholesterol levels may be tied to other health issues (see "Health problems and medications that can affect your cholesterol," at left). For most people, though, diet plays a role.

Health problems and medications that can affect your cholesterol

Diet, exercise, and genes play major roles in determining your cholesterol level, but various drugs and medical conditions can also influence it.

Medical problems that can be associated with increased cholesterol levels include an underactive thyroid gland (hypothyroidism), diabetes, some liver diseases, Cushing syndrome (a disorder caused by an excess of steroid hormones), excessive alcohol consumption, and kidney trouble. If you have one of these conditions, treating it can improve your lipid profile and may eliminate the need for lipid-lowering drugs.

Taking certain medications can also boost your lipid levels. Common offenders include thiazide diuretics (water pills), beta blockers, steroids (both anabolic steroids and glucocorticoids, such as prednisone), progestins, amiodarone (a drug for heart rhythm problems), and retinoids and other vitamin A derivatives. Adjusting the dose may help. If it doesn't, your physician may switch you to another drug that doesn't have the same effect on lipids.

The role of inflammation

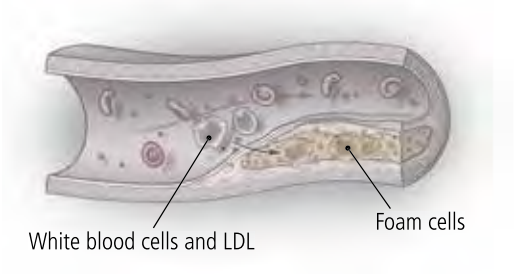
Cholesterol doesn't only clog arteries. It also triggers inflammation. Like cholesterol itself, inflammation is one of those things that's helpful in the right context, but harmful in others.

Inflammation is an essential part of the immune system's defenses. It helps guard against bacteria, viruses, and other foreign invaders; remove debris; and repair damaged tissue. But it can also be like friendly fire. Inflammation initiates the process of plaque buildup in the arteries, keeps it going, and influences the formation of artery-blocking clots, the ultimate cause of most heart attacks and many strokes.

The trouble starts when LDL particles penetrate the lining of artery walls and undergo changes like oxidation (see Figure 5, below). The immune system

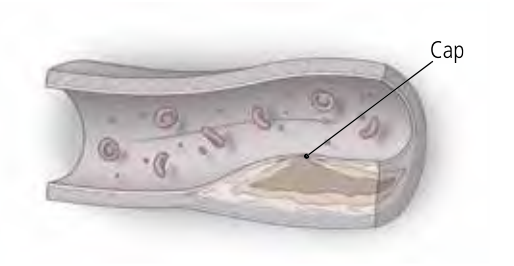
Figure 5: From cholesterol to crisis

How does cholesterol traveling in the bloodstream cause heart attack? It's not just the result of a buildup of fatty plaque in the arteries. Inflammation triggered by damage to the inner lining of an artery sets off the steady growth of atherosclerotic plaque, which can suddenly rupture, causing a heart attack. The steps play out as follows.



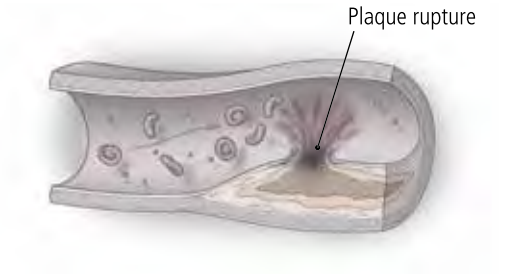
STAGE 1 Plaque builds up within the artery.

LDL cholesterol lodges in the artery wall, where it can become oxidized, triggering a harmful sequence of events. Any injury to the inner layer of cells lining the artery (caused by high blood pressure, smoking, or diabetes, for example) speeds this process. White blood cells arrive on the scene and engulf LDL cholesterol in the artery wall. These cells then enlarge and transform into fat-laden foam cells.



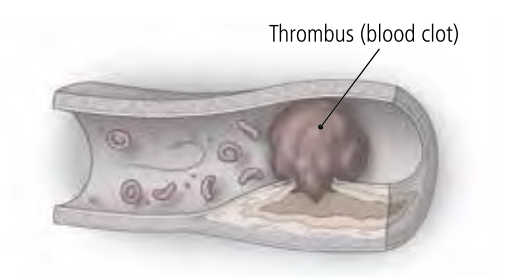
STAGE 2 A fibrous cap tops the plaque.

As foam cells die, they release soft, fatty gruel that provokes further inflammation. Smooth muscle cells in the artery wall multiply and even migrate in, helping form a cap over the whole mess to seal off the plaque. Some large plaques may be contained mainly within the vessel wall, while others can extend into the interior of the artery, limiting blood flow and the delivery of oxygen to the part of the heart served by that artery.



STAGE 3 The plaque ruptures.

About three of every four heart attacks occur because of plaque rupture. But it is not necessarily the large plaques that are most dangerous. Large plaques are often covered by thick, fibrous caps that resist breaking apart. By contrast, smaller plaques may be active, dynamic lesions teeming with inflammatory cells—and they sometimes have very thin, underdeveloped caps that rupture easily. These smaller plaques do not always produce symptoms during a cardiac stress test because they may be too small to block blood flow.



STAGE 4 A clot blocks the artery.

Once a plaque ruptures, a protein called tissue factor is released into the bloodstream, where it attracts platelets. The platelets stick to the disrupted plaque, triggering proteins in the blood to start clotting. The result is a thrombus—a clot of red blood cells, platelets, and other material—that completes the blockage and prevents blood from reaching the heart cells downstream. Deprived of blood and oxygen, a portion of the heart muscle dies. This whole process of rupture and the formation of a thrombus can happen in minutes.

recognizes oxidized LDL as a foreign substance and mobilizes white blood cells called monocytes to attack it. Monocytes make chemical messengers (cytokines) that attract more monocytes to the area. But that's not all they do. Inside the artery wall, monocytes transform into macrophages (Latin for "big eaters"), which engulf and digest LDL particles. They consume so many that they look foamy, and so are called foam cells. As LDL continues to enter the artery wall, more foam cells form. Ultimately, the accumulation of LDL inside foam cells kills them. The dying cells release their load of cholesterol, along with other inflammatory substances, into a gooey pool called plaque.

Testing for inflammation

Proteins that are markers for inflammation, such as C-reactive protein (CRP), can be elevated for years before a first heart attack. CRP is best measured using a high-sensitivity test, called an hsCRP test. When interpreted within the context of other risk factors, an hsCRP score greater than 3 milligrams per liter (mg/L) indicates a higher risk for future heart attack or stroke. A score of 1 to 3 indicates average risk, while below 1 mg/L indicates lower risk (see Table 1, below).

Individual hsCRP scores can vary widely from one person to the next. Your genes play a role, perhaps as much as 20% to 40%. So do environmental and lifestyle factors, such as smoking, drinking, diet, and exercise. Controlling these lifestyle factors is crucial to reducing CRP levels and risk.

In addition, statin therapy—which lowers cardiovascular risk largely by reducing LDL levels—may owe part of its effectiveness to reducing inflammation. An important study called JUPITER helped tease out this connection. The study included 18,000 apparently healthy men (ages 50 and older) and women (ages 60 and older) who had normal cholesterol levels but high hsCRP scores. The participants were randomly assigned to take either the widely used statin drug rosuvastatin (Crestor) or a placebo. After about two years, the results showed that rosuvastatin not only lowered LDL cholesterol, as expected, but also lowered CRP levels. The people who took rosuvastatin were also 44% less likely to suffer a major cardiovascular event, such as heart attack or stroke, compared with those taking a placebo.

Table 1: C-reactive protein and heart risk

RISK LEVEL	hsCRP SCORE
Low risk	below 1 mg/L
Average risk	1–3 mg/L
High risk	above 3 mg/L

fast fact | Among people surviving a first heart attack, 18% of men and 35% of women will have a second heart attack within six years.

Guidelines for using CRP in clinical practice are still evolving. For now, whether or not someone should get a CRP test is based on the following standards:

- If you are already being treated for heart disease or are at high risk for cardiovascular disease (greater than 20% chance in the next 10 years, based on the calculations in Tables 3 and 4 or an online risk calculator), you don't need a CRP test. Its results won't change how you and your doctor manage your condition.
- If you have a moderate risk of heart attack (10% to 20% chance in the next 10 years), an hsCRP test might help more accurately place you in a high- or low-risk category. People at moderate risk, based on conventional risk factors such as high blood pressure, might move into the high-risk category if they also have elevated CRP. Such people might need more aggressive treatment to prevent a heart attack.
- If your cholesterol levels are fine but you have other risk factors (such as diabetes, high blood pressure, or a family history of heart disease), ask your doctor whether an hsCRP test would help better assess your risk and decide how to reduce it. Think of the results as a "tiebreaker" to help you decide whether to take medications, if you're on the fence about doing so.

Understanding your cardiovascular risk

Although this report focuses on cholesterol, keep in mind that there are many contributors to heart disease. Some of them you can control; others, you can't. This chapter briefly lists various risk factors in addition to cholesterol that play a role in heart disease and includes calculators to help you gauge your overall risk.

Risk factors for heart disease

Risk factors influence your chances of having a heart attack or stroke in a number of ways. For example, high blood pressure puts stress on the walls of blood vessels. Elevated blood sugar from diabetes can damage the arterial lining and make platelets stickier and more likely to clot. Obesity increases the chances of developing several other risk factors for heart disease, including high blood pressure, type 2 diabetes, and high cholesterol or other blood lipids.

Risk factors you can't change

These risk factors are beyond your control:

- being over age 45 (for men) or 55 (for women)
- having a father or brother who developed heart disease before age 50 to 55, or a mother or sister who developed it before age 60 to 65; this represents a family history of premature (or early) coronary disease and can indicate genetic susceptibility
- being a postmenopausal woman, whether from natural or surgical menopause (a hysterectomy).

Risk factors you can treat or control

You can take steps to address these risk factors:

- high blood pressure—defined as blood pressure at or above 140/90 mm Hg, or taking medication to control your blood pressure
- cholesterol-clogged arteries (atherosclerosis); this can be silent and show no symptoms, or may appear as chest pain with exertion or stress (angina), peripheral artery disease, abdominal aortic aneurysm, carotid artery disease, or renal artery disease
- diabetes
- high triglycerides, high LDL cholesterol, or both (see Table 2, below)
- low HDL cholesterol (see Table 2, below)
- metabolic syndrome—a cluster of cardiovascular risk factors, which can overlap with another con-

Table 2: Quick guide to cholesterol and triglyceride levels in adults

Although the new guidelines no longer call for treating to specific cholesterol targets, the following guide can help you determine if your cholesterol is on the high side.

TOTAL CHOLESTEROL LEVEL	TOTAL CHOLESTEROL CATEGORY
Less than 200 mg/dL	Desirable
200–239 mg/dL	Borderline high
240 mg/dL and above	High
LDL CHOLESTEROL LEVEL	**LDL CHOLESTEROL CATEGORY**
Less than 100 mg/dL	Optimal
100–129 mg/dL	Near optimal/above optimal
130–159 mg/dL	Borderline high
160–189 mg/dL	High
190 mg/dL and above	Very high
HDL CHOLESTEROL LEVEL	**HDL CHOLESTEROL CATEGORY**
Less than 40 mg/dL	Low (representing risk)
60 mg/dL and above	High (heart-protective)
TRIGLYCERIDE LEVEL	**TRIGLYCERIDE CATEGORY**
Less than 150 mg/dL	Normal
150–199 mg/dL	Borderline high
200–499 mg/dL	High
500 mg/dL and above	Very high

Source: Adapted from the National Cholesterol Education Program.

Metabolic syndrome

Metabolic syndrome is the name for a collection of risk factors that raise your risk for heart disease, diabetes, and other health problems.

You have metabolic syndrome if you have three or more of the following:

- a large waist (greater than 40 inches for men or 35 inches for women); to measure your waist, wrap a tape measure around the largest part of your midsection, keeping the tape measure parallel to the floor
- borderline or high blood pressure (130/85 mm Hg or higher)
- high triglycerides (150 mg/dL or higher)
- low HDL (under 40 mg/dL for men or 50 mg/dL for women)
- high fasting blood sugar (110 mg/dL or higher).

In people with metabolic syndrome, blood sugar levels stay high after a meal or snack instead of dropping to a baseline level like they do in healthy people. The pancreas, sensing still-elevated glucose levels, continues to pump out insulin (the hormone that signals cells to take up glucose from the bloodstream). Constant high levels of insulin and blood sugar have been linked with many harmful changes, including damage to the lining of arteries in the heart and elsewhere, increased triglyceride levels, changes in how the kidneys handle salt, and blood that clots more easily. Long-term overstimulation of the pancreas may exhaust it, so that it stops supplying enough insulin.

This cascade of events can damage artery walls and cause the formation of blood clots that can trigger heart attacks and strokes. It can also alter the kidneys' ability to remove salt, which contributes to high blood pressure, another path to heart disease and stroke.

Metabolic syndrome overlaps with other conditions, such as prediabetes. Being diagnosed with prediabetes means that your blood sugar is higher than normal but not yet high enough to be classified as type 2 diabetes. Unless you take steps to control your blood sugar, prediabetes might become type 2 diabetes. What's more, the long-term damage caused by diabetes to the heart and circulatory system may already have started.

dition known as prediabetes (see "Metabolic syndrome," above)

- overweight—defined as a body mass index (BMI) of 25 up to 30—or obesity, a BMI of 30 or more; see www.health.harvard.edu/BMI for an online BMI calculator
- lifestyle factors such as smoking, physical inactivity, a diet high in saturated and trans fats and highly processed carbohydrates, chronic stress, and social isolation, depression, or anxiety.

Protective factors

While some factors increase your odds of having a heart attack or stroke or developing some other form of heart disease, other things help lower your odds. These protective factors include healthy eating and exercise. They are among your most powerful weapons against cardiovascular problems. They're also the first line of defense against diabetes, obesity, metabolic syndrome, and other risk factors. (For more information, see the Special Section, "Lifestyle changes to improve your lipid levels," page 28.) A naturally high HDL level, generally more than 60 mg/dL, also offers protection against cardiovascular disease (see "The role of HDL," page 4).

Weighing the benefits

Not all risk factors are created equal; some carry more weight in the calculations that predict a person's odds of illness or death. On the flip side, that means some lifestyle choices make a bigger difference than others in cutting your chances of developing cardiovascular disease or having a heart attack. You can reap significant benefits by making certain changes. For example:

- Lowering your total cholesterol by 10% can decrease your heart attack risk by 20% to 30%.
- Walking at least two hours a week can cut your chances of dying early from cardiovascular disease by up to 53%.
- If you smoke, quitting reduces your risk for a heart attack by half within a year.
- Maintaining a healthy body weight reduces your risk for heart disease by 45%.
- Eating about 1,200 mg less of sodium a day can reduce the need for blood pressure treatment by half. It can also decrease deaths from stroke by 22% and those from heart disease by 16%.

Calculating risk

In the late 1990s, researchers with the legendary Framingham Heart Study created a heart attack calculator based on several key risk factors: age, total cholesterol, smoking status, HDL level, and blood pressure. You can find this calculator online, at www.nhlbi.nih.gov. You simply enter the information into the calculator, and it tallies up your chance of having a heart attack in the next 10 years. Paper-and-pencil versions, one for women and one for men, appear in Table 3 (below) and Table 4 (page 13).

At the time the Framingham calculator was developed, it covered the key risk factors. Since then, newer calculators have been introduced that include more risk factors. One developed by the American Heart Association and American College of Cardiology to be used with their new cholesterol guidelines includes gender, age, total cholesterol level, HDL level, race, smoking status, systolic blood pressure, treatment for high blood pressure, and diabetes status. It computes an individual's 10-year risk of developing "atherosclerotic cardiovascular disease" (heart attack,

Table 3: Heart attack calculator for women

Use this form to calculate your risk for developing heart disease in the next 10 years.

