

Pharmacologic Treatment of Hyperlipidemia

ALLEN R. LAST, MD, MPH, *University of Wisconsin Fox Valley Family Medicine Residency Program, Appleton, Wisconsin*
JONATHAN D. FERENICE, PharmD, *Wilkes University Nesbitt College of Pharmacy and Nursing, Wilkes-Barre, Pennsylvania*
JULIANNE FALLERONI, DO, MPH, *University of Wisconsin Fox Valley Family Medicine Residency Program, Appleton, Wisconsin*

Pharmacologic treatment of hyperlipidemia in conjunction with therapeutic lifestyle changes can be used for both primary and secondary prevention of cardiovascular disease. Statins have the most convincing data for primary prevention, especially for higher risk patients. Therefore, risk stratification is essential. Statin therapy is also recommended for secondary prevention in all patients with known cardiovascular disease or the risk equivalent. High-dose statins should be initiated in patients with acute coronary syndrome. Omega-3 fatty acids may be a good alternative after myocardial infarction for patients who cannot tolerate statins. Fibrates and niacin have not been shown to reduce all-cause mortality in secondary prevention, but may be useful adjuncts when statins alone cannot adequately control lipid levels. Other cholesterol-lowering medications used for primary or secondary prevention of cardiovascular disease have not been shown to consistently improve patient-oriented outcomes. There is good evidence for using statins in the secondary prevention of stroke and peripheral arterial disease. (*Am Fam Physician*. 2011;84(5):551-558. Copyright © 2011 American Academy of Family Physicians.)

► **Patient information:** A handout on cholesterol-lowering medications, written by the authors of this article, is provided on page 561.

Cardiovascular disease (CVD) is the leading cause of mortality in the United States, accounting for 33.6 percent of all deaths in 2007.¹ Hyperlipidemia is a common risk factor for CVD, with 53.4 percent of adults in the United States having abnormal cholesterol values and 32 percent having elevated low-density lipoprotein (LDL) cholesterol levels.¹

National Practice Guidelines

U.S., U.K., and Canadian guidelines are available to help physicians manage hyperlipidemia (*Table 1*).²⁻⁴ These guidelines agree that therapeutic lifestyle changes are the mainstay of hyperlipidemia management, and that LDL cholesterol should be the primary target of therapy. Treatment of hyperlipidemia improves outcomes for patients with known coronary heart disease (CHD) or the risk equivalent, and for high-risk patients (i.e., those with a 10-year CHD risk of greater than 20 percent) without known CHD or the risk equivalent.

The U.S. National Cholesterol Education Program, Adult Treatment Panel (ATP) III guidelines advocate for a treat-to-target approach and are more aggressive than other guidelines.² The U.K. National Institute for Health and Clinical Excellence

(NICE) guidelines recommend offering a fixed-dose statin based on CHD risk stratification, and recommend against checking cholesterol levels after a patient starts statin therapy.³ For secondary prevention, NICE recommends a treat-to-target therapy that is less aggressive than that recommended by the ATP III. The ATP III recommendations are based on the assumption that achieving the mean LDL cholesterol level observed in clinical trials will produce similar results in practice, but no clinical trial has assessed a treat-to-target strategy.

In theory, when comparing the treat-to-target and fixed-dose approaches, essentially the same number of patients would be treated with statin therapy.⁵ A theoretical modeling study comparing approaches for primary CHD risk reduction suggests that a fixed-dose approach based on individual risk would prevent more events and save more quality-adjusted life-years.⁵ Although neither approach is clearly superior at this time, it is reasonable for physicians to engage patients in a shared, informed decision-making process and to determine treatment goals based on the patient's overall CHD risk, risk reduction that could be expected with treatment, and values and preferences.

