Treatment of Cholesterol Abnormalities

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Cardiovascular disease and its subset coronary heart disease are leading causes of morbidity and mortality in the United States and worldwide. In general, higher levels of low-density lipoprotein cholesterol are associated with an increased risk of coronary heart disease, myocardial infarction, and stroke. Reducing dietary fat can improve total cholesterol levels, but consequent reductions in cardiovascular outcomes are not well documented. The Mediterranean diet is the only dietary intervention associated with a reduction in all-cause mortality. Treatment with cholesterol-lowering medications decreases the rate of cardiovascular events, but a reduction in all-cause mortality with these agents has been found only in patients with pre-existing coronary heart disease. Drug treatment in patients with a history of heart disease and average-to-high cholesterol levels can decrease the risk for stroke. In patients with peripheral vascular disease, treatment of elevated cholesterol levels may slow disease progression. (Am Fam Physician 2005;71:1137-42, 1147-8. Copyright© 2005 American Academy of Family Physicians.)

▶ **Patient information:** A handout on cholesterol, written by the authors of this article, is provided on page 1147.

EB CME

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See page 1046 for strength-of-recommendation labels.

Coronary heart disease (CHD) is the single leading cause of death in the United States, accounting for more than one in five deaths each year, or approximately 500,000 fatalities. An estimated $130 billion was spent in 2003 to care for patients with CHD, and an estimated $7.2 billion of this cost was spent on drug therapy.[1]

The 2001 report of the National Cholesterol Education Program (NCEP)[2] expert panel estimates that therapeutic lifestyle changes should be recommended for 65 million U.S. adults and that 36 million of those persons also need drug therapy for treatment of elevated cholesterol levels. The relationship between CHD and elevated cholesterol levels has been recognized for many years, but only since the mid-1990s have studies shown an improvement in patient-oriented outcomes in patients receiving drug therapy (e.g., myocardial infarction [MI] or mortality, rather than just changes in cholesterol levels).

Current expert-based guidelines have attempted to translate these findings to specific targets for patient cholesterol levels.[2] A patient's baseline risk for CHD is an important determinant of the degree of benefit; treatment clearly has a greater impact in patients with a greater risk. Applying the evidence to lower risk populations is difficult because many more patients need to be treated to achieve benefit. Most of the demonstrated benefit in lower risk populations relates only to disease-specific outcomes (i.e., no improvement in all-cause mortality). A 2001 study[3] reviewing the four largest primary-prevention trials at the time found that up to 40 percent of men and 80 percent of women would not have met eligibility criteria. For example, persons with low total cholesterol levels but low high-density lipoprotein (HDL) cholesterol levels, or those with average total cholesterol levels and average-to-high levels of HDL cholesterol had not been studied.

Primary Prevention of Cardiovascular Disease

To address the efficacy of lifestyle interventions recommended by the NCEP and American Heart Association, a systematic review[4] of 18 trials with a total of 140,000 patients found modest reductions in blood cholesterol levels and smoking prevalence but no change in all-cause or cardiovascular mortality in patients who received counseling interventions targeting dietary habits, smoking, and physical activity. Another systematic review[5] of 27 randomized controlled trials (RCTs) looked at reducing the intake of overall fat and saturated fats during 30,000 person-years. It found a small reduction in cardiovascular events. The benefit was noted in higher risk patients who maintained their lifestyle changes for at least two years.

Strength of Recommendations

Key clinical recommendation	*Label*	*References*
Primary prevention of cardiovascular disease		
Patients with elevated cholesterol levels should reduce dietary fat consumption. However, this step may lead to only a small reduction in cardiovascular events.	A	4, 5
Statin medications are indicated to decrease cardiovascular events in patients with elevated cholesterol levels, although a decrease in cardiovascular and all-cause mortality has not been demonstrated.	A	8 to 13, 15
Following a Mediterranean diet may reduce all-cause mortality.	B	7
Secondary prevention of cardiovascular disease		
Statin medications should be used for aggressive lipid control in patients with CHD to decrease cardiovascular events, cardiovascular mortality, and overall mortality.	A	26 to 30
Cholesterol-lowering medications prevent disease progression and improve symptoms in patients with lower limb atherosclerosis. Statins can decrease cardiovascular events and all-cause mortality in these patients.	A	31, 50
Cholesterol-lowering medications should be used to reduce the risk of stroke in patients with a history of CHD and average-to-high cholesterol levels.	A	35, 45, 46, 47

CHD = coronary heart disease.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, opinion, or case series. *See page 1046 for more information.*

Dietary advice leads to an average 3 to 6 percent decrease in total cholesterol levels.[6] A recent large prospective study[7] in Greece found an association between adherence to a Mediterranean diet and lower all-cause mortality. This benefit was greater in older, heavier, sedentary nonsmokers.