I. AGE

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

II. TOTAL CHOLESTEROL LEVEL

Total cholesterol (mg/dL)	Age 20–39	Age 40–49	Age 50–59	Age 60–69	Age 70–79
Less than 160	0	0	0	0	0
160–199	4	3	2	1	1
200–239	8	6	4	2	1
240–279	11	8	5	3	2
280 or more	13	10	7	4	2

Your points _____

III. DO YOU SMOKE?

	Age 20–39	Age 40–49	Age 50–59	Age 60–69	Age 70–79	Your points
Nonsmoker	0	0	0	0	0	_____
Smoker	9	7	4	2	1	

IV. HDL LEVEL

HDL (mg/dL)	Points
60 or more	–1
50–59	0
40–49	1
Less than 40	2

Your points _____

V. BLOOD PRESSURE

Systolic BP (mm Hg)	If untreated	If treated
Less than 120	0	0
120–129	1	3
130–139	2	4
140–159	3	5
160 or more	4	6

Your points _____

Your total points

I. _____
+ II. _____
+ III. _____
+ IV. _____
+ V. _____
= _____

SCORING: Your 10-year heart attack risk

Total points	10-year risk
Less than 9	Less than 1%
9	1%
10	1%
11	1%
12	1%
13	2%
14	2%
15	3%
16	4%
17	5%
18	6%
19	8%
20	11%
21	14%
22	17%
23	22%
24	27%
25 or more	30% or more

Adapted from the Third Report of the National Cholesterol Education Program. For an online version, go to www.nhlbi.nih.gov.

stroke, angina, and any other condition caused by cholesterol-clogged arteries) and, for those under age 60, their lifetime risk. So far, the calculator is available only online; there is no paper-and-pencil version. You can find it at www.health.harvard.edu/heartrisk.

Genetic risks: When high cholesterol runs in the family

For most people with high cholesterol, the culprits are diet, lack of exercise, and other lifestyle choices. Others have a genetic disorder that causes very high cholesterol levels. The two most common of these inherited disorders are familial combined hyperlipidemia (FCHL) and familial hypercholesterolemia (FH). Both put people at a heightened risk for early heart disease. They are also manageable with medications, changes in lifestyle (see the Special Section, "Lifestyle changes to improve your lipid levels," page 28), and other treatments.

Various other genetic issues are also linked to increased cardiovascular risk, including inherited

Table 4: Heart attack calculator for men

Use this form to calculate your risk for developing heart disease in the next 10 years.

I. AGE

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

II. TOTAL CHOLESTEROL LEVEL

Total cholesterol (mg/dL)	Age 20–39	Age 40–49	Age 50–59	Age 60–69	Age 70–79
Less than 160	0	0	0	0	0
160–199	4	3	2	1	0
200–239	7	5	3	1	0
240–279	9	6	4	2	1
280 or more	11	8	5	3	1

Your points _____

III. DO YOU SMOKE?

	Age 20–39	Age 40–49	Age 50–59	Age 60–69	Age 70–79	Your points
Nonsmoker	0	0	0	0	0	_____
Smoker	8	5	3	1	1	

IV. HDL LEVEL

HDL (mg/dL)	Points
60 or more	–1
50–59	0
40–49	1
Less than 40	2

Your points _____

V. BLOOD PRESSURE

Systolic BP (mm Hg)	If untreated	If treated
Less than 120	0	0
120–129	0	1
130–139	1	2
140–159	1	2
160 or more	2	3

Your points _____

Your total points

I. _____
+ II. _____
+ III. _____
+ IV. _____
+ V. _____
= _____

SCORING: Your 10-year heart attack risk

Total points	10-year risk
Less than 0	Less than 1%
0	1%
1	1%
2	1%
3	1%
4	1%
5	2%
6	2%
7	3%
8	4%
9	5%
10	6%
11	8%
12	10%
13	12%
14	16%
15	20%
16	25%
17 or more	30% or more

Adapted from the Third Report of the National Cholesterol Education Program. For an online version, go to www.nhlbi.nih.gov.

conditions that lower HDL levels or raise levels of lipoprotein(a)—an emerging risk factor that seems to predict risk in some situations (see "Risk factors under investigation," page 18).

Familial combined hyperlipidemia

FCHL is an inherited disorder that causes the liver to make too much very-low-density lipoprotein. That leads to high levels of cholesterol, triglycerides, or both, often beginning during the teenage years. An estimated one to two people in 100 have FCHL. It's been blamed for one-third to one-half of all inherited causes of coronary artery disease and 10% of all early heart disease (before age 55 in men or before age 65 in women).

Although FCHL was first described in the early 1970s, scientists still don't fully understand the genetics of the disease, which involves multiple genes. People with the condition tend to have high levels of a type of LDL called ApoB-100; high levels of small, dense LDL particles, the most dangerous form of LDL; and low HDL levels. They also tend to have high or very high levels of triglycerides. There is some evidence that people with FCHL are more likely to develop type 2 diabetes.

Some people with FCHL develop small nodules filled with cholesterol that appear over various parts of the body. When they form over tendons, especially the Achilles' tendons of the lower leg, these growths are called xanthomas. When they appear on the eyelids, they are called xanthelasmas.

There is no single test for FCHL. Instead, it can be diagnosed with the standard lipid panel. FCHL is suspected in someone who has a total cholesterol level between 200 and 400 mg/dL, a triglyceride level between 200 and 800 mg/dL, low HDL (under 40 mg/dL), and a close family member with similar levels or early heart disease.

Treating FCHL is much like treating run-of-the-mill high cholesterol—a combination of lifestyle changes and medication—only more intense. Lifestyle changes include cutting back on foods that are rich in saturated and trans fat like red meat, cheese, and full-fat dairy foods; eating less refined carbohydrates like white bread, chips, and pastries; eating more fruits, vegetables, whole grains, fish, poultry, beans, nuts, and low-fat dairy foods; exercising more; and not smoking.

Most people diagnosed with FCHL take a cholesterol-lowering statin. Those with very high triglycerides (greater than 500 mg/dL) and moderately high cholesterol may also need to take a fibrate to prevent pancreatitis (see "Medications: Non-statin drugs and other alternatives," page 42).

Familial hypercholesterolemia

FH is an inherited disorder in which the liver can't remove LDL particles from the blood. This causes cholesterol levels to soar. If not treated, a person with FH has a 20-fold higher risk of heart attack compared with an unaffected person. Indeed, individuals with a defective gene inherited from both the mother and father can have a heart attack as early as one or two years of age.

The gene in question is responsible for making receptors on liver cell surfaces that act as docking

A dialysis-like alternative

LDL apheresis uses a special filtering machine to selectively remove LDL particles and other lipoproteins from the blood to lower total and LDL cholesterol. Blood is taken from the body through a needle placed in an arm vein. It then passes through a filter to remove LDL and other particles. The "cleaned" blood is then returned to the body through another vein. The treatment is similar to the process of dialysis used to treat kidney disease. Although the treatment can quickly bring down dangerously high cholesterol, it is expensive and is available only in a limited number of medical centers.

LDL apheresis works well when combined with cholesterol-lowering medications and a healthy, low-fat diet, but its benefits last only for a week or two, so it needs to be repeated. LDL apheresis is safe, with a low risk of side effects, but it still has possible complications, including increased bleeding in the days after the apheresis, infection, too much or too little fluid returned to the bloodstream, air in the bloodstream (air embolism), and low blood pressure during the procedure and for a few hours afterward. Apheresis requires a big time commitment—about two to four hours every other week. It can't be used by anyone who has a disorder that makes it hard for blood to clot, such as hemophilia.

points for LDL. These receptors let cells latch onto LDL so they can pull in its cargo of cholesterol and other fats. This helps clear LDL from the blood. All people have two copies of the gene, one from each parent. In people who inherit one copy of the faulty gene (heterozygous FH), half of their LDL receptors work; the other half don't. Those who inherit a faulty gene from each parent (homozygous FH) have no working receptors. With nothing to pull harmful LDL from the bloodstream, the level stays high.

Heterozygous FH, by far the more common form, can cause LDL levels as high as 350 mg/dL, more than three times higher than is considered ideal. Among the one in a million people with homozygous FH, LDL levels can reach 1,000 mg/dL.

People often don't realize they have FH because they (and their doctors) assume they simply have hard-to-treat high cholesterol. If your LDL cholesterol level was 190 mg/dL or higher before you started treatment, FH is a possibility. For children, an LDL of 160 mg/dL suggests FH. Another red flag is premature heart disease or very high cholesterol in a parent or sibling.

Like people with FCHL, those with FH can develop cholesterol-filled nodules in the skin—specifically, xanthomas on tendons and xanthelasmas on the eyelids.

Cholesterol-lowering statins are the drug of choice, but many people with FH also require additional drugs, including ezetimibe (Zetia), niacin, and colesevelam (WelChol), because they help lower cholesterol in different ways than statins. In 2013, the FDA approved lomitapide (Juxtapid) and mipomersen (Kynamro) for people with homozygous FH to further lower their LDL. Because these drugs may cause serious liver problems, they can be given only under a doctor's close supervision.

fast fact | Your blood pressure drops just 20 minutes after quitting smoking. Within 24 hours, your risk of a heart attack begins to fall. Within one year, your risk of heart disease is half that of a smoker's. Within 15 years, your risk of heart disease is similar to that of someone who has never smoked.

In addition to medication, people with homozygous FH often need LDL apheresis, a dialysis-like procedure to filter LDL out of the bloodstream (see "A dialysis-like alternative," page 14).

If you have FH, your family members should be tested. Children of a parent with heterozygous FH have a 50-50 chance of inheriting the defective gene from that parent. If a parent has homozygous FH, all of his or her children will get a copy of the defective gene, and so will have heterozygous FH (unless they happen to get a copy from the other parent, too). Most of the time, a cholesterol test can verify the diagnosis, but genetic testing can be helpful for borderline cases. More information is available from the FH Foundation (www.thefhfoundation.org), which aims to boost awareness and improve the diagnosis and treatment of FH.

Why treat cholesterol?

Many factors contribute to the development of heart disease. Therefore, to slow, reverse, or prevent heart disease, it pays to take on as many risk factors as possible rather than focusing solely on cholesterol. That said, cholesterol does play a special role in the development of heart disease and cannot be ignored.

Benefits of lowering your cholesterol

Too much LDL coursing through your bloodstream can boost your odds of having a heart attack or stroke. Lowering LDL does the opposite. Data from dozens of studies indicate that the chance of having a heart attack drops 20% to 30% for each 10% drop in cholesterol. These relationships were established after the development of drugs known as statins, whose main effect is to lower LDL levels.

Seven statins are currently available: atorvastatin (Lipitor), fluvastatin (Lescol), lovastatin (Mevacor), pitavastatin (Livalo), pravastatin (Pravachol), rosuvastatin (Crestor), and simvastatin (Zocor). (For more information, see "Medications: Statins," page 38.)

Studies on statins

The evidence that statins reduce cardiovascular risk is very strong. Multiple studies have examined this question from a variety of angles.

In the first landmark study (the Scandinavian Simvastatin Survival Study, also known as 4S), more than 4,400 people with very high cardiovascular risk (average LDL levels of about 190 mg/dL and a prior heart attack) were randomly assigned to take simvastatin, an early statin. They experienced a major reduction in cardiovascular events compared with those who were randomly assigned to take inactive, look-alike pills (placebos). Indeed, after just over five years, those taking statins were 30% more likely to still be alive, compared with those who took the placebo. The study was double-blind, meaning that, in order to remove any bias, neither the doctors nor the participants knew who was taking the statin or the placebo. This kind of randomized, double-blind, placebo-controlled clinical trial data is what doctors look to for proof that a drug works.

Since 4S, subsequent studies have shown that statins can also benefit people who haven't had a heart attack, those with fewer risk factors for heart disease, and even those with fairly average LDL levels.

Reinforcing the benefits of lowering cholesterol, other evidence suggests that stronger statins may be better at cutting disease risk. The PROVE-IT trial followed more than 4,000 men and women who had just had a heart attack, and randomized them to take either the highest dose of a stronger statin (80 mg of atorvastatin, which lowered LDL to about 65 mg/dL), or the highest dose of a milder statin (40 mg of pravastatin, which lowered LDL to about 90 mg/dL). The researchers found that people who achieved the lower LDL had a 16% lower rate of heart attack, stroke, death, and other heart-related problems than did people whose LDL levels fell only to the low 90s.

Moreover, the Treating to New Targets (TNT) study looked at people with newly diagnosed or milder heart disease. Again, the results showed that using statin medication to aggressively lower cholesterol below recommended levels resulted in fewer heart attacks and strokes.

Additional benefits of statins

Could statins even help people with normal cholesterol and no known evidence of heart disease? That's where the JUPITER study comes in. A group of seemingly healthy people who took rosuvastatin not only cut their LDL cholesterol levels by about half, but also had about half as many heart attacks and other cardiovascular events as those who took a placebo. Part of the reason may have been that their inflammation

levels declined as well (see "The role of inflammation," page 8), but it's still unclear whether the reduction in events was due to the LDL decrease or the lowering of inflammation. The idea of treating inflammation is now under study with various anti-inflammatory drugs (for example, methotrexate) that decrease inflammation but do not change LDL levels.

No matter which statistic you look at, the bottom line is the same: if you are at significant risk for heart disease, taking a cholesterol-lowering statin won't guarantee you protection from heart attack or stroke, but it can substantially improve your odds. In general, the lower your cholesterol, the better. Some researchers think that lowering LDL sufficiently might stop or reverse the progression of atherosclerosis.

Though more research is needed, preliminary evidence has raised the possibility that statins might also offer wide-ranging benefits beyond the effects on LDL and inflammation. Two clinical trials, known as METEOR and ORION, suggest that high-dose treatment with statins may change the composition of arterial plaques in ways that make them less likely to rupture—the event that starts a heart attack. Other studies offer hints that statins may help improve circulation, prevent arthritis and bone fractures, and lower the risk of dementia and Alzheimer's disease.

What are the risks of treatment?

There is virtually no downside to lowering LDL cholesterol and total cholesterol levels with healthier eating and a program of regular exercise. And there are many benefits to this type of lifestyle. Cutting back on foods rich in saturated fat, trans fat, and highly processed carbohydrates while boosting your daily consumption of fruits, vegetables, whole grains, healthy fats, and lean protein can help reduce your risk of other major ailments such as type 2 diabetes.

As for regular exercise, it can raise your risk for minor injuries. But if you choose a low-impact activity and take it slowly at first, the benefits—lower total cholesterol, lower triglycerides, higher HDL cholesterol, lower blood pressure, better control of blood sugar, a stronger heart that pumps blood more efficiently, even a better mood—far outweigh the risks.

fast fact | A large study found that even moderately elevated cholesterol levels in middle age increase the risk of developing dementia in old age. So keeping cholesterol levels in check may be good for the mind as well as the heart.

On the other hand, using medication to lower cholesterol can produce some unwanted side effects. Older but still widely used types of cholesterol-lowering drugs, like niacin and bile acid binders, can cause such symptoms as flushing, constipation, heartburn, and a bloated feeling.

Although most people who take a statin *don't* experience side effects, a small percentage do. The most common are muscle aches and pains known as myalgias (see "Statin side effects," page 38). In very rare cases, statins can break down muscle tissue, a potentially dangerous condition known as rhabdomyolysis. This is more likely to occur when a statin is taken along with certain other medications (see "Muscle pain," page 39). In large clinical studies, the percentage of individuals with any side effects was about five out of 100 people—a rate that was not very different from that of the placebo group. In the real world, this rate may be higher, although still low.

While some countries already offer a low dose of statin as an over-the-counter treatment, experts in the United States continue to debate this issue. Studies suggest that many individuals labeled as being "statin-intolerant" can in fact take these medications without issues. Given the potential risk reduction and even lifesaving benefits of statins, individuals with significant cardiovascular risk, like heart attack or stroke survivors, should be especially careful about deciding they can't take a statin.