Table 1. Summary of Major Hyperlipidemia Guidelines

<i>Risk category</i>	<i>LDL cholesterol goal</i>	<i>Drug therapy recommendations</i>
National Cholesterol Education Program, Adult Treatment Panel III*		
High risk CHD or risk equivalent† 10-year CHD risk > 20 percent	< 100 mg per dL (2.59 mmol per L) Optional goal of < 70 mg per dL (1.81 mmol per L) is favored in patients at very high risk (CHD plus multiple major or poorly controlled risk factors)	Initiate if LDL cholesterol is ≥ 100 mg per dL Consider if level is < 100 mg per dL‡
Moderately high risk ≥ two risk factors§ 10-year CHD risk of 10 to 20 percent	< 130 mg per dL (3.37 mmol per L) Optional goal < 100 mg per dL	Initiate if LDL cholesterol is ≥ 130 mg per dL Consider if level is 100 to 129 mg per dL (2.59 to 3.34 mmol per L)
Moderate risk ≥ two risk factors§ 10-year CHD risk < 10 percent	< 130 mg per dL	Consider if LDL cholesterol is ≥ 160 mg per dL (4.14 mmol per L)
Low risk One or no risk factors§	< 160 mg per dL	Consider if LDL cholesterol is ≥ 190 mg per dL (4.92 mmol per L)
National Institute for Health and Clinical Excellence		
Primary prevention	No target level for total or LDL cholesterol	Initiate simvastatin (Zocor), 40 mg daily, if CHD risk is ≥ 20 percent (routine measurement of lipid levels is not necessary)
Secondary prevention	< 78 mg per dL (2.02 mmol per L)	Initiate simvastatin, 40 mg daily, as soon as possible Consider increasing dosage to 80 mg daily if LDL cholesterol goal is not achieved Consider a higher-intensity statin in patients with acute coronary syndrome
Canadian Cardiovascular Society		
High risk CHD, peripheral vascular disease, atherosclerosis (i.e., any vascular bed, including carotid arteries) Usually diabetes mellitus Framingham or Reynolds risk score ≥ 20 percent	< 78 mg per dL or 50 percent LDL cholesterol reduction (alternate apolipoprotein B level < 80 mg per dL [0.80 g per L])	Offer treatment to all patients
Moderate risk Framingham risk score 10 to 19 percent	< 78 mg per dL or 50 percent LDL cholesterol reduction (alternate apolipoprotein B level < 80 mg per dL)	Consider for patients with any of the following factors: LDL cholesterol > 136 mg per dL (3.52 mmol per L) Total/HDL cholesterol > 193 mg per dL (5 mmol per L) High-sensitivity CRP > 2 mg per L (19.05 nmol per L) Men older than 50 years Women older than 60 years Family history and high-sensitivity CRP increases risk (Reynolds risk score)
Low risk Framingham risk score < 10 percent	≥ 50 percent reduction in LDL cholesterol	Consider if LDL cholesterol is ≥ 193 mg per dL (5 mmol per L)

CHD = coronary heart disease; CRP = C-reactive protein; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

*—Intensity of drug therapy should be sufficient to achieve at least a 30 to 40 percent reduction in LDL cholesterol.

†—CHD = history of myocardial infarction, unstable angina, stable angina, coronary artery procedures, or evidence of clinically significant myocardial ischemia; risk equivalent = peripheral arterial disease, abdominal aortic aneurysm, carotid artery disease, diabetes, two or more risk factors with 10-year CHD risk > 20 percent.

‡—Initiation of drug therapy is an option on the basis of available clinical trial results.

§—Cigarette smoking; hypertension (systolic blood pressure ≥ 140 mm Hg or on antihypertensive therapy); low HDL cholesterol (< 40 mg per dL [1.04 mmol per L]); family history of premature CHD (male first-degree relative younger than 55 years, female first-degree relative younger than 65 years); age 45 years or older in men, age 55 years or older in women.

||—Initiation of drug therapy to achieve an LDL cholesterol level < 100 mg per dL is an option on the basis of available clinical trial results.

Information from references 2 through 4.

Primary Prevention

Primary prevention of CVD consists of treating patients with hyperlipidemia before clinical CHD manifests (e.g., myocardial infarction). The evidence supporting treatment of hyperlipidemia for primary prevention is inconsistent. Patients with the highest baseline risk are most likely to benefit. Medications should be chosen based on a favorable balance between the likelihood of benefits (e.g., patient-oriented outcomes, mortality, CVD events, functional status, quality of life) and harm (adverse effects), as well as cost.⁶ *Table 2* summarizes medications used to treat lipid disorders.⁷⁻²⁰

