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## Treatment of Elevated Cholesterol

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**A**s we age, cholesterol builds up in the arteries of the heart and neck, placing us at risk for heart attacks, strokes, and premature death. Treatment that lowers cholesterol in the blood has therefore become the cornerstone of prevention of future heart attack, stroke, and death, both in persons who definitely have heart disease and in those who are at risk of developing it in the future. Evidence suggests that millions of people who could benefit from cholesterol-lowering medicines are currently untreated. According to the American Heart Association, nearly 38 million patients in the United States would benefit from the combination of diet and drug therapy, and an additional 30 million should follow diet and exercise programs to reduce cholesterol levels.<sup>1</sup> Given that there are 290 million adults in the United States, this issue affects 1 of every 3 to 5 adults. Unfortunately, cholesterol-lowering treatment is widely underutilized because of the lack of awareness, fear of side effects, reluctance of otherwise healthy people to take medication, and cost. We hope this overview of the treatment of elevated cholesterol for patients (and persons who are not “patients”) will help ensure that all affected people will get their elevated cholesterol treated.

### What Is Cholesterol?

Cholesterol is a fatty substance that circulates in the blood and is an important structural component of all human cells. The body obtains cholesterol through 2 methods: via the liver, which produces about 75% of cholesterol, and through food, which accounts for 25%. Cholesterol comes in several forms, notably a “good” and a “bad” cholesterol. High levels of low-density lipoprotein (LDL) cholesterol, the “bad” cholesterol, are associated with an increased risk of heart attacks and strokes. By contrast, increased levels of high-density lipoprotein (HDL) cholesterol, the “good” cholesterol, offer protection against heart attacks and strokes. (See the Cardiology Patient Page on HDL at <http://circ.ahajournals.org/cgi/reprint/111/5/e89.2>) The total cholesterol value you receive after a blood test is the sum of *all* types of cholesterol, as discussed in a previous Cardiology Patient Page (<http://circ.ahajournals.org/cgi/content/full/110/11/e296>).<sup>3</sup> Triglycerides are another form of circulating fatty substance that, when elevated, are also associated with heart attacks and strokes.

### What Problems Can Cholesterol Cause?

The body requires *some* cholesterol to function, but increased levels of cho-

lesterol can lead to cholesterol deposits within the walls of the arteries that eventually form “atherosclerotic plaques.” These plaques grow over time and can break open into the artery and trigger the formation of a blood clot. The sudden blockage of an artery by the blood clot prevents oxygen from arriving at the heart muscle or brain, causing heart attacks or strokes, respectively.

### How Do Cholesterol Levels Predict Risk?

Many studies have shown that people with elevated total cholesterol are at an increased risk for future heart attacks and death. Although in the past the emphasis had been on total cholesterol, because it was easy and less expensive to measure, national guidelines now recommend that, in addition to total cholesterol, everyone should know their LDL and HDL levels because they offer a more specific estimate of the risk of developing arterial blockages.<sup>4</sup> People with elevated levels of LDL, which accounts for the majority of the total cholesterol measurement, are more likely to suffer heart attacks or die prematurely. For every 10-milligram (mg) increase in LDL per deciliter (dL) of blood, the risk of a

The information contained in this *Circulation* Cardiology Patient Page is not a substitute for medical advice or treatment, and the American Heart Association recommends consultation with your doctor or healthcare professional.

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TABLE 1. Cholesterol-Lowering Medications

| Generic Name                             | Trade Name                            | Dose Range                              | Usual Dose Required to Lower LDL 30% to 40% | Percentage Decrease in LDL With Maximum Dose |
|--|---------------------------------------|---|---|--|
| <b>Statins</b>                           |                                       |   |   |  |
| Atorvastatin                             | Lipitor                               | 10 to 80 mg                             | 10 mg                                       | 50%  |
| Fluvastatin                              | Lescol                                | 20 to 80 mg                             | 40 to 80 mg                                 | 35%  |
| Lovastatin                               | Mevacor                               | 20 to 80 mg                             | 40 mg                                       | 40%  |
| Pravastatin                              | Pravachol                             | 10 to 40 mg                             | 40 mg                                       | 34%  |
| Rosuvastatin                             | Crestor                               | 10 to 40 mg                             | 5 to 10 mg                                  | 55%  |
| Simvastatin                              | Zocor                                 | 10 to 80 mg                             | 20 to 40 mg                                 | 47%  |
| <b>Cholesterol-absorption inhibitors</b> |                                       |   |   |  |
| Ezetimibe                                | Zetia                                 | 10 mg                                   |   | 18%  |
| Ezetimibe/simvastatin                    | Vytorin                               | 10 mg ezetimibe/10 to 80 mg simvastatin | 10 mg/10 mg                                 | 60%  |
| <b>Niacin*</b>                           |                                       |   |   |  |
| Nicotinic acid                           | Niaspan                               | 1 to 3 g                                |   | 17%  |
| <b>Fibrates</b>                          |                                       |   |   |  |
| Fenofibrate                              | Tricor                                | 67 to 200 mg                            |   | 20%  |
| Gemfibrozil                              | Lopid                                 | 600 to 1200 mg                          |   | 20%  |
| Diet                                     | Atkins, Zone, Weight Watchers, Ornish |   |   | 7% to 12%                                    |

\*Dietary-supplement niacin must not be used as a substitute for prescription niacin, and over-the-counter niacin should be used only if approved and monitored by a physician.