Is treatment worth the trouble and cost?

The most cost-effective way to treat moderately high cholesterol is to eat healthy foods and exercise daily. Over time, small changes—such as using the stairs instead of the elevator, parking the car farther away from your destination, avoiding the snack and cookie

Risk factors under investigation

Cholesterol is by no means a perfect indicator of cardiovascular disease risk; in fact, many heart attack victims have normal cholesterol levels, while some people with worrisome lipid test results never suffer heart problems. To better identify who's most at risk, researchers are constantly on the lookout for markers that may provide clues. The following factors are among the most promising candidates for risk factors that tomorrow's doctors may be testing and treating.

Markers of oxidative stress. Oxidants, also known as free radicals, are unstable oxygen molecules that damage cell membranes, proteins, and DNA. This damage is known as oxidative stress. Since 1999, evidence has suggested that biomarkers of oxidative stress may indicate the presence of cardiovascular disease. One example is myeloperoxidase (MPO), an enzyme present in substantial quantities in inflammatory cells such as macrophages. These cells release MPO into the bloodstream in response to inflammation or infection. In addition, several other biomarkers of oxidative stress have been approved for clinical application, and tests have been developed to help clinicians use them to assess cardiovascular risk.

Lipoprotein(a), abbreviated as Lp(a), is a molecule of LDL cholesterol with an extra protein attached. High levels of Lp(a) in the blood have been found to predict cardiovascular disease. Testing Lp(a) is not yet a conventional method of predicting risk of heart disease because no studies have shown that lowering Lp(a) levels—which can be done with niacin—actually reduces the risk of heart disease. New medications in development can also reduce Lp(a) levels, and it is possible that one of these newer drugs may someday be shown to be of therapeutic value. Lp(a) levels vary among different ethnic groups, and standardization of the blood test used to measure the biomarker is needed.

Apolipoprotein B (ApoB). This substance is found in many lipid-carrying particles in the blood, including chylomicrons, VLDL, IDL, LDL, and Lp(a). Since each of these particles contains a single ApoB molecule, measurements of ApoB reflect the total number of such particles. Some studies indicate that the ApoB level is a better predictor of death from heart disease than LDL or non-HDL levels. ApoB measurements do not require a fasting blood sample, and the test has been standardized. This test is not widely used in the United States, but some experts are arguing for ApoB testing to be done more frequently.

Apolipoprotein M (ApoM). This is a protein found mainly in HDL particles. Although its function has yet to be defined, experiments in mice suggest that ApoM helps protect against the formation of plaques in the arteries. A study in humans indicated that testing for ApoM levels could help identify risk for heart disease. However, more research is needed to verify this finding.

PCSK9. This gene helps control the number of receptors for LDL in the liver. People with an overactive PCSK9 gene have fewer LDL receptors, meaning that the liver doesn't take up as much LDL from the blood. Eliminating the gene increases the liver's LDL receptors, which in turn reduces blood LDL levels. A drug is currently in development that works to block PCSK9, though it is too early to say whether it will make it to the market.

aisles of supermarkets, eliminating sugar-sweetened beverages, going on short walk breaks, working out with a personal trainer, or engaging in any type of physical activity—can make a big difference.

When therapy is expensive, as can be the case with brand-name cholesterol-lowering drugs, the cost-effectiveness of treating large groups of people has been debated. Fortunately, many statins are now available in inexpensive generic versions. The cost of statins also includes medical appointments, blood tests, and treatments for any adverse side effects. Still, for people with established cardiovascular disease or significant enough cardiovascular risk, like elevated LDL cholesterol levels or diabetes, cost-benefit analyses weigh heavily in favor of treatment with statins, given the expense of heart attack treatments, coronary stenting, and heart bypass surgery. Still under debate is the cost-effectiveness of using statins in people with no history of heart disease or cardiovascular problems and a lower risk for a future event.

Your cholesterol test

A cholesterol test (also known as a lipid profile or lipid panel) measures total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride levels. You'll get the most accurate results with a fasting lipid profile, in which you fast overnight before having your blood drawn. Though advanced testing can offer additional information, for many people it is not necessary (see "Ask the Doctor: Advanced lipoprotein testing," page 22).

When to test

Because the process of atherosclerosis starts during childhood, the American Academy of Pediatrics recommends LDL cholesterol testing for all children between the ages of 9 and 11, and once again between the ages of 17 and 21. The idea is to identify the estimated two out of 10 children who have high cholesterol (see Table 5, above) as a result of poor diet or lack of exercise. The goal is not to start them on statin drugs, but to identify those at significant risk, so they can be encouraged to adopt better lifestyle habits.

Testing can also detect the smaller number of children (an estimated one in 300 to 500) who have very high LDL due to a genetic disorder (see "Genetic risks: When high cholesterol runs in the family," page 13). Children ages 2 to 8 should have a cholesterol test if they have a parent, grandparent, aunt, uncle, or sibling who has an inheritable cholesterol disorder, or who had a heart attack or stroke or needed bypass surgery or angioplasty at a young age (under 55 years in a man, under 65 years in a woman).

For adults, the U.S. Preventive Services Task Force recommends cholesterol testing for all men ages 35 and older, and for men and women over age 20 with other risk factors, such as diabetes, obesity, or smoking. Men ages 20 to 35 and women ages 20 and older who don't have other risk factors for heart disease can decide with their doctors whether to get tested. That's because for people in these groups, the benefits and harms of treatment are so balanced that it's not possible to make a blanket recommendation.

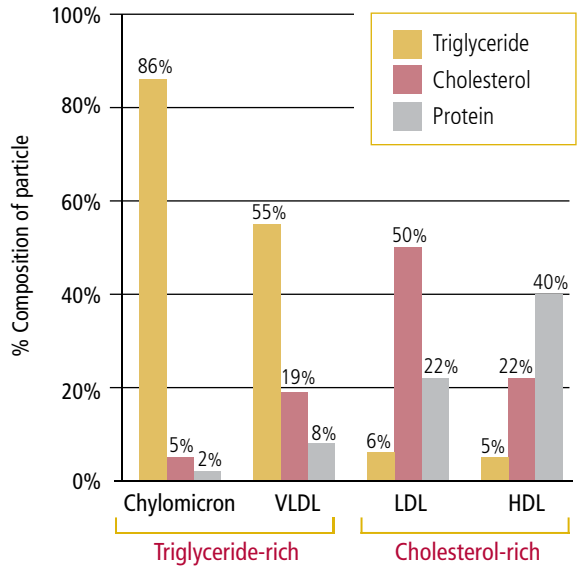
If you have a low risk of heart disease, the American Heart Association recommends that you get a

Table 5: LDL categories for children and adolescents

LDL CHOLESTEROL LEVEL	CATEGORY
less than 110 mg/dL	Acceptable
110–129 mg/dL	Borderline high
130 mg/dL or higher	High

Source: National Cholesterol Education Program.

Figure 5: Fat particles: What's inside?



Depending on your cholesterol profile, you have more of some lipoproteins and less of others. A person with high total cholesterol levels, for example, usually has lots of LDL particles because LDLs carry more cholesterol than other particles. But some people have high total cholesterol because they have more protective HDLs. Others have a high triglyceride level, which usually means more chylomicrons and VLDLs, because their cargo is primarily triglycerides.

fasting lipid profile once every five years. But your doctor might recommend more frequent testing if any of the following applies:

- Your total cholesterol is 200 mg/dl or more.
- You are a man over age 45 or a woman over age 50.
- Your HDL cholesterol is less than 40 mg/dL.
- You have other risk factors for heart disease and stroke.

Preparing for the test

Getting a cholesterol test is easy. It involves having a tube's worth of blood drawn from your arm during a routine visit to your physician. The preparation, however, takes a little effort. Food and drink can affect your triglyceride level, so you should fast for 12 hours to get an accurate reading. You should also avoid drinking alcohol for at least 24 hours before the test. You can drink water and take most medications you normally use, as these should not affect the test results. If you are not sure about your medications, check with your doctor before getting the test done.

Variations in test results

After your blood is drawn, a technician uses the sample to measure your total cholesterol, HDL, and triglyceride levels. Your LDL level is typically calculated from these results. However, some labs routinely measure LDL levels directly.

Results from cholesterol tests seem quite precise, but the numbers can mask some uncertainty in the testing and calculation processes. For example, different labs may give slightly different readings. Results can be affected by how the sample is prepared, the purity of added chemicals, the quality or performance of the equipment, or the skill of the lab technician, though laboratory standards have reduced this variability to such a small margin that it should not be a major focus of attention or concern.

More important is the issue of biological variability, or natural variations in the amount of cholesterol in your blood. The numbers on the laboratory report reflect the level at just a single point in time. Changes in your cholesterol values from one test to the next may reflect changes in your diet, weight, exercise routine, or use of medications. Results can even change with the season of the year. In fact, one study showed that a person's total cholesterol reading can fluctuate by as much as 11% over the course of a year. The same study found that triglyceride measurements can vary by 13% to 41%, and HDL levels by 4% to 12%. What this means is that a small change in your cholesterol level from one test to another does not necessarily represent a real gain or loss—and an unusually high or low level may be a fluke.

What you can do to minimize variability

You can't control lab variations, but you *can* do something about biological variability from one test to the next. For routine total cholesterol measurements, try to have your blood drawn at the same time of day each time you have the test—and follow a similar eating, exercising, and medication-taking pattern. Other steps you can take to improve the accuracy of a cholesterol test may include sitting for at least five minutes before your blood is taken, remaining seated during the procedure, and informing your doctor of any fevers you've had recently or medications you've taken. Ultimately, the test is a tool to help you, and your doctor, identify your risk; in this sense, you want it to reflect the way you currently live and eat, even if this test is a first step toward making changes (see "What to tell the doctor," page 21).

Keep in mind that no one test is definitive enough to justify important decisions about therapy. Any results need to be validated with a second measurement. If your doctor suggests drug treatment based on a single cholesterol test, ask for a second one to double-check the results. Then you and your physician can make an informed decision about the best way to bring any wayward cholesterol levels back in line.

Interpreting your test results

There are several numbers to pay attention to. They will tell you if your cholesterol and triglyceride levels are considered desirable, borderline high, or high.

Total cholesterol

This number is the sum of all the cholesterol in all the lipoprotein particles in your blood, including HDL,

What to tell the doctor

Going to the doctor can be stressful, or even overwhelming. It's easy to forget the questions you wanted to ask or recent events that might have skewed a blood test result. Bringing a written list of questions or topics you want to cover can help. Below are some issues you might want to raise with your doctor when discussing your lipid profile.

- ✔ Tell the doctor if you had the flu or another illness shortly before the blood test. Such conditions can have a dramatic effect on your lipoprotein levels.
- ✔ If your diet was very different from your typical diet in the weeks leading up to the lipid test, this is worth noting, because high levels of alcohol or carbohydrates can raise triglycerides.
- ✔ If you were expected to fast and didn't, don't be embarrassed to say so. Otherwise, you could end up on the wrong medication.

LDL, and VLDL. Although the total cholesterol level closely parallels the LDL level in most people, there are enough exceptions to make it useful to measure LDL, HDL, and triglyceride separately. A total cholesterol level below 200 mg/dL is desirable, 200 to 239 mg/dL is borderline high, and 240 mg/dL is high.

LDL cholesterol

LDL cholesterol is considered the most dangerous blood lipoprotein particle.

From 2004 to 2013, treatment guidelines defined an LDL below 100 mg/dL as optimal; 100 to 129 mg/dL as near optimal; 130 to 159 mg/dL as borderline high; 160 to 189 mg/dL as high; and 190 or above as very high. For people at higher risk, like those who had already had a heart attack, experts recommended getting LDL down to 70; some advocated for even lower targets, like 40 to 60 for people at the highest risk for heart attack or stroke or with recurrent events despite treatment. The target of 70 or lower was based on several clinical trials in which high-risk people had fewer coronary events when they lowered their LDL level substantially below 100 mg/dL.

The new guidelines, published in late 2013, move away from LDL targets for statin therapy. Instead, they identify four groups of people who should take a moderate- or high-intensity statin (see Table 6, page 26), based on their overall cardiovascular risk profile (see "Making sense of the new guidelines," page 24). This kind of patient-centered approach should increase statin treatment, which is warranted given the existing studies. In these four groups, however, there is no specific recommendation to hit a specific LDL target, such as getting LDL down to 70 mg/dL in those with established cardiovascular disease. Some experts disagree with this approach, pointing to considerable evidence that lower LDL levels reduce risk, and they continue to use the old targets.

HDL cholesterol

HDL fights plaque buildup in the heart's arteries, so the more HDL cholesterol you naturally have, the better. The Framingham Heart Study suggests that every 1 mg/dL increase in HDL cholesterol reduces the risk of cardiovascular disease by 2% to 3%.

A level of 60 mg/dL or above is considered protective, while a value below 40 mg/dL increases your risk for heart disease. Some clinicians use the ratio of total cholesterol to HDL to identify people who need

ASK THE DOCTOR
Concerns about low HDL

Q ***I have been taking a statin to bring down my LDL cholesterol, but my HDL is still on the low side. Do I need to worry about my HDL level if my LDL is okay? If so, what should I do?***

A The bottom line is that we do not know. There have been several large clinical trials to evaluate the use of medications to raise HDL, but so far no drug treatment for raising "good" HDL cholesterol has clearly been shown to reduce cardiovascular risk in people already taking a statin drug to lower "bad" LDL cholesterol. Right now, the best bet for boosting your HDL level is to make lifestyle changes, such as increasing your level of aerobic activity and losing weight, especially if your triglycerides are elevated. You may also want to sign up for one of the current clinical trials looking at the effect of HDL-raising drugs in people already on statins and with well-controlled LDL levels. You can find out about trials going on in your area at the National Institutes of Health Clinical Trials website (http://clinicaltrials.gov/).

—Jorge Plutzky, M.D.
Medical Editor

ASK THE DOCTOR

Advanced lipoprotein testing

Q ***A friend of mine had his blood drawn and sent to a private lab for advanced lipoprotein testing. What is this, and should I have it done?***

A Several private laboratories, including LipoScience and Atherotech, offer what's known as advanced lipoprotein testing. The tests offer more detailed and specific measurement of lipoproteins.

For example, LipoScience provides an FDA-approved blood test that directly quantifies your LDL particle number, or LDL-P. Some studies suggest that LDL-P might be a better predictor of heart disease risk than a simple measurement of LDL cholesterol. That's because size matters: larger, fluffier LDL particles are less dense, less prone to oxidation, and probably less harmful than smaller ones (see "LDL particle size," page 5). If the LDL particles in your blood are on the large side, you will have fewer LDL particles overall for a given LDL level; if your LDL particles tend to be small, you need more of them to carry same amount of cholesterol. Thus, in an LDL-P reading, fewer particles are better: LDL-P values range from 600 to more than 2,000 nanomoles per liter (nmol/L).

Atherotech offers an even more detailed analysis, called the VAP test. It directly measures the cholesterol concentrations of HDL, LDL, VLDL, and IDL, and provides information on particle numbers. The test also measures lipoprotein(a), which is considered an "emerging" risk factor. Lipoprotein(a) is a type of LDL that carries a sugar-coated protein called apolipoprotein A, which may keep the body's natural clot busters from doing their job, among other effects. Several lines of study suggest lipoprotein(a) may contribute to cardiovascular risk, especially in certain families. The same is true for apolipoprotein B (ApoB), the key protein found on all LDL particles (which the VAP also measures).

Both tests cost about the same as a standard cholesterol test and are covered by most insurance carriers. But for most people, there's little evidence that the information from these tests would alter your doctor's advice and treatment plan, especially considering that the new cholesterol treatment guidelines have shifted away from focusing on specific numbers (see "Making sense of the new statin guidelines," page 24).