STATINS

Two large meta-analyses have evaluated statins for primary prevention of CVD.^{16,21} The first analysis pooled 10 trials and found that statins were superior to placebo for all-cause mortality (number needed to treat [NNT] = 172), major coronary events (NNT = 81), and major cerebrovascular events (NNT = 244).¹⁶ However, the second meta-analysis was conducted because the first did not exclusively evaluate primary prevention, including trials with up to 20 percent of patients with CHD or the equivalent. The second analysis, which excluded such groups and included newer studies, showed no difference between statins and placebo for all-cause mortality.²¹

Studies have evaluated statin therapy based on C-reactive protein level. The JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) study included participants with LDL cholesterol levels of less than 130 mg per dL (3.37 mmol per L) and elevated high-sensitivity C-reactive protein levels who received rosuvastatin (Crestor) or placebo for two years.²² Compared with placebo, statin therapy reduced the risk of the primary composite end point (myocardial infarction, stroke, hospitalization for unstable angina, arterial revascularization, and cardiovascular death; NNT = 84). However, the benefit of statin therapy on individual outcomes varied widely, with NNT ranging from 150 for arterial revascularization to 244 for myocardial infarction.

Critics argue against using the JUPITER study results to justify broadly expanding statin use in primary prevention.²³⁻²⁵ The study ended early and excluded non-adherent patients, which could exaggerate the positive effects of treatment without allowing sufficient time for adverse effects to develop.^{23,24} Furthermore, if “hard cardiac” clinical outcomes are taken out, the study included only 240 events.²³ The JUPITER study also failed to compare rosuvastatin with other interventions, such as lifestyle changes, aspirin, or less-expensive statins, and did not evaluate cost-effectiveness. Several authors had

financial ties to the sponsor, and one held the patent to the high-sensitivity C-reactive protein assay used to determine study eligibility.

Treatment with statins as primary prevention should be offered to those at the highest risk of developing CHD based on validated prediction models, such as the Reynolds risk score (<http://www.reynoldsriskscore.org/>) or the Framingham risk assessment tool (<http://hp2010.nhlbihin.net/atpiii/calculator.asp>). No statin has been proven superior at preventing CHD and, at equivalent doses, all statins substantially reduce LDL cholesterol.²⁶

NONSTATINS

Some patients will have low levels of high-density lipoprotein (HDL) cholesterol or high levels of triglycerides even after meeting their LDL cholesterol target. Evidence for treating these secondary lipid abnormalities with medications other than statins for primary prevention is not convincing.

For example, there is no evidence that fibrates have mortality benefit in primary prevention, and there is some evidence that they are harmful.¹¹ None of the four trials that have compared fibrates with placebo in patients without a history of CHD showed that fibrates reduce overall mortality.²⁷⁻³⁰ In three of the trials, fibrates reduced the risk of coronary events compared with placebo (NNT = 125 with clofibrate [not available in the United States]; NNT = 72 with gemfibrozil [Lopid]; NNT = 8 with bezafibrate [not available in the United States]).²⁷⁻²⁹ Clofibrate was associated with an increased risk of overall mortality (number needed to harm [NNH] = 9 for 13.2 years).²⁷ Combining fibrate with statin therapy does not appear to be beneficial.³¹

Niacin is the only drug consistently proven to raise HDL cholesterol levels³²⁻³⁴; however, there is no evidence that it reduces all-cause or cardiovascular mortality in primary prevention.⁷ In the JUPITER study, patients taking rosuvastatin had fewer CHD outcomes regardless of HDL cholesterol level.²² This implies that significantly lowering LDL cholesterol levels may be just as effective at protecting against CHD as artificially raising HDL cholesterol levels.²²

When used in primary prevention, bile acid-binding resins (e.g., cholestyramine [Questran], colestipol [Colestid], colesvelam [Welchol]) reduce LDL cholesterol levels, but do not affect mortality.⁷ There are no studies of resin therapy to reduce CHD risk in patients at low risk (less than 0.6 percent annual risk) or at high risk (1.5 percent or greater annual risk) of a primary event. The one study evaluating resins in patients with moderate risk (0.6 to 1.4 percent annual risk) did not show a clear mortality benefit.³⁵

Although omega-3 fatty acids were previously thought to reduce CHD risk, a 2004 systematic review concluded