Data adapted from *Physician's Desk Reference*, 2004, and *JAMA*. 2005;293:43.

heart attack increases by almost 20%. Conversely, people with higher levels of the “good” HDL cholesterol have a lower risk of cardiac events. In addition, treatments for high LDL or low HDL are different, and thus, to choose the right treatment, both are measured. You can estimate your cardiovascular risk over the next 10 years by using a risk score developed by the Framingham Heart Study that incorporates age, sex, cholesterol, and blood pressure (<http://hin.nhlbi.nih.gov/atpiiii/calculator.asp?usertype=prof>).

### Lifestyle Changes to Lower Cholesterol

You can reduce your cholesterol through changes in your diet and exercise. Cholesterol intake should be less than 200 mg per day, and total fat intake should account for no more than 20% to 25% of all calories. In addition, saturated fats and *trans-fatty acids* (a manufactured-type of saturated fat found in hard margarine, shortening, and many cooking oils) should be min-

imized or eliminated from your diet. Weight loss, exercise, and sustained changes in your diet will improve cholesterol levels, in particular, by increasing the HDL and reducing triglycerides. With an optimal diet and exercise regimen, you can lower your total and LDL cholesterol by 10% to 15%. The American Heart Association web page offers many suggestions on diet and exercise to lower cholesterol levels at <http://www.americanheart.org/presenter.jhtml?identifier=1516>.

### Drug Treatment of Cholesterol

Despite lifestyle changes, the majority of people require drug therapy to adequately reduce their LDL cholesterol level. There are several different classes of medications that reduce cholesterol. *Statins* are the most common and powerful class of drugs. They reduce LDL cholesterol by blocking a key step in the process of manufacturing cholesterol in the liver. The average starting dose of all statins will reduce LDL by approximately 25% to

40% and raise HDL by 5% to 10%. Higher doses of some stronger statins can reduce LDL by 50% to 60%. In addition to their effects on cholesterol, statins have other beneficial effects. The most important may be their ability to reduce inflammation, and in particular, C-reactive protein (CRP), which is elevated in people who are at higher risk of having heart attacks.<sup>5</sup>

Statins should be the first drug used in most people to control cholesterol. Your doctor may use other drugs that lower cholesterol by different means if a statin does not sufficiently lower your cholesterol or if you do not tolerate the statin because of side effects. These other drugs include *ezetimibe*, which blocks cholesterol absorption in the intestines and lowers LDL; *nicotinic acid (niacin)*, which lowers LDL and raises HDL; and *fibrates*, which help the body lower triglycerides and raise HDL. All these drugs may be used alone or in combination to achieve the goal level of cholesterol (Table 1).

**TABLE 2. Overview of Current Recommendations From the National Cholesterol Education Program**

| Risk Category  | LDL Goal                      | Initiate Lifestyle Changes When LDL Is | Consider Drug Therapy When LDL Is                             |
|--|-------------------------------|--|---|
| Very high risk: ACS, or CHD with DM, multiple CRF  | Less than 70 mg/dL (optional) | 70 mg/dL or more (optional)            | 70 mg/dL or more (optional)                                   |
| High risk: CHD or CHD risk equivalents (10-year risk greater than 20%) if LDL is less than 100 mg/dL | Less than 100 mg/dL           | 100 mg/dL or more                      | 100 mg/dL or more   |
| Moderately high risk: at least 2 risk factors (10-year risk 10% to 20%)                              | Less than 100 mg/dL           | 130 mg/dL or more                      | 130 mg/dL or more (100 to 129 mg/dL: consider drug treatment) |
| Moderate risk: at least 2 risk factors (10-year risk less than 10%)                                  | Less than 130 mg/dL           | 130 mg/dL or more                      | 160 mg/dL or more   |
| Lower risk: 0 to 1 risk factor   | Less than 160 mg/dL           | 160 mg/dL or more                      | 190 mg/dL or more   |

Definitions: ACS indicates acute coronary syndrome (heart attack or acute cardiac chest pain); CHD, coronary heart disease; and DM, diabetes mellitus. CRF indicates cardiac risk factors: smoking, high blood pressure (blood pressure more than 140/90 or patient is taking medications), low HDL cholesterol (less than 40 mg/dL), family history of early heart disease, and age (men older than 45 years; women older than 55 years). CHD risk equivalents are peripheral vascular disease, abdominal aortic aneurysm, and carotid artery disease, diabetes, or at least 2 cardiac risk factors.