In addition, your doctor can glean much of the relevant information from your standard lipid profile. For example, all lipoproteins except HDL contain ApoB, so your non-HDL cholesterol value (a calculated number; see "Non-HDL cholesterol," page 23) often lines up closely with your ApoB level. Also, if your triglyceride level is higher than 400 mg/dL (which is common in people who are overweight and who have diabetes), chances are good that you have higher amounts of smaller, denser LDL. That may warrant more aggressive treatment—something most doctors would already have considered.

That said, some doctors do turn to advanced lipoprotein testing and other nonstandard lipid tests in specific cases. Examples of individuals who might benefit from this testing include those with

- a history of cardiovascular disease, including a stroke, heart attack, or peripheral artery disease (clogged vessels in the limbs) but without obvious risk factors such as smoking, high blood pressure, high cholesterol, or diabetes
- a history of early cardiovascular disease, defined as occurring before age 55 in men or before age 65 in women, especially when there are not obvious risk factors to explain these events
- a parent, brother, or sister with early heart disease.

If any of the above applies to you, it would be reasonable to discuss advanced lipoprotein testing with your doctor. If the testing reveals high levels of subparticles thought to potentially raise your risk of cardiovascular disease, your doctor may start you on a statin, or if you're already taking one, switch you to a higher dose or a stronger statin or consider targeting other aspects of your lipid profile. But so far, there are no data to support the health advantages of advanced lipoprotein testing, and it is not routinely advocated.

Finally, it's important to know that the tried-and-true advice of eating a healthy diet, getting regular exercise, and maintaining a normal weight can lead to beneficial changes in abnormal lipoprotein values, including those that show up on advanced lipoprotein testing.

—Jorge Plutzky, M.D.
Medical Editor

to bring down their LDL levels. A lower ratio—more HDL cholesterol relative to total cholesterol—is better. Reports from the Framingham Heart Study suggest that for men, a total-to-HDL cholesterol ratio of 5 means average risk, 3.4 is about half the average, and 9.6 is double the average. For women, a ratio of 4.4 means average risk, 3.3 is half the average, and 7 is twice the average. Despite the fact that higher HDL levels correspond to lower risk, however, recent studies have failed to show that treatment to raise HDL levels lowers a person's odds of having a heart attack or stroke.

For most people, whatever the ratio, your doctor will probably recommend a statin if you have high total or LDL cholesterol. Still, a few people find that the ratio provides a strikingly different assessment of their coro-

nary risk. Someone with a total cholesterol of 195 mg/dL would ordinarily be considered at low risk—unless a low level of HDL cholesterol drove up the total-to-HDL cholesterol ratio. Conversely, a total cholesterol of 250 mg/dL would typically be considered reason for medication, unless a very high HDL level accounted for a good proportion of the total.

Triglycerides

Many studies have linked high triglycerides to heart disease, but the association seems influenced by other factors, with the relationship being less apparent when other issues are taken into account. Complicating matters further, triglyceride levels can change greatly in response to what you've eaten before a blood test. Also, medical conditions (such as uncontrolled diabetes), medications (such as corticosteroids and thiazide diuretics), and drinking too much alcohol can raise triglyceride levels.

A triglyceride level below 150 mg/dL is considered normal; 150 to 199 mg/dL is borderline high; 200 to 499 mg/dL is high; and 500 mg/dL and above, very high. High triglycerides should prompt a search for an underlying cause, such as alcohol abuse, obesity, liver disease, triglyceride-raising medications, an underactive thyroid gland, or undetected or undertreated diabetes. People with combined hyperlipidemia, a condition marked by high LDL and triglyceride levels, often have a genetic disorder.

If your triglyceride level is very high (500 mg/dL or above), your doctor will probably recommend triglyceride-focused treatment to avoid inflammation of the pancreas (pancreatitis), which can be a serious problem. Even with high triglycerides (200 mg/dL or above), some intervention may be necessary. Ways to lower triglycerides include following a diet low in fat and highly processed carbohydrates, exercising more, losing weight if needed, and taking a medication like niacin, a fibrate, or fish oil supplements.

Non-HDL cholesterol

If you subtract your HDL level from your total cholesterol level, you get your non-HDL cholesterol level. Some experts recommend non-HDL cholesterol as a secondary target for lipid lowering in people with normal LDL levels but high triglycerides. When triglyceride levels are above 200 mg/dL, non-HDL cholesterol should be no more than 30 mg/dL above recommended LDL levels. For example, if your LDL target is under 100 mg/dL, you'd aim for a non-HDL cholesterol level of less than 130 mg/dL.

Physical examination and further tests

A physical examination can determine if you have other factors that might increase your likelihood of developing heart disease. Typically, your doctor will measure your blood pressure and check your pulse to make sure that your heartbeat is regular and forceful. Sometimes he or she will feel the thyroid gland in your neck to determine its size (an underactive or overactive thyroid can affect blood lipid levels). Your doctor may also feel the pulses of the carotid arteries in your neck and listen to the blood flow there to look for any suggestion of blockages. To assess your cardiovascular function in more detail, most doctors will listen to your heart and feel the pulses in your legs, which can fade away if there are significant blockages in any of the arteries that go to the feet.

Any abnormal findings will generally lead to more lab tests or imaging procedures. These could include an electrocardiogram (ECG), chest x-ray, echocardiogram (ultrasound picture of the heart), or tests of thyroid or kidney function. Reduced pulses in the legs are often assessed by Doppler (ultrasound) measurements or an equivalent noninvasive test. When the results come back, your doctor is armed with the information he or she needs to make recommendations about treating your lipid levels.

Making sense of the new statin guidelines

For years, doctors prescribed cholesterol-lowing statins based largely on cholesterol test results. The goal was to lower total cholesterol to under 200 mg/dL, and LDL (bad) cholesterol to under 100 mg/dL. But in late 2013, new guidelines on statin use issued by the American Heart Association (AHA) and the American College of Cardiology (ACC) proposed a major change to that strategy.

The new guidelines shift from a numbers-based approach to a risk-driven approach. Instead of aiming for a specific cholesterol value, doctors are now urged to look at a person's entire cardiovascular risk profile when considering treatment. Given what we now know about cholesterol and statins, this is a reasonable approach that can help simplify how doctors think about whom to treat.

The new guidelines were met with more than the usual criticism, however. In fact, they've generated considerable debate. For starters, they don't provide a comprehensive review and update of cholesterol and lipid evaluation and treatment, as past guideline updates had done. The new guidelines don't, for example, specify normal and abnormal levels for total cholesterol, LDL, HDL, and triglycerides. Perhaps the best way to look at these guidelines is as a scientific statement reviewing what has been definitively established to date.

Why did the guidelines change?

The experts who created the previous guidelines accepted the evidence that LDL was the key culprit in heart disease and extrapolated the available evidence to create cholesterol targets for statin therapy. The new guidelines called into question the validity of that approach, given that no specific study has ever investigated differences in outcomes when one group gets treated to a lower LDL level than another group using the same statin. In essence, the expert panel that created the new guidelines took a more purist approach in terms of what had been specifically proven in trials, deciding that it was the *intensity* of statin treatment (meaning the percentage reduction in LDL and the dose of the statin employed) that was primarily responsible for reducing heart attacks and strokes, not how low LDL fell.

Who should take a statin?

The new guidelines recommend a daily statin for individuals who fall into the following four categories:

- anyone age 21 or older with a very high level of harmful LDL cholesterol (190 mg/dL or higher)
- anyone who has cardiovascular disease, including stable or unstable angina (chest pain with exercise or stress); has had a heart attack, stroke, or transient ischemic attack ("mini-stroke"); has peripheral artery disease; or has had bypass surgery or angioplasty to treat a cholesterol-clogged artery
- anyone age 40 to 75 who has diabetes
- anyone age 40 to 75 who does not have cardiovascular disease but has a greater than 7.5% chance of having a heart attack or stroke or developing another form of cardiovascular disease in the next 10 years (as determined using the online risk calculator cited below).

That last category represents a major shift. If doctors follow the guidelines and start treating people who don't have heart disease but are at risk for it, several million more people will take a statin every day.

To determine an individual's future risk of developing cardiovascular disease, the AHA/ACC panel created a risk calculator. It's available online at www.health.harvard.edu/heartrisk. The calculator takes into consideration your age, sex, race, total cholesterol, "good" HDL cholesterol, blood pressure, and whether you are being treated for high blood pressure, have diabetes, or smoke.

People with diabetes

The fight for a healthy heart is especially important for people with diabetes, because cardiovascular disease is the leading cause of diabetes-related death. It is two to four times more likely to develop in people with diabetes, in part because they are more likely to also have such risk factors as obesity, hypertension, and cholesterol problems. In addition, high levels of blood sugar and insulin damage arteries and nerves.

Thinkstock

The new guidelines recommend statins not just for people with high LDL cholesterol, but also for those with other cardiovascular disease risk factors, such as diabetes.

Many people with diabetes have low HDL, high triglycerides, and high LDL. An LDL value that is acceptable for someone without diabetes may be too high for those with the disease. The high blood sugar associated with diabetes can accelerate a chemical change in LDL known as oxidation. Oxidized LDL cholesterol plays a key role in initiating the inflammatory damage that causes atherosclerosis. The benefit of statins in people with diabetes has been quite clear, as seen in several studies.

Following a healthy diet and being active are also key strategies for living with diabetes. Limiting the intake of foods high in cholesterol—like fatty meats, egg yolks, butter, and other full-fat dairy foods—and also simple carbohydrates may help, too. But even the best diet and exercise program may not be enough to bring cholesterol under control without medication. The strength of data showing that statins reduce cardiovascular events in people with diabetes is what has driven the recommendation that they should take a statin from ages 40 to 75. Although there is evidence that statins may carry a small risk of modestly increasing blood sugar, this may happen more in people with risk for diabetes, and the benefit of the statin is thought to far outweigh any risk associated with small changes in the glucose numbers.

People with chronic kidney disease

Anyone living with chronic kidney disease—at any stage—is at high risk for developing heart disease. The cholesterol guidelines in place from 2004 to 2013 defined kidney disease as a heart disease "risk equivalent"—meaning that people with kidney disease are in the same high-risk category as people who have already had a heart attack or stroke. If you have both diabetes and chronic kidney disease, the risk is even greater.

Although there are many reasons that having chronic kidney disease increases the risk of heart disease, cholesterol clearly plays a role. People with chronic kidney disease tend to have abnormal blood cholesterol levels, leading to atherosclerosis. However, it also appears that a decline in kidney function can lead to high cholesterol and the accumulation of artery-damaging toxins, both of which can promote atherosclerosis.

If you've been diagnosed with chronic kidney disease, have your cholesterol levels tested every year, or more often if you experience any health problems.

The new guidelines don't offer specific recommendations for people with kidney disease. It is likely that doctors will continue to follow the old guidelines and recommend a statin for anyone with kidney disease, just as they would for anyone with heart disease.

New guidance on choosing a statin

The old guidelines focused on the *effect* of treatment—in other words, how low your cholesterol level should go. The new guidelines focus on the treatment itself. They help doctors choose the right statin at the right dose by dividing treatment into low-intensity, moderate-intensity, and high-intensity statin therapy. Some statins are better at lowering cholesterol than others, so intensity is determined partly by statin choice and partly by dose. Someone without heart disease and a lower risk of 10-year cardiovascular disease could take a low-intensity statin, while someone with a history

Table 6: Statin intensity

Some statins are better at lowering cholesterol than others, so intensity is determined partly by statin choice and partly by dose.

GENERIC NAME (Brand name)	HIGH-INTENSITY DOSAGE (lowers cholesterol by 50% or more)	MODERATE-INTENSITY DOSAGE (lowers cholesterol by 30% to 50%)	LOW-INTENSITY DOSAGE (lowers cholesterol by less than 30%)
atorvastatin (Lipitor)	40–80 mg a day	10–20 mg a day	—
fluvastatin (Lescol XL)	—	80 mg a day	—
fluvastatin (Lescol)	—	—	20–40 mg a day
lovastatin (Mevacor)	—	40 mg a day	20 mg a day
pitavastatin (Livalo)	—	2–4 mg a day	1 mg a day
pravastatin (Pravachol)	—	40–80 mg a day	10–20 mg a day
rosuvastatin (Crestor)	20–40 mg a day	5–10 mg a day	—
simvastatin (Zocor)	—	20–40 mg a day	10 mg a day

Source: 2013 ACC/AHA Guidelines on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

of heart disease may need a high-intensity statin (see Table 6, above; for more information about specific statins, see "Medications: Statins," page 38).

Questions about combination therapy

When cholesterol therapy focused on reaching a particular LDL target, like under 100 mg/dL, doctors often boosted the cholesterol-lowering power of a statin by adding a non-statin drug like niacin or ezetimibe. The new guidelines question this approach. There's no doubt that combining drugs further reduces LDL. But there's no solid evidence to date that it works better to prevent heart attacks and strokes than high-intensity statin therapy alone. The new guidelines don't discourage adding a non-statin drug to reach a particular LDL level, but they don't encourage it, either.

The guidelines do support using an add-on nonstatin drug for people whose LDL didn't fall as expected on a statin, or who can't take a statin.

Race, gender, age, and risk

The more researchers and clinicians learn, the clearer it becomes that cutting heart disease risk is not simply a matter of reducing cholesterol levels. While the principle of lowering cholesterol makes perfect sense in general, individuals face very different risks and respond very differently to treatment—often because of such basic factors as race, gender, and age. Because so much of what we know still comes from studies of middle-aged white men, scientists are working to learn more about how cholesterol and cholesterol-lowering therapies work in different racial and ethnic groups, women, the young, and the elderly—and whether reducing cholesterol will produce similarly positive results for them.

Racial and ethnic groups

African Americans have high rates of death from heart disease. The reasons have yet to be identified, but a high prevalence of risk factors may play a role. High blood pressure, type 2 diabetes, obesity, and other such conditions occur at a higher rate in African Americans than they do in whites or Latinos. Culturally sensitive public health efforts and individual actions can make a difference in the burden of heart disease carried by African Americans and other ethnic groups.

Guidelines to help prevent cardiovascular disease specifically in African Americans set similar

goals as for other populations but suggest even more aggressive lifestyle interventions and more aggressive treatment of high blood pressure. Among the most important goals are to increase physical activity, to strive for a diet high in fruits and vegetables and whole grains, and to get regular screening tests for cardiovascular disease, including cholesterol and blood pressure readings.

Women

In the United States and many other countries, more women than men die from cardiovascular disease each year. Heart disease develops about 10 to 15 years later in women than it does in men, but by the time they're in their mid-60s, women's risk of heart attack and stroke is similar to that of men of the same age. Most heart disease in women occurs after they turn 65. At that age, there's little difference in treatment recommendations between men and women.

Before menopause, women have a lower risk of heart disease than men, and therefore, fewer women require treatment. When it comes to cholesterol, the U.S. Preventive Services Task Force strongly recommends regular testing for all men ages 35 and older. Things are more murky for women. The group recommends regular cholesterol testing for women ages 45 and older if they are at increased risk for coronary artery disease. But it makes "no recommendation for or against routine screening for lipid disorders" in women ages 20 and older who are *not* at increased risk for coronary artery disease, because there's no good evidence that treating high cholesterol in this group would yield more benefit than harm.

Women with multiple risk factors or metabolic syndrome (see page 11) may be at risk for premature cardiovascular disease. Certain risk factors associated with metabolic syndrome (such as low HDL, elevated triglycerides, and insulin resistance) may put women at greater risk of heart disease than men with the same conditions. If you are a woman with risk factors, you might be considered for cholesterol-lowering medication, particularly if you smoke or have high triglyceride levels.