Hyperlipidemia Medications

Table 2. Characteristics of Medications to Treat Lipid Disorders

Medication	Contraindications	Adverse effects	Effectiveness
Bile acid-binding resins ⁷	Contraindicated in complete biliary or bowel obstruction	Constipation, nausea, and bloating are common, leading to poor adherence in most patients May increase triglycerides; use with caution when triglyceride level is > 200 mg per dL (2.26 mmol per L)	Combined primary/secondary prevention: reduces relative risk of cardiovascular mortality by 30 percent Primarily reduces LDL cholesterol by 15 to 30 percent
Ezetimibe ⁸	No serious safety concerns with monotherapy Contraindicated in active liver disease when combined with a statin (e.g., Vytorin)	Well tolerated as monotherapy; side effect profile similar to placebo Arthralgias and myalgias more common when combined with a statin ^{9,10}	Lacks clinical outcome data (monotherapy or combined with a statin) Monotherapy reduces LDL cholesterol by 18 percent May increase likelihood of attaining LDL cholesterol goals when combined with a statin
Fibrates ^{7,11-13}	Contraindicated in severe hepatic or renal disease	Gastrointestinal upset, rash, and abdominal pain are common Decreased renal function and myopathies are rare Increases risk of gallstones by 1 to 2 percent	No effect on all-cause mortality Combined primary/secondary prevention: NNT = 46 to 125 to prevent one coronary event; NNT = 53 to 150 to prevent one nonfatal myocardial infarction
HMG-CoA reductase inhibitors (statins) ^{7,14-18}	Contraindicated in active liver disease and pregnancy	Generally better tolerated than other agents Myopathies occur in less than 1 percent of patients; increased incidence when used with fibrates Rhabdomyolysis occurs in less than 0.2 percent of patients Liver function test results greater than three times the upper limit of normal occur in less than 2 percent of patients	Primary prevention: NNT = 81 for four years to prevent one coronary event; NNT = 244 for four years to prevent one cerebrovascular event Secondary prevention: NNT = 50 for five years to prevent one death Acute coronary syndrome: NNT = 77 treated with high-dose statins for two years to prevent one death
Nicotinic acid (niacin) ^{7,19}	Contraindicated in severe peptic ulcer disease, chronic liver disease, and severe gout	Flushing is common; may be reduced with aspirin pretreatment May increase uric acid and glucose levels	Does not affect all-cause mortality When combined with statins, improves disease-oriented outcomes‡ Primarily increases HDL cholesterol by 15 to 35 percent
Omega-3 fatty acids ²⁰	Use with caution in patients with fish allergy	Dyspepsia, burping, and fishy taste most common	Secondary prevention: NNT = 57 for two years to prevent one death in patients with previous myocardial infarction; NNH = 159 for two years resulting in one sudden cardiac death in patients with angina

HDL = high-density lipoprotein; LDL = low-density lipoprotein; NNH = number needed to harm; NNT = number needed to treat; OTC = over-the-counter.

*—Monthly retail cost based on information from <http://www.drugstore.com> (accessed May 16, 2011). \$ = < \$25, \$\$ = \$25 to \$75, \$\$\$ = \$75 to \$125, \$\$\$\$ = > \$125.

†—Available at discounted prices (\$10 or less per prescription) at national retail chains.

‡—Changes in mean carotid intima-media thickness or proximal coronary artery stenosis.

Information from references 7 through 20.

Cost*	Administration
Generic Cholestyramine \$\$\$ Colestipol \$\$\$\$	Many drug interactions; separate from warfarin (Coumadin), digoxin, and amiodarone by at least two hours Must be mixed with water or orange juice and taken before meals
No generic available Brand Zetia \$\$\$\$ Vytorin (ezetimibe/simvastatin) \$\$\$\$	Taken once daily No known effect on absorption of other medications
Generic Gemfibrozil† Micronized fenofibrate \$\$\$ Brand Multiple prescription preparations (fenofibrate) \$\$\$	Gemfibrozil taken twice daily before meals Micronized fenofibrate tablets and capsules should be taken with food
Generic Lovastatin† Pravastatin† Simvastatin \$\$ Brand Atorvastatin (Lipitor) \$\$\$ Fluvastatin (Lescol) \$\$\$ Rosuvastatin (Crestor) \$\$\$\$	All statins are taken once daily Fluvastatin, lovastatin, pravastatin, and simvastatin should be taken in the evening
Generic Multiple OTC preparations (immediate or controlled release) \$ Brand Multiple prescription preparations (controlled release) \$\$\$\$	Taken twice daily with food OTC preparations may be less effective, but have fewer adverse effects
Generic Multiple OTC preparations \$ Brand Multiple prescription preparations \$\$\$\$	Four prescription capsules taken once or twice daily OTC preparations may require multiple capsules to achieve doses used in clinical trials

that it is unclear if dietary or supplemental omega-3 fatty acids reduce the risk of total mortality or cardiovascular events in persons at high risk of CVD or in the general population.³⁶ However, there is also no evidence to support advising patients to stop consuming rich sources of omega-3 fats.