CHOLESTEROL-LOWERING DRUGS

The use of cholesterol-lowering drugs for primary prevention of heart disease initially was a matter of controversy. The first study to show clear improvement in patient-oriented outcomes in a primary-prevention population using cholesterol-lowering medications found a decreased incidence of nonfatal MI and CHD deaths in patients with elevated cholesterol levels who were treated with pravastatin.[8] More recently, large systematic reviews reached similar conclusions about the use of cholesterol-lowering medications for the primary prevention of CHD. A review[9] of 23 trials in which patients were treated with statin drugs found a significant reduction in nonfatal MI, but the primary-prevention trials were underpowered to detect effects on mortality. A meta-analysis[10] of four primary-prevention studies with 10,000 patients who had elevated cholesterol levels found a lower incidence of cardiovascular events and reduced cholesterol levels (8 percent with cholestyramine, 10 percent with gemfibrozil, and 20 percent with statins), but no reduction in overall or cardiovascular mortality. This means that 60 patients need five years of treatment to prevent one coronary artery disease (CAD) event.

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Similarly, lovastatin reduces the risk for first coronary events but not all-cause mortality when used for primary prevention in patients with low HDL cholesterol levels but average total cholesterol levels (number needed to treat [NNT], 24).[11] Interestingly, smokers taking lovastatin had outcomes similar to outcomes in nonsmokers taking placebo, which strongly suggests the relative cost effectiveness of smoking cessation. A recent study[12] of simvastatin in more than 20,000 compliant, high-risk, primary-prevention patients found a decreased risk of major coronary events, revascularizations, and stroke (risk decreased from 25 to 20 percent; NNT, 21).

Finally, the Anglo-Scandinavian Cardiac Outcomes Trial[13] found reductions in major cardiovascular events in a high-risk (average 3.7 risk factors) primary-prevention population treated with atorvastatin. Similarly, low-dosage atorvastatin delays the development of

cardiovascular events in diabetic patients who are treated with a 10-mg dose.[14] These studies also suggest that the benefit of drug interventions increases with increasing baseline risk. This suggestion is reflected in the *British Medical Journal (BMJ) Clinical Evidence* group's conclusion that for primary prevention of coronary events, "reducing cholesterol concentration in asymptomatic people lowers the rate of cardiovascular events,"[15] but not cardiovascular or overall mortality.

One approach to further risk stratification of patients for primary prevention may include assessment of the C-reactive protein (CRP) level, which appears to be an independent predictor of cardiovascular risk.[16] However, only preliminary evidence shows that healthy patients with high CRP levels and low or normal cholesterol levels could benefit from drug treatment.

Ezetimibe, an agent introduced in 2002, blocks the absorption of cholesterol from the intestine. A recent RCT[17] found that therapy with 10 mg of ezetimibe plus 10 mg of atorvastatin had effects on lipid levels similar to the effects of therapy with 80 mg of atorvastatin alone. However, no outcome data are available for CAD events, cardiovascular mortality, or total mortality.

SAFETY OF CHOLESTEROL-LOWERING DRUGS

Because cholesterol-lowering drugs have been shown to affect cardiovascular mortality more than total mortality, concern has arisen that these agents might increase mortality from other causes. A meta-analysis[18] of 19 RCTs found no increase in noncardiovascular disease mortality in patients taking cholesterol-lowering drugs. This finding was most convincing in patients taking statins; there was a trend toward increased deaths and violence in the dietary and non-statin–drug groups.

HERBAL SUPPLEMENTS FOR CHD PREVENTION

Garlic consumption appears to result in moderate decreases in cholesterol levels,[19] and weaker evidence indicates that the same may be true for red yeast rice, soy,[20] artichoke,[21] fenugreek, and guggul,[22] although a recent study[23] found that guggulipid was not effective and had significant side effects. A small crossover RCT[24] found that healthy hyperlipidemic patients on a low-fat diet reduced cholesterol levels by an additional 4 to 5 percent with a diet high in soluble fiber (e.g., barley, beans, oat bran, psyllium). A meta-analysis[25] of 67 RCTs estimated that 3 g of soluble fiber from oats can decrease total and low-density lipoprotein (LDL) cholesterol by 5 mg per dL (0.15 mmol per L). Unfortunately, none of the studies evaluating dietary and herbal interventions looked at patient-oriented outcomes.

Secondary Prevention of Cardiovascular Disease

The 1994 Scandinavian Simvastatin Survival Study[26] found lower mortality rates (absolute risk decreased from 11.5 to 8.2 percent; NNT, 30) and fewer coronary events (NNT, 15) in patients with angina or acute MI who were treated with simvastatin to a total cholesterol target of less than 200 mg per dL (5.20 mmol per L). Subsequent RCTs and systematic reviews have strongly confirmed the benefits of cholesterol treatment in this population. A systematic review[27] of seven RCTs of high-risk diabetic patients found that medications to lower cholesterol in patients with a history of cardiovascular disease substantially reduced cardiovascular disease. The *BMJ Clinical Evidence* group concludes that for secondary prevention, "lowering cholesterol … substantially reduces overall mortality, cardiovascular mortality, and nonfatal cardiovascular events."[15] Of current drug treatments, statins appear to have the greatest effect on outcomes. A large systematic review[28] that included 66 RCTs found that statins decreased overall mortality and CAD mortality. Bile-acid resins had a borderline effect on CAD mortality, but the use of resins and other medications (i.e., resins, niacin, fibrates, and hormones combined) showed a trend toward higher all-cause mortality. The Women's Health Initiative found an increase in adverse cardiovascular outcomes in women taking hormone therapy. Niacin fell short of statistical significance for improving cardiovascular outcomes in a 1996 review[29] of 23 secondary-prevention trials. In