The elderly

Most heart attacks occur in people 65 or older. While high LDL and low HDL levels still carry weight in predicting risk for cardiovascular disease in older people, doctors might want to add noninvasive testing, such as ultrasound, to look for atherosclerosis and determine risk of heart attack or stroke. Statins can clearly reduce the risks of heart attack and stroke in this population, and statin therapy is generally well tolerated and effective in older people. However, the drugs should be used with caution in the oldest people (especially those ages 80 or older) and in those who are small and frail. These people may be at increased risk of muscle pain (myopathy). Many seniors also have other medical problems that can make treatment with cholesterol medications more complicated. Drug interactions or organ damage may affect the metabolism of the drugs. In addition, seniors are more likely to have reduced function of the liver, kidneys, or heart.

This does not mean that treatment with statins should be avoided. Many senior citizens struggle to buy and make healthy foods, and a stringent heart-healthy diet may worsen an already marginal nutritional status. Statins may help to compensate for a less than ideal diet. The treatment may just need to be individualized. Often elderly people can be effectively treated with lower doses of a statin because of slower drug clearance times or smaller body mass.

Lifestyle changes to improve your lipid levels

Two important lifestyle changes—switching to a healthier diet and exercising more—are the cornerstones of any strategy to improve your blood lipids, especially LDL. Their effects go far beyond improving cholesterol numbers. A healthy lifestyle helps prevent heart attack and stroke. It works to fight the development of other chronic conditions like diabetes, some forms of cancer, and vascular dementia and other types of memory loss. It can also make you feel better and look better.

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Switching to a healthier diet is a cornerstone of any strategy to improve your blood lipid levels and prevent heart attacks.

For some people, lifestyle changes are all that are needed to control cholesterol. Others need cholesterol-lowering medication. But these drugs don't work magic. Instead, they should be combined with the true magic that exercising more, following a healthy diet, and making other smart lifestyle choices can conjure.

This Special Section details the latest thinking about how to optimize your eating and activity patterns and make other changes to improve your cholesterol and triglyceride levels and, in turn, your heart and overall health.

Eat for heart health

How much can you bring down your cholesterol with dietary changes? It's a complicated question for many reasons: different types of lipoproteins respond differently to changes in diet, and the response to diet varies from person to person, as does how well different people stick to a new, healthier diet. But the changes can be impressive.

For many years, a main focus of dietary recommendations was to reduce the intake of dietary cholesterol and fat, but this thinking has been changing (see "The low-fat myth," page 29). Many other components in food affect heart health, so focusing only on the amount of fat or cholesterol can lead you astray. For instance, don't be fooled into thinking that foods labeled "cholesterol free," "low cholesterol," or "no fat" are necessarily heart-healthy—or, for that matter, that foods containing cholesterol are heart-risky.

The reality is that improving the overall quality of your diet is more important than focusing on how much you get of one nutrient or another. Table 7 (page 30) provides an overview of foods to emphasize in your diet, as well as those to avoid. More information is available in the Harvard Special

Health Report *Healthy Eating for a Healthy Heart* (see "Resources," page 47, for ordering information).

Favor the "good" fats

For years, low-fat diets were recommended as the antidote to high cholesterol and heart disease. But that strategy didn't work, and it may have helped fuel the twin epidemics of obesity and diabetes by encouraging people to replace healthy fats with sugar and refined carbohydrates. Current dietary guidelines give considerable leeway in dietary fat, recommending that you get 20% to 35% of your daily calories from fat. Even more may be fine, as long as it's mostly healthy fats from fish and plant sources, such as avocados, nuts, and vegetable oils. These are considered good for the heart because they tend to lower total and LDL cholesterol and may even be associated with reduced levels of chronic, low-grade inflammation—the kind that fuels heart disease.

The worst are trans fats. They are the byproduct of partially hydrogenating vegetable oils to prevent them from turning rancid. Trans fats are found in some commercial baked goods, solid margarines, and deep-fried restaurant foods. They not only increase LDL, but also raise triglyceride levels and reduce HDL cholesterol. In 2013, the FDA removed trans fats from its list of substances that are "generally recognized as safe." As a result, these harmful fats should soon disappear from our food supply. In the meantime, you're most likely to encounter trans fats in fried or baked goods sold in small, local restaurants, because most major food suppliers and restaurants have already substituted healthier fats in their products.

Limit saturated fat

The other type of fat that affects cholesterol levels is saturated fat. This type of fat is found mostly in animal products, such as meats, whole-fat dairy products, and eggs, but also in a few vegetable oils, such as palm oil, coconut oil, and cocoa butter. Saturated fat can increase LDL cholesterol in your body much more than cholesterol-containing foods such as eggs. But it has some benefits, too. It lowers triglycerides and nudges up HDL.

The role of saturated fat in heart disease is currently under debate. In 2014, a major study in *Annals of Internal Medicine* suggested that diets high in saturated fat may not be as bad as we thought when it comes to heart disease risk. The findings, gleaned from 72 different studies involving more than 650,000 people, confirmed that saturated fat in the diet does raise LDL, but doesn't appear to boost the risk of heart attack. Since the studies in that report were observational, and not randomized controlled trials, it's possible that something may be obscuring the real effect of saturated fat. Some types of saturated fat, for example, have less effect on cholesterol.

But some experts challenged the study's results. Dr. Walter Willett, chair of the Department of Nutrition at Harvard School of Public Health, warned that its conclusions may be seriously misleading. In a comment on the study on the *Annals of Internal Medicine* website, he wrote: "This paper is bound to cause confusion. A central issue is what replaces saturated fat if someone reduces the amount of saturated fat in their diet. If it is replaced with refined starch or sugar, which are the largest sources of calories in the U.S. diet, then the risk of heart disease remains the same. However, if saturated fat is replaced with polyunsaturated

The low-fat myth

Although low-fat diets were once thought to be key to helping people lose weight and avoid heart disease, experts now know that's not true. Over the past three decades, the percentage of calories from fat in the average American's diet has dropped, but obesity rates have soared. Why? When people eliminate fat from their diets, they tend to substitute refined carbohydrates like white bread, white rice, potatoes, breakfast cereals, and other sugary foods. These foods cause blood sugar levels to rise quickly, which can leave you hungry and prone to overeating. That, in turn, leads to weight gain—which makes you more likely to develop diabetes and heart disease.

Table 7: Foods to eat and foods to limit or avoid

	HOW MUCH TO EAT*	NOTES
▼ Foods to emphasize in the diet		
Fruits and vegetables	2 to 2½ cups (four to five servings) of fruits and 2 to 2½ cups (four to five servings) of vegetables per day	Choose a variety of fruits and vegetables every day. Eat canned or frozen varieties (no salt added) when fresh aren't available.
Whole grains	Three servings of whole grains per day; one serving is one slice of whole-grain bread, 1 cup of cooked whole-grain cereal, or ½ cup cooked brown rice	Don't simply add whole grains to your diet; eat them in place of starches (like potatoes), refined carbohydrates (like white bread, white rice, and low-fiber breakfast cereals), and sweets.
Fish and seafood	At least two servings (3–4 ounces each) per week, including at least one serving of oily (dark meat) fish	Oily, cold-water fish, such as salmon, herring, sardines, and tuna, contain higher levels of heart-healthy omega-3 fats.
Vegetable oils	5–6 teaspoons per day, including oil found in foods	Healthy vegetable oils include extra-virgin olive, canola, peanut, corn, soybean, safflower, and cottonseed oils.
Nuts	Four to five servings (1 ounce each) per week, with a serving equal to ¼ cup nuts or 2 tablespoons of peanut butter	All types of nuts contain beneficial compounds, so simply choose a variety that you like, such as peanuts, almonds, walnuts, cashews, etc.
Dairy products	Two to three servings per day, with one serving equal to 1 cup of milk or yogurt, or 1 ounce of cheese	More study is needed to determine exactly which type of dairy is best for the heart, but based on the current evidence, most dietary guidelines recommend low-fat milk, cheese, and yogurt over full-fat versions, and they recommend avoiding butter.
▼ Foods to eat in moderation		
Unprocessed red meat	2 to 3 ounces of red meat per serving, up to a few times per week	Unprocessed red meats include fresh beef, lamb, or pork. Unprocessed red meats don't seem to raise risk of heart disease very much, but there is no evidence that red meat is good for the heart, and there are healthier protein choices, such as fish, nuts, and poultry.
Eggs	One egg per serving, up to a few times per week	There's little evidence that eggs raise risk very much, but there's also no evidence that eggs are good for the heart.
▼ Foods to avoid or eat in small amounts		
Processed meat	Preferably none, or at most two servings per week	Processed meats include hot dogs, bacon, sausage, salami, and other deli or luncheon meats—including deli ham, turkey, bologna, and chicken.
Highly refined and processed grains and sugars	Preferably none, or at most one serving per day	Refined or processed foods include white bread, white rice, low-fiber breakfast cereals, and sweets and sugars.
Sugary drinks	Preferably none, or at most one 8-ounce serving per day	Avoid or limit sugar-sweetened soda, energy drinks, sweet teas, and fruit drinks.

** Note that the serving amounts and sizes are based on a 2,000-calorie diet. The amount of calories you need may be less or more than that, which will alter the servings you need to consume.*

fat or monounsaturated fat in the form of olive oil, nuts, and probably other plant oils, we have much evidence that risk will be reduced."

Until the true role of saturated fat in heart disease is known, many experts, as well as the American Heart Association (AHA), still recommend limiting saturated fat to under 7% of your total calories each day. For someone who usually takes in 2,000 calories a day, that corresponds to about 16 grams of saturated fat.

Replacing saturated fat with unsaturated vegetable oils—for example, using olive oil instead of butter or margarine—is one way to lower your LDL. It's a good idea to cook foods using monounsaturated or polyunsaturated fats, such as vegetable oils and nut oils. Olive, peanut, sesame, and canola oils are rich in monounsaturated fats; soybean, corn, safflower, sunflower, and fish oils are high in polyunsaturated fats. You can also replace saturated fat with healthier fats if you eat more fish, nuts, seeds, and vegetables and less red meat and cheese.

Fill up on whole foods

The healthiest foods for your heart are generally those that have undergone the least amount of processing—especially fruits, vegetables, and grains. Processing strips foods of their vitamins, minerals, and other nutrients. It also removes fiber.

Fiber is a carbohydrate that your body can't break down, so it passes through the body undigested. It comes in two varieties: insoluble and soluble. Insoluble fiber does not dissolve in water. It is found in whole grains, wheat cereals, and vegetables such as carrots, celery, and tomatoes. Soluble fiber dissolves in water, creating a gooey paste. Good sources include barley, oatmeal, beans, nuts, flaxseed, and fruits such as apples, berries, citrus fruits, and pears. Soluble fiber affects cholesterol and has been linked to heart disease prevention. Insoluble fiber has been linked more to protection against constipation, diverticular disease, and other digestive conditions.

fast fact | Compared with a physically active woman of the same age, a middle-aged woman who does fewer than 60 minutes a week of exercise has double the risk of dying from a cardiovascular event.

Soluble fiber binds to cholesterol in the digestive system and helps usher it out of the body before it gets into the bloodstream. It also binds to the bile acids that help absorb fats in the small intestine, and moves them into the large intestine for excretion. To replace these lost bile acids, the liver makes more, using cholesterol in the process. When there isn't enough cholesterol in the liver, some is pulled from the bloodstream via LDL, lowering LDL in circulation.

Insoluble fiber may also play a role in regulating LDL by filling you up and thus crowding other cholesterol-raising foods out of your diet.

The soluble fiber found in psyllium seed husks can help lower cholesterol. Other fibers used to lower total and LDL cholesterol include guar gum and pectin. Guar gum has been used to reduce cholesterol for decades, and has been incorporated into such foods as breads, crackers, pasta, and snack bars. Pectin, a soluble fiber found mostly in citrus fruits (oranges, lemons, and grapefruits) and apples, can modestly lower total and LDL cholesterol.

The average American man gets about 18 grams of fiber a day, under half of the recommended 38 grams. The average woman gets 14 grams, or a little more than half of the recommended 25 grams.

If you plan to add more fiber to your diet (see Table 8, page 32, for foods to boost your fiber intake), take it slow. Add a little more each week to give your digestive system time to adjust. At first, the digestive system has trouble breaking down all these complex carbohydrates and generates a higher-than-usual amount of gas. Although eating fiber can help prevent constipation, a rapid increase in dietary fiber can cause it. Drinking extra water can avert constipation.

Try plant sterols and stanols

Plants contain a host of compounds that are chemically related

Table 8: Sources of fiber

A label can claim a food is a "good source" of fiber if it delivers at least 10% of your daily dose of fiber—a minimum of 2.5 grams per serving. The terms "rich in," "high in," or "an excellent source of" fiber are allowed if the product contains 20% of your daily dose—that is, 5 or more grams of fiber per serving. Spooning up a bowl of high-fiber cereal is one of simplest ways to reach your fiber target. Look for brands with 6 or more grams of fiber per serving. Your best bet for bread? Look for the words "100% whole wheat" or "100% whole grain" on the label and at least 3 grams of fiber per slice.

FOOD	SERVING SIZE	FIBER (GRAMS)
▼ Cereals		
Fiber One	½ cup	14
All-Bran	½ cup	10
Shredded Wheat	1 cup	6
Oatmeal (cooked)	1 cup	4
▼ Grains		
Barley (cooked)	1 cup	9
Brown rice (cooked)	1 cup	4
▼ Baked goods		
Whole-wheat bread	1 slice	3
Bran muffin	1	2
▼ Vegetables		
Spinach (raw)	1 cup	3.5
Broccoli	½ cup	3
Brussels sprouts	½ cup	2
Carrot	1 medium	2
Green beans	½ cup	2
▼ Legumes		
Kidney beans (cooked)	½ cup	6
Lima beans (cooked)	½ cup	6
Baked beans (canned)*	½ cup	5
▼ Fruit		
Pear (with skin)	1 medium	6
Apple (with skin)	1 medium	4
Banana	1 medium	3
▼ Dried fruits		
Prunes	6	4
Raisins	¼ cup	1.5
▼ Nuts and seeds		
Peanuts*	10	1
Popcorn*	1 cup	1

**Choose no-salt or low-salt versions of these foods.*

to cholesterol. There are two main families: sterols and stanols. They do for plants what cholesterol does for us—help make hormones, vitamins, and the "skin" that surrounds plant cells. When eaten, plant sterols and stanols (also called phytosterols and phytostanols) compete with cholesterol for absorption into the body. Since the liver needs cholesterol to make bile acids for digestion, it then grabs LDL (bad) cholesterol from the bloodstream while leaving HDL (good) cholesterol alone. The result is lower levels of total and LDL cholesterol.

Eating foods that naturally contain sterols or stanols is one way to lower cholesterol, although the effects are modest. Sterols and stanols are also added to some brands of butter and margarine, certain breads and cereals, low-fat milk, low-fat yogurt, and fruit juices. These products can help reduce LDL cholesterol by as much as 20%, or not at all—it depends on how high your cholesterol levels are and what kind of diet you eat. If your LDL levels are very high, plant stanols or sterols are unlikely to be effective enough on their own. If you have slightly elevated LDL cholesterol and your diet is relatively high in fat, you might see better results. To have an effect, you'll need a daily intake of at least 2 grams—about as much as in two 8-ounce servings of plant sterol–fortified orange juice. But be cautious about overconsuming

foods that may cause their own problems. They're safe and effective unless you have a rare genetic disorder known as phytosterolemia or sitosterolemia.

Shun sugar and refined carbs

Growing evidence suggests a connection between the amount of added sugar you eat and your cholesterol—specifically, low levels of HDL. The National Health and Nutrition Examination Survey, a large study that tracks the dietary habits of a group of American adults, found that people who consumed at least 10% of total calories from added sugar were up to three times more likely to have low HDL as those who took in half that much sugar. People who consumed the most sugar had HDL levels that were, on average, about 11 points lower than the low-sugar-intake group. Another study found that people who took in 25% or more of their calories as sugar were more than twice as likely to die from heart disease as those whose diets included less than 10% added sugar. One reason may be that a high-sugar diet stimulates the liver to dump more triglycerides into the bloodstream.