Secondary Prevention

STATINS

Statins are indicated in virtually all patients with a history of CHD, reducing the risk of all-cause mortality (NNT = 50 for five years) and cardiovascular mortality.⁷ Most patients with a CHD risk equivalent also benefit from statin therapy. The ATP III guidelines recommend initiating statins in patients with a history of CHD, and adjusting the intensity of therapy to achieve at least a 30 to 40 percent reduction in LDL cholesterol or an absolute LDL cholesterol level below 70 mg per dL (1.81 mmol per L) or 100 mg per dL (2.59 mmol per L).² The Canadian guidelines recommend a similar treat-to-target approach.⁴ The NICE guidelines recommend simvastatin (Zocor), 40 mg, for all patients with clinical evidence of CHD and a higher-intensity statin for patients with acute coronary syndrome.³

Statins may benefit patients with CHD independent of baseline cholesterol levels or age.³⁷⁻⁴⁰ The effectiveness of statin therapy on reducing mortality, myocardial infarction, and stroke does not appear to differ among atorvastatin (Lipitor), pravastatin (Pravachol), and simvastatin.⁴¹ No study has directly compared equivalent dosages of two different statins for secondary prevention. The ideal starting dose in patients with CHD depends on the presence of acute coronary syndrome.

A meta-analysis including patients with recent acute coronary syndrome compared high-dose statin therapy (40 mg of simvastatin daily for one month followed by 80 mg daily, or 80 mg of atorvastatin daily) with moderate-dose therapy (placebo for four months followed by 20 mg of simvastatin daily, or 40 mg of pravastatin daily).¹⁷ High-dose statins reduced overall mortality (NNT = 77 for two years), primarily from a decrease in cardiovascular mortality (NNT = 112 for two years).

A second meta-analysis compared the effectiveness of high-dose statin therapy (80 mg of simvastatin daily) with lower-dose statin therapy (up to 20 mg of simvastatin daily) in patients with recent acute coronary syndrome or stable CHD.⁴² Higher-dose statin therapy reduced overall mortality (NNT = 91 for two years) in patients with acute coronary syndrome. High-dose statins did not reduce mortality in patients with stable CHD, but decreased adverse cardiovascular events by

SORT: KEY RECOMMENDATIONS FOR PRACTICE

<i>Clinical recommendation</i>	<i>Evidence rating</i>	<i>References</i>	<i>Comments</i>
Statin therapy should be used in the primary prevention of cardiovascular events in high-risk patients.	B	16	Inconsistent results in numerous studies and two large meta-analyses
Statin therapy should be initiated in patients with a history of cardiovascular disease or the risk equivalent.	A	7, 37-40	Consistent results in large-scale randomized controlled trial and systematic review
High-dose statin therapy should be initiated in patients with acute coronary syndrome.	A	17, 42	Consistent results in large-scale meta-analyses
Ezetimibe (Zetia), niacin, fibrates, and bile acid-binding resins lower cholesterol, but do not change patient-oriented outcomes.	A	7, 9, 11	Consistent results in meta-analyses and systematic review
Omega-3 fatty acids are a reasonable alternative in patients with coronary heart disease who cannot tolerate statins.	B	20, 43-45	Inconsistent results in studies and systematic review
Aggressively lowering lipid levels increases mortality in patients 80 years and older.	A	57	Consistent results in meta-analysis

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to <http://www.aafp.org/afpsort.xml>.

1.9 percent over 4.7 years (NNT = 53). Based on these findings, it is reasonable to initiate lower doses of statins in patients with stable CHD and reserve initial high-dose statins for those with recent acute coronary syndrome.