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another study,[30] gemfibrozil reduced the risk of cardiovascular events in men with CAD, normal LDL levels, and low HDL levels, but this study did not address overall mortality.

A recent large RCT[31] involving 20,000 high-risk patients found reductions in all-cause mortality, vascular mortality, major CAD events, and stroke in patients who took simvastatin. In an RCT[32] of 9,000 patients, pravastatin reduced all-cause mortality (11.0 versus 14.1 percent; NNT, 34 for six years) and cardiovascular mortality. Elderly patients may derive more benefit from pravastatin treatment than younger patients.[33,34] In the large Cholesterol and Recurrent Events (CARE) RCT,[35] the benefits of secondary prevention extended to patients with average cholesterol levels, although all-cause mortality was not studied.

Lovastatin decreased rates of major cardiovascular events and overall mortality rates in high-risk patients with asymptomatic carotid stenosis.[36] Rosuvastatin has a greater effect on lipid profiles than other available statins, but there currently are no outcome studies. Atorvastatin also has a marked effect on lipid profiles.[37] It has not yet been proved to decrease mortality in an ambulatory population but is at least as effective as percutaneous transluminal coronary angioplasty in reducing the rate of ischemic events in patients with stable CAD.[38] High-dosage atorvastatin[39] and high-dosage simvastatin[40] also reduce recurrent ischemic events in hospitalized patients with acute coronary syndrome, and atorvastatin decreases coronary atheroma burden in CAD patients as measured by intravascular ultrasonography. Intensive lipid-lowering therapy has not been shown to decrease cardiovascular events or mortality in patients without acute coronary syndrome, and current guidelines should continue to be used as treatment goals until larger ongoing trials are completed.[41,42]

The difficulty of generalizing results of statin studies to a class effect is illustrated by the recent withdrawal of cerivastatin, but not other statins, from the market because of adverse effects. In addition, a review[43] of the pharmacology of the various agents concluded that there may be important clinical differences between individual statins, including "subtle differences in nonlipid effects" that may lead to clinically important differences in efficacy as well as safety.

Overall, statins seem to have the greatest effect of all cholesterol-lowering medications on the reduction of cardiovascular and all-cause mortality.[28] However, their high cost per life-year gained (estimated at $2,500 to $6,000) places them behind aspirin ($25), advice for smoking cessation, diuretics in elderly patients with hypertension ($20), beta blockers following MI ($150), and the Mediterranean diet following MI ($150) in cost effectiveness.[9] As with primary prevention, cost effectiveness is better in groups with higher baseline risk.[44]

Prevention and Treatment of Stroke

Cholesterol-lowering medications reduce the risk of stroke in patients with CHD and average or high cholesterol levels, but not in patients with previous stroke or transient ischemic attack (TIA). The 2001 Veterans Affairs HDL Intervention Trial[45] found that men with documented CHD and low HDL levels lowered their risk of stroke by taking gemfibrozil. The 1999 CARE trial[35] found that pravastatin decreased the risk of stroke in 65- to 75-year-old patients with a history of MI and average cholesterol levels.

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A meta-analysis[46] of a mixed primary- and secondary-prevention population of 29,000 patients found an absolute risk reduction for stroke of 0.5 percent in patients treated with statins. A 1999 review[47] of 13 RCTs of almost 20,000 statin-treated patients with LDL levels greater than 155 mg per dL (4.00 mmol per L) found a decreased incidence of stroke in patients with documented CHD or at least two additional risk factors (NNT, 143 to prevent one stroke in four years), but stroke incidence was unchanged in the primary-prevention studies.

Simvastatin reduced the rate of stroke in compliant patients at high risk for CHD or with known CHD (NNT, 72 for 4.3 years), but not in patients with known cerebrovascular disease.[48] A Cochrane review[49] of five studies with 1,700 patients showed no evidence of benefit or harm in patients with a history of stroke or TIA but no history of CHD.

Treatment of Peripheral Vascular Disease

A recent Cochrane review[50] of seven trials involving 698 men and women showed that lipid-lowering therapy with a variety of drugs reduced disease progression as measured by angiography and somewhat improved claudication symptoms. When peripheral vascular disease is used as a marker for high risk of cardiovascular events, treatment of these patients with simvastatin results in lower mortality, fewer major coronary events, lower stroke rates, and revascularizations without increasing nonvascular mortality.[31]

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