The AHA recommends that women consume less than 100 calories of added sugar per day (the equivalent of about 6 teaspoons) and men consume less than 150 per day (about 9 teaspoons). To put that in perspective, a 12-ounce can of regular soda contains about 9 teaspoons of sugar, so quaffing even one a day would put all women and most men over the daily limit. Sugar-sweetened beverages such as sodas, energy drinks, and sports drinks are by far the biggest sources of added sugar in the average American's diet. They account for more than one-third of the added sugar we consume as a nation. Other important sources include cookies, cakes, pastries, and similar treats; fruit drinks; ice cream, frozen yogurt, and the like; candy; and ready-to-eat cereals.

Foods made with highly refined wheat, oats, and other grains are a staple of the American diet. Think white bread, white rice, bagels, donuts, crackers, and chips. These foods deliver easily digested starch to the body, which quickly converts it into sugar. When such foods are eaten instead of fat—say, by someone on a low-fat diet—they increase the level of triglycerides and extra-harmful small LDL particles, and reduce protective HDL cholesterol.

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The best way to get fiber is to eat a diet rich in whole grains, nuts, legumes, fresh fruits, and vegetables.

Current guidelines on diet recommend cutting back on foods made with highly refined grains and instead eating whole grains or foods made from them. Examples of such substitutions include

- brown rice, wheat berries, or other whole grain instead of white rice
- whole-wheat pasta instead of regular pasta
- whole-wheat or whole-oat flour instead of white flour
- popcorn instead of chips.

Sip your alcohol: Moderation is key

If you like a drink of wine, beer, or spirits now and then, it's good to know that mild to moderate drinking can elevate protective HDL cholesterol by about 10%, or somewhere between 9 and 13 mg/dL. But be sure to follow the guidelines for moderate consumption: no more than one drink per day for women and two for men.

A large and consistent body of research has shown that moderate drinkers have a lower rate of coronary artery disease than either teetotalers or heavy drinkers. In addition to boosting HDL, alcohol dampens the body's ability to form blood clots, similar to aspirin.

But these benefits must be weighed against the known hazards of drinking alcohol. Alcohol

Targeting high triglycerides

Obesity, alcohol abuse, a diet high in saturated fat, or illnesses such as poorly controlled diabetes, chronic kidney disease, or liver disease can cause high triglyceride levels.

If your triglycerides are elevated, the American Heart Association suggests the following dietary changes, many of which overlap with the strategies in this chapter for improving cholesterol values:

Choose carbs wisely. Triglycerides go up when you eat a lot of easily digested carbohydrates like white bread, white rice, chips, sugar-laden breakfast cereals, and sugar-sweetened drinks. Choose whole grains whenever possible, and avoid foods with a lot of added sugar. Remember that even foods like whole-wheat bread can still contain a significant amount of carbohydrates.

Focus on fats. Cut back on saturated fats from meat, milk, and other dairy products, and trans fats found in commercially baked goods—both types elevate triglycerides. Try to eat more unsaturated fat from plants, oils, and fish, which bring down triglycerides.

Keep an eye on fructose. Fructose, or fruit sugar, has become abundant in the American diet. It is in table sugar, the cane and beet sugars used to sweeten cereals and baked goods, and high-fructose corn syrup. The breakdown of fructose turns on triglyceride production. Don't give up fruit. Instead, ratchet back fructose intake by consuming less sugar and sugar-sweetened foods and beverages.

Go fish. Eating fish twice a week, especially fatty fish like salmon, tuna, and sardines, is good for triglyceride levels. Bake, broil, steam, or poach—fried fish isn't quite as good for you.

Be aware of alcohol. In some people, drinking alcohol, usually in significant amounts, can significantly elevate triglycerides. If your triglycerides are high, you may want to avoid alcohol completely for a few weeks and have your triglycerides tested again.

can worsen various coronary risks, including high blood pressure and diabetes. Heavy use can cause cirrhosis of the liver, is linked to several forms of cancer, and clearly plays a role in suicides and accidental deaths, especially from car crashes. It can also lead to alcoholism. So while a daily drink probably won't hurt nonalcoholics who are already accustomed to it, experts do not recommend that anyone take up drinking in the hopes of raising HDL cholesterol.

Remember everyone is unique

People vary widely in how their bodies respond to dietary changes. In some people—call them responders—cholesterol levels closely reflect the amount of unhealthy fats in their diets. In others, cholesterol levels more closely reflect how much cholesterol their livers make rather than how much they consume.

There are two important messages from the research on responses to dietary fat and cholesterol:

Determine whether dietary changes work for you. Say your cholesterol is creeping up into the high range, and your physician suggests that you try a healthier diet for three to six months. You make an effort to do so. But at the end of the trial period, a blood test shows that your cholesterol levels haven't budged. Your physician might misinterpret the lack of change and chide you for not sticking with the new diet. But if you have followed the diet carefully, make sure the doctor knows it. You may be less responsive to changes in diet and need a different kind of diet, or medication, to control your cholesterol.

One size doesn't fit all. When a friend or relative tells you how much his or her cholesterol level dropped after trying a particular diet, you may be tempted to try the same diet. But if after a few months you discover that the diet has no effect, chalk it up to genetic and physiological differences. There just isn't a one-size-fits-all recommendation for diet or cholesterol consumption, which means you may have to try several different approaches to find one that works for you.

Start an exercise program

Being physically active can increase your life span, regardless of any "bad genes" you might have inher-

ited. At any age, exercise protects against a multitude of chronic health problems, including cardiovascular disease and diabetes. Even if you already have these conditions, small increases in physical fitness can make significant improvements. Exercise helps control weight and blood pressure, eases inflammation, and improves the overall health of your blood vessels. It's also one of the most reliable ways to boost protective HDL.

How much should you exercise?

Given the wide range of health benefits associated with regular physical activity, the Physical Activity Guidelines for Americans recommend at least 150 minutes (2 hours and 30 minutes) a week of moderate-intensity physical activity, or 75 minutes (1 hour and 15 minutes) a week of vigorous-intensity activity. You can also do an equivalent combination of moderate and vigorous aerobic exercise.

For most people, more exercise is better. A landmark study of 17,000 Harvard alumni found that men who burn an extra 700 or so calories a week by walking, playing sports, or doing some other physical activity live longer than those who aren't active (see Table 9, at right, for ways to burn 150 calories). The health benefits continue to increase up to about 2,000 calories expended a week, then seem to level off. Data from the long-term Nurses' Health Study show similar trends for women.

Get going with exercise

If you don't currently exercise and want to start, it's probably safe for you do so without talking with your doctor if you can honestly answer "no" to all of the following questions:

- Has your doctor ever suggested that you have heart trouble?
- Do you frequently have pain in your heart and chest?
- Do you often feel faint or have spells of severe dizziness?
- Has your doctor ever said your blood pressure was too high?
- Has your doctor ever told you that you have a bone or joint problem, such as arthritis, that has been aggravated by exercise or might be made worse by it?
- Are you over 65 and not accustomed to vigorous exercise?

Table 9: Ways to burn 150 calories

Following are some activities you can do to burn 150 calories. If you do two of these activities every day of the week, you'll burn a little over 2,000 calories per week. These figures are based on a body weight of 150 pounds. If you weigh less than 150 pounds, it'll take you longer to burn the same amount of calories. The opposite is true if you weigh more than 150 pounds.

ACTIVITY	TIME
Biking, 6 mph	38 minutes
Biking, 12 mph	22 minutes
Jogging, 5.5 mph	12 minutes
Running, 10 mph	7 minutes
Walking, 2 mph	38 minutes
Walking, 3 mph	28 minutes
Walking, 4.5 mph	20 minutes
Tennis, singles	23 minutes
Gardening	30–45 minutes
Washing windows or floor	60 minutes
Water aerobics	35 minutes
Swimming, 25 yards/minute	33 minutes
Swimming, 50 yards/minute	18 minutes
Raking leaves	35 minutes
Shooting baskets	35 minutes

- Is there a good reason not mentioned here why you should not exercise?

If you answered "yes" to any of these questions, see your physician before exercising. He or she will take a medical history, conduct a physical examination, and—if you are over age 35 and sedentary—may suggest further tests to look for signs of subtle coronary artery disease, abnormal heart size, or abnormal heart rhythms.

Some people—including those with heart failure, serious arrhythmias, unstable angina, uncontrolled high blood pressure, significant aortic valve disease, aortic aneurysm, or uncontrolled epilepsy—shouldn't exercise or should only do so under close supervision. If you have heart disease or other significant cardiovascular problems, consult your physician for an appropriate exercise program.

Once you are cleared to exercise, determine your maximum and target heart rates so you can exercise at a level that improves your cardiovascular fitness. To calculate your maximum heart rate, subtract your age from 220. For a 50-year-old, that would be 220 minus 50, or 170 beats per minute. To find your target heart rate, multiply that number by 50% and 85%. For that 50-year-old with a maximum heart rate of 170, that would be 170 times 0.5, or 85 beats per minute, and 170 times 0.85, or 145 beats per minute. When starting, that person would aim to exercise with enough intensity to keep his or her heart beating about 85 times a minute for about 20 minutes. Over time, he or she would push the target to 145 beats per minute.

fast fact | For every hour an adult spends doing regular vigorous physical activity, he or she may gain up to two hours of life expectancy.

To check your heart rate, find the pulse point on the side of your neck or on your wrist. Count the number of beats as your watch ticks off 6 seconds, and multiply that number by 10. You can also buy an inexpensive monitor that will do this for you.

Even this isn't absolutely necessary—walking, biking, or running to the point at which you are just able to say four or five words between breaths correlates well with the aerobic benefit of heart rates in the 110–130 range. Exercise shouldn't seem like punishment, but it should feel like exertion. It should also be slow, steady, and frequent.

Shed excess pounds

Carrying too many pounds for your frame can be detrimental to your health on many fronts and in many ways. One beneficial side effect of combining a healthier diet with more exercise is weight loss. Modest weight loss, even just 5% to 10% of your weight, can have dramatic effect on lowering triglycerides, which in turn helps shift LDL to the fluffier, less damaging type (see "LDL particle size," page 5).

If you've tried to lose weight, you know it isn't always easy—or permanent. How best to lose weight is beyond the scope of this report. Some helpful resources include *The Harvard Medical School 6-Week Plan for Healthy Eating* and *Simple Changes, Big Rewards* (see "Resources," page 47, for ordering information).

Monitor your progress

Starting a program of dietary change and exercise is a great first step for anyone with high cholesterol. But be patient. It can take months for your body to gradually adjust to your new regimen, and for you to change longstanding habits. To see if your program is working, have your cholesterol tested after two or three months and again at six months. If the follow-up measurements show

that you've achieved your goals for LDL, HDL, and triglyceride levels, continue to have follow-ups every six months. But note that some insurance companies don't cover repeat blood tests.

If your blood cholesterol levels don't respond to three months of diet and exercise, ask your doctor for a referral to a dietitian, who can do a more thorough review of your food choices and suggest more and better ways to adjust your diet. If your cholesterol levels still don't improve, drug therapy might be in order.

Other lifestyle changes

Since your ultimate goal is to avoid heart attacks, strokes, and other forms of cardiovascular disease, it is important to note that other lifestyle changes beyond diet and exercise can dramatically decrease your chances of developing heart problems, even though they don't affect cholesterol levels. First and foremost is stopping smoking. Practicing stress management through meditation or other stress-reduction techniques is also important. Modest changes in lifestyle can have many, compounded effects, like lowering blood pressure, improving sleep, and increasing a sense of well-being.

Medications: Statins

Statins, the most widely prescribed cholesterol-lowering drugs, block a key liver enzyme called HMG-CoA reductase, which is involved in producing cholesterol (see Figure 7, below). These drugs can reduce death and major cardiovascular events (such as heart attack or stroke) by 20% to 30%. They can also help your body stabilize plaque on your artery walls, preventing ruptures that can cause heart attacks.

The primary way these drugs help the heart is by lowering LDL cholesterol by 20% to 60%. They can also raise HDL cholesterol by a modest 2% to 10%, but it's unclear how much of a health benefit this HDL-raising activity adds. In addition, the statins appear to have other beneficial effects. Evidence suggests they may

- protect heart and blood vessel cells directly by speeding DNA repair and slowing cell death
- have anti-inflammatory and antioxidant properties that may protect the arterial wall from being damaged by cholesterol
- help arteries widen to carry more blood to the heart muscle and other tissues
- stabilize cholesterol-laden arterial plaques, reducing the chance that they will rupture and trigger heart attacks
- inhibit platelets, which helps to prevent artery-blocking blood clots
- reduce blood viscosity or "thickness," perhaps easing blood flow through partially blocked arteries.

Table 10 (page 39) lists the currently available statins.

Choosing a statin

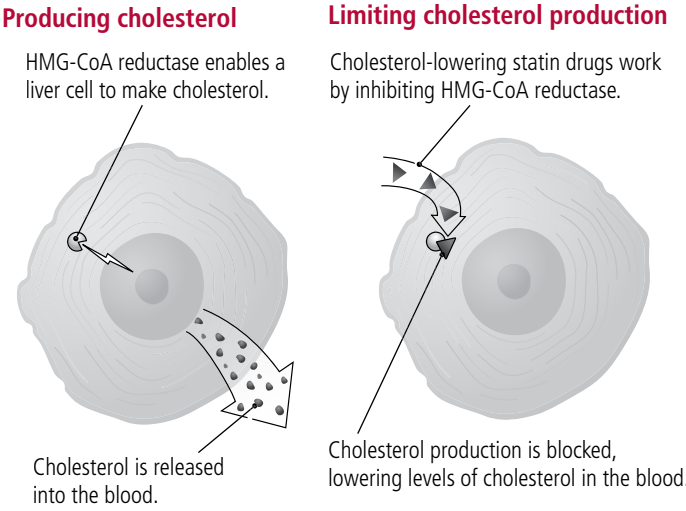
Your doctor's choice of a statin for you will depend in part on whether you already have heart disease or, if not, how high your risk is for developing it—the higher your risk, the stronger a statin you will need (see Table 6, page 26, for a list of high-, moderate-, and low-intensity statins).

Another consideration is the price. Most statins are available as generics and cost as little as $10 for a three-month supply if you buy them from a large chain store such as Target, Walmart, or Sam's Club, according to *Consumer Reports Best Buy Drugs*. By contrast, brand-name statins can cost as much as $600 per month, which is particularly important when you consider you'll likely be taking the drugs for years and perhaps the rest of your life.

Statin side effects

In general, the vast majority of people tolerate statins very well. In double-blind clinical trials, where neither participants nor their doctors knew who was taking the actual statin versus a placebo (sugar pill), roughly 90% to 95% of people had no worrisome side effects. Nevertheless, side effects can and do occur. Some of

Figure 7: How statins work



Most of the cholesterol circulating in your blood is made by your liver; it does not come from the food you eat. An enzyme called HMG-CoA reductase plays a key role in determining how much cholesterol the liver makes. Statins work by blocking the activity of HMG-CoA reductase.

Table 10: Statins: The first-line treatment

GENERIC NAME	BRAND NAME
atorvastatin*	Lipitor
fluvastatin*	Lescol, Lescol XL
lovastatin*	Mevacor, Altoprev
pitavastatin	Livalo
pravastatin*	Pravachol
rosuvastatin	Crestor
simvastatin*	Zocor

**available in generic form (does not include Lescol XL)*

these—including muscle and joint aches, nausea, diarrhea, and constipation—typically go away gradually as your body adjusts to the medication. However, there are two rare, but potentially serious, side effects you need to be aware of: liver damage and a breakdown of muscle tissue called rhabdomyolysis. Other reported side effects include changes in memory and a modest increase in the risk of diabetes.