NONSTATINS

A meta-analysis demonstrated that fibrates reduced the risk of subsequent coronary events (NNT = 35), but not overall mortality, compared with placebo.¹¹ Combination statin-fibrate therapy has not been shown to improve all-cause mortality compared with statins alone.⁹ A statin/ezetimibe combination may increase the likelihood of attaining LDL cholesterol goals, but has no known effect on all-cause mortality.⁹

Niacin monotherapy for secondary prevention does not reduce the risk of overall mortality.⁷ When added to statin therapy in patients with CHD, niacin improves disease-oriented outcomes (e.g., changes in mean carotid intima-media thickness or proximal coronary artery stenosis) compared with ezetimibe (Zetia) and antioxidants.^{10,19}

Individual trials have yielded conflicting evidence for omega-3 fatty acids in secondary risk reduction.⁴³⁻⁴⁵ The optimal quantity and type of omega-3 fatty acid are unclear.⁴⁶ In a recent systematic review comparing omega-3 fatty acids with control diets or placebo in patients with CHD, omega-3 fatty acids were associated with a reduced risk of sudden cardiac death (NNT = 98), cardiac death (NNT = 66), and all-cause mortality (NNT = 57) in the subgroup with a history of CHD and myocardial infarction.²⁰ In the baseline subgroup with only a history of CHD (e.g., angina), omega-3 fatty acids increased the risk of sudden cardiac death (NNH = 159) and did not alter the risk of cardiac death or all-cause mortality. Although their benefit is small, using omega-3 fatty acids

may be a reasonable alternative after myocardial infarction in patients who cannot tolerate statin therapy.

Bile acid-binding resins have no statistically significant effect on overall mortality when used for secondary prevention (relative risk = 0.84; 95% confidence interval, 0.66 to 1.08).⁷

CEREBROVASCULAR DISEASE

A Cochrane review of statins for secondary prevention of cerebrovascular disease reported that statins reduced recurrent strokes (NNT = 76), but not all-cause mortality.⁴⁷ Other lipid-lowering medications, including fibrates, increased the risk of subsequent strokes. In an acute setting, initiating statin therapy may reduce stroke severity and disability, with data supporting 40 to 80 mg of atorvastatin daily over 20 to 80 mg of simvastatin daily.⁴⁸ However, initiating high-dose atorvastatin after ischemic stroke has been shown to increase the risk of hemorrhagic stroke (NNH = 106 over five years of treatment), while reducing recurrent ischemic strokes (NNT = 42 over five years of treatment) and not affecting overall mortality.⁴⁹ Thus, initiating a moderate-dose statin is an option to reduce the risk of recurrent strokes.

PERIPHERAL ARTERIAL DISEASE

A Cochrane review concluded that statin use did not reduce mortality in patients with peripheral arterial disease.⁵⁰ However, using statins in these patients increased maximal walking distance by 499 ft (152 m) and pain-free walking distance by 295 ft (90 m). Lipid therapy did not change ankle-brachial index scores. Statin therapy for patients with abdominal aortic aneurysms has not been shown to change the rate of expansion, but patients who are taking statins at the time of a rupture have a lower mortality rate (NNT = 3.5).^{51,52}

Statin Therapy in Specific Populations

WOMEN

All women with a history of CHD should be offered treatment with a statin. There are arguments for and against recommending statins in women to reduce primary CHD risk.^{53,54} Some believe that women may respond differently to statins than men. Women also have a different baseline risk than men and therefore may not derive the same benefit. A systematic review concluded that lipid-lowering therapy in women does not change overall mortality, but may reduce the risk of coronary events in secondary, but not primary, prevention.⁵⁵

OLDER PERSONS

Clinical trials rarely include older patients, and extrapolating data from younger to older populations may be problematic. A meta-analysis found that in patients 62 to 85 years of age with CHD and hyperlipidemia, statins reduced overall mortality risk (NNT = 28), nonfatal myocardial infarction (NNT = 38), and stroke (NNT = 58) over five years.⁵⁶ A meta-analysis of patients 80 years or older receiving lipid-lowering therapy found that low cholesterol levels were associated with an increase in overall mortality compared with high cholesterol levels.⁵⁷ The decision to use statins for prevention of CHD in older patients should depend on individual baseline cardiovascular risk, expected degree of risk reduction, life expectancy, potential risks of therapy, and patient preference.