Adapted with permission from *Circulation*. 2004;110:227.

### Clinical Trial Evidence

Many clinical trials have compared statin therapy with placebo (“inactive pills”) in patients with known heart disease as well as in persons without heart disease but at risk of future heart disease. A consistent message from all the trials was that persons treated with statins have a 30% to 40% reduction in the chance of having a heart attack or of dying from heart disease as compared with those persons taking the placebo. These studies have also seen a reduction by 30% in the risk of stroke and in the need for angioplasty and coronary bypass surgery. Two recent studies also found that for patients who had just suffered a heart attack or who had heart disease, higher doses of statins lowered LDL cholesterol by 50% and were even more effective than standard doses of statins in preventing death, recurrent heart attacks, or severe chest pain.<sup>6,7</sup>

### How Low Should My Cholesterol Be?

Persons should focus on achieving their goal LDL level. Each person will have a different LDL goal, depending on his or her individual risk of heart disease, as determined, for example, by the Framingham Risk Score. National guidelines strongly recommend that persons with a history of heart disease, documented atherosclerosis, or risk factors such as diabetes, which greatly increase the chance of heart

disease, should aim for an LDL level less than 100 mg/dL.<sup>4,8</sup> In addition, the latest guidelines recommend an optional goal of an LDL level of less than 70 mg/dL in those persons at very high risk, which is defined as patients with known heart disease and multiple risk factors (especially diabetes), multiple or poorly controlled risk factors (for example, continued cigarette smoking), or a recent heart attack or acute cardiac chest pain.<sup>4,6–8</sup>

Persons without heart disease who have other risk factors for developing heart disease (for example, diabetes mellitus, hypertension, a family history of heart disease, or smoking) should aim for LDL levels less than 130 mg/dL and, ideally, less than 100 mg/dL. Table 2 presents the latest national guidelines for cholesterol levels. A small percentage of persons have greatly elevated levels of triglycerides or extremely low HDL that requires more individualized treatment. You and your doctor should discuss your individual treatment goals.

### Side Effects

Cholesterol-lowering drugs have been used in hundreds of millions of persons over the past 15 years and are generally very safe medications. One to two months after starting or changing the dose of a statin, your doctor will order blood tests to make sure there is no irritation of the liver and muscles caused by the medication. In

3% to 4% of people, liver and muscle enzyme tests are elevated, the statin dose will either be reduced or stopped, and a different statin may be tried. Rarely, statins or fibrates can cause muscle aches or more severe muscle damage. If you are taking one of these medications and feel muscle aches, contact your physician. In general, higher doses of the statins are more likely to cause side effects, but even in the highest doses, the chance of the most severe muscle inflammation is less than 1 in 20,000. Treatment with nicotinic acid can cause flushing and a warm sensation, but this can be reduced with newer formulations and can be minimized by taking an aspirin 30 minutes before the nicotinic acid. Ezetimibe does not appear to be absorbed into the body and has few side effects.

### New Frontiers

Future research is likely to define further the optimal cholesterol levels for all persons. In addition, there are several promising drugs under investigation that specifically raise the beneficial HDL and may offer further benefit even when LDL has been controlled.

### Glossary of Terms in Cholesterol Treatment

- **Cholesterol:** A fatty substance that circulates in the blood and is an important structural component of

all human cells. The total cholesterol level is the sum of all types of cholesterol (that is, LDL, HDL, triglycerides).

- **LDL:** Low-density lipoprotein (LDL) cholesterol, or the “bad” cholesterol. Elevated levels are associated with an increased risk of heart attacks and strokes.
- **HDL:** High-density lipoprotein (HDL) cholesterol, or the “good” cholesterol. Higher levels appear to offer protection against heart attacks and strokes.
- **Statins:** Statins are the most common and powerful class of drug. They reduce cholesterol by blocking a key step in the liver where cholesterol is made.
- **C-reactive protein (CRP):** CRP is produced by the liver and elevated with inflammation. Small elevations in CRP are associated with increased risk of heart attacks and death. Treatment with statins reduces CRP levels.

### Web Resources

- American Heart Association web site on cholesterol presents informa-

tion on the importance of testing cholesterol, dietary and life-style changes (including recipes), and treatment options for treating elevated cholesterol. Available at: <http://www.americanheart.org/presenter.jhtml?identifier=1516>.

- American Heart Association Heart Profile web page offers free, confidential, and personalized treatment options for elevated cholesterol. Available at: <http://www.americanheart.org/presenter.jhtml?identifier=3000416>.
- Framingham Heart Study Risk Calculator estimates a person’s risk of a heart attack or cardiac death over the next 10 years, incorporating a person’s age, sex, blood pressure, cholesterol, and smoking. Available at: <http://hin.nhlbi.nih.gov/atpiii/calculator.asp?usertype=prof>.

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