Liver damage

Because statins target liver cells, there was early concern that they could damage the liver. When statin therapy was relatively new, people taking these drugs routinely had blood tests to check for changes in liver enzyme levels, an early warning sign of liver damage. A 10-year analysis from Sweden showed that therapy with simvastatin produced only minor, temporary changes in liver enzyme levels. Since then, other studies have found that even people with liver abnormalities can take statins safely without further damage to the liver.

Acknowledging that statin therapy generally doesn't harm the liver, the FDA in March 2012 changed the requirement regarding liver testing for people on statins. Instead of routine testing, the agency now recommends a single test of liver enzymes when an individual starts taking a statin or switches to a new one. If you have known liver problems, however, the decision of whether to take a statin should be based on your needs and medical history. And tell your doctor right away if you have symptoms of liver injury, which include unusual fatigue, loss of appetite, discomfort in the upper abdomen, dark-colored urine, or yellowing of the skin or whites of the eyes.

Rhabdomyolysis

Rhabdomyolysis is a breakdown of muscle tissue that releases the contents of muscle fibers into the blood. These substances can damage the kidneys, sometimes causing kidney failure and even death. Rhabdomyolysis was a rare side effect with some of the first statins but received widespread attention after a powerful statin called cerivastatin (Baycol) came on the market. Cerivastatin was eventually pulled from the market when its use was linked to fatal cases of rhabdomyolysis, especially when it was combined with other lipid-lowering drugs.

Early statin users were advised to have regular blood tests to spot rising levels of creatine kinase, a byproduct of muscle breakdown. Doctors hoped the tests would help identify the earliest stages of rhabdomyolysis, which occurs in only about one in 10,000 statin users.

In 2012, the FDA recommended that creatine kinase tests be given only at the start of statin therapy or if muscle pain or weakness developed. Rhabdomyolysis is not accurately predicted by routine blood testing, they said, and common statin-related muscle discomfort often resolves with a lower statin dose or a change to a different statin. Rhabdomyolysis may be more common among people taking other medications cleared by the liver, including certain antibiotics, HIV medications, and some other lipid-lowering drugs.

Muscle pain

Up to one in 10 people taking a statin reports muscle aches, pains, and weakness. But that doesn't necessarily mean the statin is causing all these muscle problems, because people get muscle aches all the time. Doing vigorous exercise or yard work (particularly if you're out of shape) or even just logging too many hours on the computer can cause muscle aches and fatigue. How can you tell if a statin is responsible? It may be causing the problem if the ache or pain

- is recent: the ache or weakness usually begins within a few weeks of starting the statin

- is symmetrical: the muscle problem affects both sides of the body (if the ache is in one leg, for example, it's less likely to be from the statin)
- is unexplained: there is no other obvious reason for the muscle ache or weakness, like a day's worth of gardening or an injury.

If you notice new muscle symptoms after starting a statin, your doctor may advise you to stop taking it, wait a month or two, and then try taking it again. If the muscle troubles return, your doctor can change the dose or type of statin, or take you off the drug. Many therapies have been suggested for resolving statin muscle aches, including supplements like CoQ_{10}, but the evidence for any of these measures making a difference is scant (see "Ask the doctor: Should I take CoQ_{10} for muscle aches?" below left).

Diabetes

In a small number of people, statins raise blood sugar levels—sometimes high enough to trigger a new diagnosis of diabetes. The increase is usually small, but it is important enough that the FDA has issued a warning on statin labels about blood sugar and diabetes.

On the other hand, doctors prescribe statins to people with diabetes to reduce the risk of heart disease associated with the condition. The cardiac benefit appears to outweigh the slight added risk of diabetes, according to various studies. In a 2014 study in *The American Journal of Cardiology* that followed 9,000 people at risk for diabetes, 29% of those taking statins ended up with diabetes compared with 24% of those who didn't take statins. However, the statin users had 30% fewer cardiovascular problems. Statins may simply bring on diabetes in people already at high risk for the problem.

Memory loss

Some statin users have reported memory loss or confusion while taking the drug. In 2012, the FDA ordered that statin drugs carry a warning about this. The agency did not conclude that statins caused these symptoms—just that doctors prescribing statins and people taking the medications ought to be aware of the possible problem.

The evidence supporting the claim that statins cause memory loss or confusion is very weak. The warning was apparently based on a number of case reports, which are considered less reliable than other types of studies, such as those that compare users of a drug to nonusers. The latest research, in *Annals of Internal Medicine*, included data from 27 studies and found no proof linking statin use to dementia or other problems associated with thinking and memory.

The study authors also looked at data collected by the FDA from people who reported side effects while taking statins or either of two other drugs, the blood pressure drug losartan (Cozaar) and the anti-clotting drug clopidogrel (Plavix). Reported rates of cognitive problems were similar for all three medications, yet

ASK THE DOCTOR

Should I take CoQ_{10} for muscle aches?

***Q** I am taking simvastatin for high cholesterol. Should I take coenzyme Q_{10} to prevent muscle pain?*

A There is no convincing medical evidence to suggest that coenzyme Q_{10} (CoQ_{10}) prevents muscle pain in people taking statins. But because the risk of side effects from CoQ_{10} is low, many doctors would recommend a one- to-two month trial of the supplement (doses range from 100 to 200 mg daily) to help with statin-related muscle cramps, pain, or weakness. Make sure your doctor knows you are taking it.

The connection between CoQ_{10} and statin-related muscle symptoms is circumstantial. Taking a statin to lower "bad" LDL cholesterol also lowers CoQ_{10}, a naturally occurring chemical in the body involved in energy production in cells. Muscle aches are a common side effect of statins, and CoQ_{10} is important for muscle function, so scientists have wondered if raising blood levels of CoQ_{10} might relieve the aches. However, there is no solid evidence that the supplement does so. If you decide to try it, look for the United States Pharmacopeial Convention (USP) mark on the supplement packaging, indicating that the product meets basic standards for quality and purity.

As for other health claims you may have heard for CoQ_{10}, taking the supplement does not make much sense. It is expensive (about $30 a month) and has not been shown to boost your energy, cure any health conditions, or help you live longer.

—William Kormos, M.D.
Editor in Chief, Harvard Men's Health Watch

ASK THE DOCTOR
Grapefruit juice and statins

Q ***I've heard that people shouldn't drink grapefruit juice if they're taking a statin. Why?***

A Certain classes of drugs—most notably statins—are metabolized (broken down) in your intestines by an enzyme called CYP3A, which normally reduces the amount of drug that enters your bloodstream. Grapefruit juice contains compounds called furanocoumarins that stop CYP3A from doing its job. As a result, more of the drug is absorbed, making it more powerful than it's meant to be, even toxic in some cases.

Not all statins are affected equally by grapefruit juice, so grapefruit fans might want to switch to a statin that's less affected (see Table 11, below). But if you can't switch, experts say it's probably okay to enjoy a small glass. That's because the studies showing dangerous effects used massive amounts of furancoumarins, found in a quart or more of the juice. Also, eating a half grapefruit lowers your risk even more, since it takes several fruits to make a single glass of juice. But to be on the safe side, check with your doctor, and avoid taking your pills with grapefruit juice.

Table 11: The grapefruit effect

Grapefruit juice affects certain statins more than others.

BIG EFFECT	LITTLE OR NO EFFECT
atorvastatin (Lipitor)	fluvastatin (Lescol)
lovastatin (Mevacor)	pitavastatin (Livalo)
simvastatin (Zocor)	pravastatin (Pravachol)
	rosuvastatin (Crestor)

—Jorge Plutzky, M.D.
Medical Editor

the FDA has not issued similar warnings on losartan or clopidogrel (nor does it need to).

Despite the reassuring results from the new study, the authors caution that larger and better-designed trials are still needed. The available evidence is limited, especially with regard to high doses of statins.

Drug interactions

If you develop side effects on a statin, check to see if any other drugs you take—prescription, over-the-counter, or herbal—interact with statins. In 2013, a study in the *Journal of Clinical Lipidology* found that many people who quit taking statins because of possible side effects were also taking an average of three other drugs that affected statin metabolism. Often, the drugs boosted statin levels throughout the body. Doctors don't always pick up these potential interactions, so double-check with your pharmacist or online at www.health.harvard.edu/drugcheck. Taking a lower dose, using drugs that don't interact with statins, or trying a different type of statin can help.

Getting the most from your statin

Whichever statin you end up taking, you can do several things to make sure your particular statin is working as well as it can.

- Follow your doctor's instructions on taking your statin either with food or on an empty stomach. Different statins behave in different ways and may be absorbed better under one condition or the other. If you're on lovastatin, for example, take it with food. This almost doubles the amount of medication that gets into your bloodstream. If you're taking pravastatin, take it on an empty stomach. The rest of the statins can be taken either with or without food.
- Ask your doctor whether it's best to take your statin in the morning or evening. Those that are rapidly metabolized and eliminated should be taken in the evening, when the body's cholesterol-making machinery is working hardest. These include lovastatin, pravastatin, simvastatin, and fluvastatin. Others that work more slowly—atorvastatin, pitavastatin, and rosuvastatin—last long enough in the body that it doesn't matter when you take them.
- Avoid drinking grapefruit juice if you're taking lovastatin, simvastatin, or atorvastatin (see "Ask the doctor: Grapefruit juice and statins," at left).
- Beware of drug interactions. Mention all other drugs and supplements you are taking when talking with your doctor about a statin. If you are on other medications, you may want to try pravastatin, which is less likely than the other statins to interact with other medications.

Medications: Non-statin drugs and other alternatives

People who can't tolerate statins because of side effects have several other options, including bile acid binders, fibrates, and niacin (see Table 12, below right). These medications have also been used in combination with statins to drive LDL cholesterol down to specific targets. Though targets are no longer recommended under the new guidelines from the American Heart Association and American College of Cardiology, your doctor may feel you would benefit from greater reductions than you're achieving with a statin alone.

Ezetimibe

Ezetimibe (Zetia) blocks cholesterol in food from crossing the intestinal wall and getting into the bloodstream. It can lower LDL levels by roughly 15%. However, there are no definitive studies showing that ezetimibe reduces cardiovascular risk.

In one study, ezetimibe and simvastatin (marketed as the combination drug Vytorin) decreased cardiovascular events significantly more than placebo in people with chronic kidney disease, a clinical setting in which statins alone had not previously worked. A very large study on Vytorin's effectiveness, called IMPROVE-IT, was slated to wrap up as this report went to press. Results from IMPROVE-IT may clarify some of the issues around the drug's usefulness in patients with coronary disease.

In the meantime, most experts believe that ezetimibe should be thought of as a safe way to lower LDL cholesterol when a statin can't be taken. Ezetimibe has an excellent safety record and is generally well tolerated.

Bile acid binders

These medications work by grabbing cholesterol-rich bile acids in the intestine and locking them into a watery goo that is excreted in the stool. They include cholestyramine (Prevalite, Questran), colesevelam (Welchol), and colestipol (Colestid). Typically, these drugs lower LDL cholesterol by 15% to 30%, depending on the daily dose. Larger amounts produce greater reductions, but also heighten the side effects—including constipation, heartburn, and a bloated feeling. Interestingly, bile acid binders also modestly decrease blood sugar levels. But they can further raise triglycerides in people with elevated levels. For this reason, people with high triglyceride levels should not take bile acid binders.

Table 12: Non-statin drugs to lower cholesterol

GENERIC NAME (BRAND NAME)	BENEFITS	POSSIBLE SIDE EFFECTS
Bile acid binders		
cholestyramine (Questran) colesevelam (Welchol) colestipol (Colestid)	Lower LDL	Constipation, bloating, nausea, gas; may increase triglycerides
Cholesterol absorption inhibitor		
ezetimibe (Zetia)	Lower LDL, slightly lower triglycerides, slightly higher HDL	Stomach pain, fatigue, muscle soreness
Fibrates		
fenofibrate (TriCor) gemfibrozil (Lopid)	Lower triglycerides, higher HDL	Nausea, stomach pain, gallstones
Niacin (vitamin B_3, nicotinic acid)		
niacin (prescription Niaspan, nonprescription Slo-Niacin, others)	Lower LDL and triglycerides, higher HDL	Facial and neck flushing, nausea, vomiting, diarrhea, gout, high blood sugar, peptic ulcers

fast fact | Studies conclusively show that lowering levels of LDL cholesterol can reduce the short-term risk for heart disease by as much as 40%.

They can also bind with substances other than bile acids and may interfere with the body's ability to absorb some medications, including digitalis, beta blockers, warfarin, thiazide diuretics, anticonvulsants, and thyroid medications.

Fibrates (fibric acid derivatives)

Fibrates lower triglycerides by reducing your liver's production of VLDL cholesterol and speeding up its removal from the bloodstream. The two most commonly prescribed fibrates are gemfibrozil (Lopid) and fenofibrate (TriCor, Lofibra). They reduce triglyceride levels by 20% to 50% and raise HDL levels by 10% to 15%, but they have only a modest effect, if any, on LDL levels. In general, they're prescribed for people with high triglyceride levels. Studies looking at adding a fibrate for people taking a statin failed to show additional benefit in decreasing cardiovascular events, although there was a suggestion of benefit in those with higher triglyceride and lower HDL levels.

Fibrates are usually taken once (fenofibrate) or twice (gemfibrozil) a day with meals. Most people don't experience side effects, although a few develop feelings of fullness, bloating, or heartburn after eating. Other possible side effects include dizziness or changes in sensations such as touch and taste. Gemfibrozil and fenofibrate can also increase the risk for gallbladder disease.

When used with a statin, fibrates have caused rare cases of rhabdomyolysis, a potentially deadly breakdown of muscle tissue. This may be a greater issue with gemfibrozil than with other fibrates. Fibrates can also boost the action of blood thinners, such as warfarin (Coumadin). Because of these uncommon but significant side effects, if you are taking a fibrate, you should have a liver function test and blood cell count before and during therapy. If you are taking a blood-thinning medication as well, have your prothrombin time (a measure of clotting ability) monitored closely.

Niacin

Niacin, also known as vitamin B_3, was the first cholesterol-lowering substance shown to reduce the risk of heart disease. It works by limiting your liver's ability to make VLDL particles. It's a good alternative for lowering LDL if you can't take a statin. But adding niacin to statin therapy offers little in the way of extra protection. A major study was stopped in 2011 because niacin failed to add any benefit to statin therapy. Indeed, several recent studies with niacin have been disappointing, showing no reduction in cardiovascular events despite increases in HDL. Recent studies have also raised concerns over side effects with niacin. As such, use of niacin has decreased, especially since niacin can also be difficult to tolerate.

Various prescription and over-the-counter preparations are available, including ones taken once a day at night (Niaspan).

In people with chronic liver disease or certain other conditions, niacin can worsen diabetes, increase uric acid levels (possibly leading to gout), and cause peptic ulcers. Other side effects include flushing and rashes. When you first start taking niacin, you may notice facial flushing for several minutes soon after a dose. But this reaction often stops after taking niacin for about two weeks and can be reduced by taking aspirin or ibuprofen 30 minutes before the niacin. Many people start by taking low doses and gradually build up the dose. Since niacin is one of the few medications that can lower lipoprotein(a), your doctor might suggest it for that purpose. However, given the available evidence, be careful about using niacin.

Drug combinations

Statins have become the mainstay for treating high cholesterol and atherosclerosis-related heart disease because they work better than any other currently available medication. Because so many people take one, drug makers have created several statin combi-

nations that aim to make treatment easier for people who need extra cholesterol-lowering power or who must take another heart medication (see Table 13, at right).

Advicor and Simcor combine a statin with niacin, one of the oldest cholesterol-lowering medicines. Liptruzet and Vytorin pair a statin with ezetimibe, a newer cholesterol-lowering drug. These four medications are intended to lower cholesterol more than a statin. Each of these combination medications is available in several dosages.