Data Sources: A PubMed search was completed in Clinical Queries using the key terms primary cardiovascular risk reduction, secondary cardiovascular risk reduction, hyperlipidemia, cholesterol, HMG CoA reductase inhibitors, fibric acid derivatives, bile-acid binding agents, ezetimibe, niacin, and omega-3 fatty acids. The search included meta-analyses, randomized controlled trials, clinical trials, and reviews. Also searched were the Cochrane database, Dynamed, Clinical Evidence, Essential Evidence Plus, National Guideline Clearinghouse database, and U.S. Preventive Services Task Force. Search dates: June 3, 2010; September 10, 2010; and February 11, 2011.

The Authors

ALLEN R. LAST, MD, MPH, is an assistant professor in the Department of Family Medicine at the University of Wisconsin School of Medicine and Public Health in Madison. He is also program director of the university's Fox Valley Family Medicine Residency Program in Appleton.

JONATHAN D. FERENCE, PharmD, BCPS, is an associate professor at the Wilkes University Nesbitt College of Pharmacy and Nursing in Wilkes-Barre, Pa., and director of pharmacotherapy education at the Wyoming Valley Family Medicine Residency Program in Kingston, Pa.

JULIANNE FALLERONI, DO, MPH, is an assistant professor in the Department of Family Medicine at the University of Wisconsin School of Medicine and Public Health. She is also a faculty member with the university's Fox Valley Family Medicine Residency Program.

Address correspondence to Allen R. Last, MD, MPH, University of Wisconsin Fox Valley Family Medicine Residency Program,

229 S. Morrison St., Appleton, WI 54911 (e-mail: allen.last@fammed.wisc.edu). Reprints are not available from the authors.

Author disclosure: No relevant financial affiliations to disclose.

REFERENCES

- American Heart Association. Heart disease and stroke statistics—2011 update. <http://circ.ahajournals.org/cgi/content/full/123/4/e18>. Accessed May 27, 2011.
- Grundy SM, Cleeman JI, Merz CN, et al.; National Heart, Lung, and Blood Institute; American College of Cardiology Foundation; American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines [published correction appears in *Circulation*. 2004;110(6):763]. *Circulation*. 2004;110(2):227-239.
- National Institute for Health and Clinical Excellence. Lipid modification. Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. NICE clinical guideline CG67. May 8, 2008. <http://www.nice.org.uk/CG67>. Accessed September 13, 2010.
- Genest J, McPherson R, Frohlich J, et al. 2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult—2009 recommendations. *Can J Cardiol*. 2009;25(10):567-579.
- Hayward RA, Krumholz HM, Zulman DM, Timbie JW, Vijan S. Optimizing statin treatment for primary prevention of coronary artery disease. *Ann Intern Med*. 2010;152(2):69-77.
- Ong HT. The statin studies: from targeting hypercholesterolaemia to targeting the high-risk patient. *QJM*. 2005;98(8):599-614.
- Studer M, Briel M, Leimenstoll B, Glass TR, Bucher HC. Effect of different antilipidemic agents and diets on mortality: a systematic review. *Arch Intern Med*. 2005;165(7):725-730.
- Morris S, Tiller R. Ezetimibe for hypercholesterolemia. *Am Fam Physician*. 2003;68(8):1595-1596.
- Sharma M, Ansari MT, Abou-Setta AM, et al. Systematic review: comparative effectiveness and harms of combination therapy and monotherapy for dyslipidemia. *Ann Intern Med*. 2009;151(9):622-630.
- Taylor AJ, Villines TC, Stanek EJ, et al. Extended-release niacin or ezetimibe and carotid intima-media thickness. *N Engl J Med*. 2009;361(22):2113-2122.
- Jun M, Foote C, Lv J, et al. Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. *Lancet*. 2010;375(9729):1875-1884.
- Abourbih S, Filion KB, Joseph L, et al. Effect of fibrates on lipid profiles and cardiovascular outcomes: a systematic review. *Am J Med*. 2009;122(10):962.e1-8.
- Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106(25):3143-3421.
- Davidson MH. Safety profiles for the HMG-CoA reductase inhibitors: treatment and trust. *Drugs*. 2001;61(2):197-206.
- Joy TR, Hegele RA. Narrative review: statin-related myopathy. *Ann Intern Med*. 2009;150(12):858-868.
- Brugts JJ, Yetgin T, Hoeks SE, et al. The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials. *BMJ*. 2009;338:b2376.
- Murphy SA, Cannon CP, Wiviott SD, et al. Effect of intensive lipid-lowering therapy on mortality after acute coronary syndrome (a patient-level analysis of the Aggrastat to Zocor and Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 trials). *Am J Cardiol*. 2007;100(7):1047-1051.
- Knopp RH. Drug treatment of lipid disorders. *N Engl J Med*. 1999;341(7):498-511.