The benefits and risks of such combination therapy haven't been conclusively shown. The new cholesterol guidelines published in 2013 cast doubt on taking a non-statin drug to hit a particular LDL target. If that's why your doctor wants you to take a combination instead of just a statin, ask him or her if you need to do this.

Caduet combines the powerful statin atorvastatin with amlodipine, a widely used calcium-channel blocker used to treat high blood pressure. This combination can be useful if you need to take both a statin and a medication to lower your blood pressure.

An advantage of taking a combination drug is that you take one pill instead of two. A drawback is that if the medication doesn't work as intended, it can be difficult to figure out which component needs to be adjusted or which one is causing unwanted side effects. Cost is another issue. Atorvastatin and simvastatin are both available as inexpensive generic medications. But when either is combined with ezetimibe, the pill becomes a higher-priced, brand-name medication.

Table 13: Combination cholesterol-lowering medications

These medications pair a statin with another drug.

GENERIC NAME	BRAND NAME	DOSAGE OPTIONS
atorvastatin plus ezetimibe	Liptruzet	atorvastatin: 10, 20, 40, 80 mg ezetimibe: 10 mg
lovastatin plus extended-release niacin	Advicor	lovastatin: 20, 40 mg niacin: 500, 750, 1,000 mg
simvastatin plus extended-release niacin	Simcor	simvastatin: 20, 40 mg niacin: 500, 750, 1,000 mg
simvastatin plus ezetimibe	Vytorin	simvastatin: 10, 20, 40, 80 mg ezetimibe: 10 mg
atorvastatin plus amlodipine	Caduet	atorvastatin: 10, 20, 40, 80 mg amlodipine: 2, 5, 10 mg

Targeting triglycerides

Elevated triglycerides are typically considered to be a risk factor for cardiovascular disease, but they are so influenced by other factors that their value as an independent risk factor is still debated. When triglycerides are elevated, a healthy diet and exercise are the first-line treatments for reducing them. Cutting back on foods rich in saturated fat is one important dietary change that will help. Another is cutting back on sugar-sweetened foods and beverages and those made from rapidly digested simple carbohydrates, like white bread, white rice, pastries, fruit juice, and the like.

If those efforts don't work, medications are available.

- Fibrates can lower triglycerides by 40% to 60% (see "Fibrates," page 43). If your triglycerides are very high, especially if you have pancreatitis, your doctor may prescribe a fibrate right away.
- Fish oil, which contains omega-3 fatty acids, can lower triglycerides by 30% to 50%. Prescription forms are available, as are over-the-counter versions.
- Niacin (nicotinic acid) can lower triglycerides, but with the caveats noted earlier (see "Niacin," page 43).
- Statins modestly lower triglycerides by 20% to 40%.

Looking to the future: Possible new therapies

Researchers around the world are hot on the trail of new ways to treat high LDL, low HDL, and other lipid problems. To prove that a new treatment makes a difference, it must be compared to the standard of care. Given the success of statins, finding a new drug

Dietary supplements: Are any worth a try?

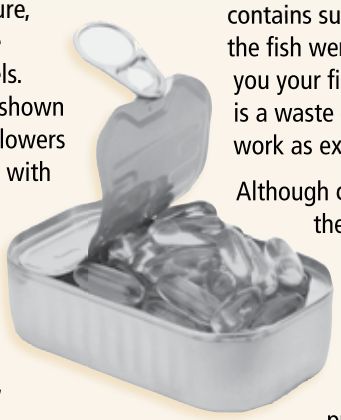
Various herbs and other supplements have been touted for their ability to improve lipid levels. Here's what the research shows—and doesn't show—about some of the best-known products.

Hawthorne. The leaves, berries, and flowers of this plant are used to make medicine that was traditionally used to treat cardiovascular diseases. It may lower cholesterol by increasing the excretion of bile and decreasing the body's production of cholesterol. **Verdict: It may possibly help.**

Red yeast rice. This Chinese medicine has been marketed in the United States to lower cholesterol levels. Some red rice yeast products contain a chemical that's identical to the active ingredient in lovastatin. An independent analysis of 12 red yeast rice products found that although all claimed to have 600 mg of the active ingredient in each capsule, the actual content varied between 0.10 mg and 10.9 mg. In addition, one-third of the products were contaminated with a potentially toxic compound called citrinin, which can cause kidney failure. This cautionary tale illustrates the potential pitfalls of taking dietary supplements, which are virtually free of the testing and manufacturing requirements that apply to pharmaceutical drugs. **Verdict: It may possibly help, but purity remains a problem.**

Garlic. Some preliminary studies suggested that garlic might lower blood cholesterol levels slightly. But a study funded by the National Center on Complementary and Alternative Medicine on the safety and effectiveness of three garlic preparations (fresh garlic, dried powdered garlic tablets, and aged garlic extract tablets) found no effect on cholesterol levels. **Verdict: Save your money.**

Fish oil. Oil from fatty fish such as salmon and sardines contains omega-3 fatty acids. Omega-3s have several heart-healthy effects: they lower heart rate and blood pressure, and they improve the health of blood vessels. Several studies have shown that eating fatty fish lowers heart risks for people with heart failure or a previous heart attack. Fish oil might not have the same impact, however. A 2013 study in *The New England Journal of Medicine* found that fish oil supplements don't lower heart attack or stroke risk in people at high risk of heart disease. High doses of fish oil can lower triglycerides, but at the same time, they cause a small increase in LDL. **Verdict: Eat fish instead.**



Thinkstock

Note: "Natural" doesn't necessarily mean better. New drugs are tested and scrutinized every step of the way for their safety, effectiveness, and purity. Almost the opposite is true for herbs and many other alternative remedies, which the U.S. government treats as food, not medicine. Under the 1994 Dietary Supplement Health and Education Act, a supplement maker is supposed to make sure a product is safe before it's sold. But the company doesn't have to track safety, and the FDA doesn't check. Nor does it check what's in a supplement. This lack of oversight means you can't tell how much garlic is in your garlic extract, whether your hawthorne contains substances it shouldn't, what the fish were fed before they provided you your fish oil, or if your supplement is a waste of money because it doesn't work as expected or purported.

Although conventional drugs can have their own issues, careful FDA approval standards and scientific scrutiny before, during, and after the approval process, as well as other federal regulations provide increased assurance regarding what you are getting when you buy a drug, what you can expect in terms of the response for a particular condition, and how safe it is. You can't do that for most alternative therapies. The simple assumption that an over-the-counter preparation or supplement is safer or better for you is not necessarily the case.

that improves on this already-high bar is a challenge. Following are a number of potential new treatments.

Lowering LDL

In the "promising-but-still-preliminary" realm for treating high cholesterol are agents that target a protein called PCSK9 (see "Risk factors under investigation," page 18). PCSK9 inhibitors, which are initially being developed as injected drugs, work by boosting the liver's ability to clear LDL from the blood, slashing LDL levels by more than half, even with relatively infrequent injections. In a yearlong trial, participants used a penlike device to inject the PCSK9 inhibitor evolocumab once a month. Some took the drug alone, with changes in diet. Others took it in addition to a statin or another cholesterol-lowering drug. In all groups, evolocumab dramatically lowered LDL. A separate study of evolocumab showed similar LDL reductions in people unable to take a statin because of intolerable side effects. Two other PCSK9 inhibi-

tors, alirocumab and bococizumab, have also shown similar positive results in early clinical trials.

Another target of therapy is microsomal transfer protein. This protein helps move cholesterol and triglycerides into VLDLs as they are being formed. Inhibiting its action prevents this transfer and thus lowers the production of VLDLs. Drugs that inhibit microsomal transfer protein have been shown to lower LDL by 70% or more and triglycerides by up to 40%. One such drug, lomitapide (Juxtapid), was approved by the FDA to treat familial hypercholesterolemia (see page 14). Others are under investigation. Lomitapide is not for use in the general population.

So-called antisense therapies halt the production of specific proteins. Researchers are testing antisense therapies aimed at slowing production of apolipoprotein B (ApoB), the main protein found on the surface of chylomicrons and LDL. Less ApoB means fewer chylomicrons and LDL particles. Early tests show that antisense drugs can lower LDL by as much as 60%. The FDA has approved one antisense drug, mipomersen (Kynamro), to treat familial hypercholesterolemia. Others are under investigation, for example, targeting PCSK9.

But just because these drugs lower LDL doesn't mean they will prevent heart attacks or lower the risk of dying of heart disease. Studies to answer those questions are under way, with results expected in several years. It would be important to know if these new agents have the same cardiovascular benefits and overall safety as statins. Also worth noting: while generic statin medications cost very little, the newer drugs are likely to be very expensive.

Raising HDL

Several novel approaches to raising HDL are also under way, including treatments that increase levels of ApoA1, the protein carried by HDL cholesterol. One possible approach in people with severe heart disease is intravenous administration of a synthetic form of a particular type of ApoA1, called ApoA1 Milano. Research suggests that ApoA1 Milano can raise HDL levels and reverse atherosclerosis. Other potential approaches include the use of small proteins called peptides that mimic the benefits of ApoA1.

Raising HDL doesn't automatically translate into prevention of heart attacks and strokes. Drugs that block cholesterol esterase transfer protein (CETP) can increase HDL powerfully. But in a trial that included 15,000 men and women at high risk of heart disease, those taking the experimental CETP inhibitor torcetrapib had increases in blood pressure, too. Even worse, there were more deaths in the torcetrapib group than among those taking the placebo. The trial was suspended early, and research on torcetrapib folded. A number of other CETP inhibitors have also been abandoned, though two, anacetrapib and evacetrapib, are still being pursued. Both significantly raise HDL and lower LDL, but do not appear to raise blood pressure as torcetrapib did.

All of these drugs will have to show that they actually improve cardiovascular health before the FDA will approve them, so it remains to be seen if they will ever reach the pharmacy. In the meantime, the tools in this report can help you reduce your heart-attack risk and start promoting your heart health—today.

Resources

Organizations

Academy of Nutrition and Dietetics
120 S. Riverside Plaza, Suite 2000
Chicago, IL 60606
800-877-1600 (toll-free)
www.eatright.org

This nonprofit organization operates a dietitian referral line. The website features extensive nutrition news and information, plus a dietitian locator.

American Heart Association
7272 Greenville Ave.
Dallas, TX 75231
800-242-8721 (toll-free; or check the Yellow Pages for your local affiliate)
www.heart.org

This nonprofit organization operates a consumer hotline to answer questions on general heart health. It also offers educational pamphlets, posters, and audiovisual materials on cholesterol and diet modification, all at no charge or for a nominal fee.

National Cholesterol Education Program
NHLBI Health Information Network
P.O. Box 30105
Bethesda, MD 20824
301-592-8573
www.nhlbi.nih.gov

This is a program of the National Heart, Lung, and Blood Institute. The NCEP guidelines from 2003, which contain a lot of still-useful information about cholesterol, are available on the website.

Harvard Special Health Reports

If you want to learn more about some of the topics covered in this report, the following Special Health Reports from Harvard Medical School can help. To order, visit www.health.harvard.edu or call 877-649-9457 (toll-free).

Healthy Eating for a Healthy Heart
Dariush Mozaffarian, M.D., and Ellen di Bonaventura, M.S., R.D., L.D.N., Medical Editors
(Harvard Medical School, 2011)

This report explains how food affects your heart and discusses healthy dietary patterns. Includes information on smart shopping, 36 heart-healthy recipes, and sample meal plans for a week.

Simple Changes, Big Rewards
Edward M. Phillips, M.D., Medical Editor
(Harvard Medical School, 2014)

Making major changes in your life—losing weight, eating healthier, exercising more, reducing your stress level, getting your finances under control—can seem impossible. But these goals don't have to be beyond your reach if you approach them one step at a time. This report includes easy, medium, and more challenging steps to achieving all these targets.

The Harvard Medical School 6-Week Plan for Healthy Eating
Teresa Fung, Sc.D., R.D., L.D.N., and Kathy McManus, M.S., R.D., L.D.N., Medical Editors
(Harvard Medical School, 2013)

This report provides a step-by-step plan for improving the nutritional quality of your meals at breakfast, lunch, and dinner. Includes 14 recipes, tips for sensible snacking, and advice on how to maintain your progress.

Glossary

antioxidant: A substance that inhibits oxidation.

apolipoproteins: Proteins that combine with cholesterol and triglyceride to form lipoproteins.

atherosclerosis: Development of cholesterol-rich plaque on the inner walls of arteries, which can eventually obstruct blood flow.

atherosclerotic plaque: A cholesterol-rich deposit on an artery wall.

biological variability: Fluctuations that occur naturally over time in the levels of a substance, such as cholesterol in a person's body.

cholesterol: A fatlike substance that is produced by the liver and found in all food from animal sources; an essential component of body cells and a precursor of bile acids and certain hormones.

chylomicron: A large, extremely low-density lipoprotein that transports triglyceride from the intestine to fat tissue in the body.

combined hyperlipidemia: A condition in which LDL and triglyceride levels are very high.

cytokines: The immune system's messengers, which help regulate an immune response.

familial combined hyperlipidemia: An inherited disorder in which the liver overproduces VLDL, causing high levels of cholesterol, triglycerides, or both.

familial hypercholesterolemia: An inherited disorder in which the liver cannot properly remove LDL particles from the blood, causing a very high cholesterol level.

fasting lipid profile: A laboratory test to determine the relative levels of HDL, LDL, and total cholesterol in the blood. Also referred to as a lipoprotein analysis, full lipid profile, or cholesterol profile.

fatty acids: The primary building blocks of lipids.

foam cells: Lipid-laden macrophages, named for their foamy appearance under the microscope, which contribute to the formation of atherosclerotic plaque.

high-density lipoprotein (HDL): A lipoprotein that protects the arteries by transporting cholesterol from body cells to the liver for elimination.

hydrogenation: The addition of hydrogen to a compound, particularly to solidify unsaturated oils.

intermediate-density lipoprotein (IDL): A lipoprotein type consisting of remnants of VLDL that eventually turn into LDL.

lipids: Fats, oils, and waxes that serve as building blocks for cells or as energy sources for the body.

lipoproteins: Protein-covered fat particles that enable cholesterol to move easily through the blood.

low-density lipoprotein (LDL): A lipoprotein that transports cholesterol from the liver to the rest of the body, which can cause the buildup of plaque in the arteries.

macrophages: Cells that develop from monocytes, a type of white blood cell. Macrophages stay in the lining of the artery and ingest bacteria, foreign cells, and damaged and dead cells.

metabolic syndrome: A cluster of risk factors that accelerate the progression of heart disease.

monocytes: Circulating white blood cells that take up residence in tissues, including the artery wall, and become macrophages.

monounsaturated fat: A type of healthy unsaturated fat that is abundant in olive, peanut, sesame, and canola oils.

non-HDL cholesterol: The sum of all cholesterol types other than HDL, including very-low-density lipoprotein, low-density lipoprotein, and intermediate-density lipoprotein.

oxidation: A process in which oxygen combines with a substance, altering its structure and changing or destroying its normal function.

platelets: Tiny, colorless disks in the blood that are instrumental in clotting.

polyunsaturated fat: A type of unsaturated fat that is abundant in soybean, corn, cottonseed, safflower, and sunflower oils.

saturated fats: Fatty acids that are abundant in red meat, lard, butter, cheese, and some vegetable oils, in which each molecule carries the maximum number of hydrogen atoms.

trans fats: Fatty acids (such as those found in solid margarine) that have been reshaped by hydrogenation; also called trans fatty acids.

triglyceride: The primary type of fat in the body and in the diet, formed from three fatty-acid molecules and one glycerol molecule.

unsaturated fats: Fatty acids in which some of the hydrogen atoms in each molecule have been replaced by double bonds; includes monounsaturated and polyunsaturated fats.

very-low-density lipoprotein (VLDL): A lipoprotein that transports triglyceride manufactured in the liver to fat tissue in the body; eventually becomes low-density lipoprotein (LDL) after the triglyceride has been removed.

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