Hyperlipidemia Medications

19. Brown BG, Zhao XQ, Chait A, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med*. 2001;345(22):1583-1592.
20. Zhao YT, Chen Q, Sun YX, et al. Prevention of sudden cardiac death with omega-3 fatty acids in patients with coronary heart disease: a meta-analysis of randomized controlled trials. *Ann Med*. 2009;41(4):301-310.
21. Ray KK, Seshasai SR, Erqou S, et al. Statins and all-cause mortality in high-risk primary prevention: a meta-analysis of 11 randomized controlled trials involving 65,229 participants. *Arch Intern Med*. 2010;170(12):1024-1031.
22. Ridker PM, Danielson E, Fonseca FA, et al.; JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359(21):2195-2207.
23. de Lorgeril M, Salen P, Abramson J, et al. Cholesterol lowering, cardiovascular diseases, and the rosuvastatin-JUPITER controversy: a critical reappraisal. *Arch Intern Med*. 2010;170(12):1032-1036.
24. Kaul S, Morrissey RP, Diamond GA. By Jove! What is a clinician to make of JUPITER? *Arch Intern Med*. 2010;170(12):1073-1077.
25. Green LA. Cholesterol-lowering therapy for primary prevention: still much we don't know. *Arch Intern Med*. 2010;170(12):1007-1008.
26. Weng TC, Yang YH, Lin SJ, Tai SH. A systematic review and meta-analysis on the therapeutic equivalence of statins. *J Clin Pharm Ther*. 2010;35(2):139-151.
27. WHO cooperative trial on primary prevention of ischaemic heart disease with clofibrate to lower serum cholesterol: final mortality follow-up. Report of the Committee of Principal Investigators. *Lancet*. 1984;2(8403):600-604.
28. Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med*. 1987;317(20):1237-1245.
29. Elkeles RS, Diamond JR, Poulter C, et al. Cardiovascular outcomes in type 2 diabetes. A double-blind placebo-controlled study of bezafibrate: the St. Mary's, Ealing, Northwick Park Diabetes Cardiovascular Disease Prevention (SEND CAP) Study. *Diabetes Care*. 1998;21(4):641-648.
30. Hanefeld M, Fischer S, Schmechel H, et al. Diabetes Intervention Study. Multi-intervention trial in newly diagnosed NIDDM. *Diabetes Care*. 1991;14(4):308-317.
31. Ginsberg HN, Elam MB, Lovato LC, et al.; ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus [published correction appears in *N Engl J Med*. 2010;362(18):1748]. *N Engl J Med*. 2010;362(17):1563-1574.
32. Alrasadi K, Awan Z, Alwaili K, et al. Comparison of treatment of severe high-density lipoprotein cholesterol deficiency in men with daily atorvastatin (20 mg) versus fenofibrate (200 mg) versus extended-release niacin (2 g). *Am J Cardiol*. 2008;102(10):1341-1347.
33. Chapman MJ, Redfern JS, McGovern ME, Giral P. Niacin and fibrates in atherogenic dyslipidemia: pharmacotherapy to reduce cardiovascular risk. *Pharmacol Ther*. 2010;126(3):314-345.
34. Alwaili K, Awan Z, Alshahrani A, Genest J. High-density lipoproteins and cardiovascular disease: 2010 update. *Expert Rev Cardiovasc Ther*. 2010;8(3):413-423.
35. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. *JAMA*. 1984;251(3):351-364.
36. Hooper L, Thompson RL, Harrison RA, et al. Omega 3 fatty acids for prevention and treatment of cardiovascular disease. *Cochrane Database Syst Rev*. 2004;(4):CD003177.
37. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med*. 1996;335(14):1001-1009.
38. Lewis SJ, Moye LA, Sacks FM, et al. Effect of pravastatin on cardiovascular events in older patients with myocardial infarction and cholesterol levels in the average range. Results of the Cholesterol and Recurrent Events (CARE) trial. *Ann Intern Med*. 1998;129(9):681-689.
39. Serruys PW, de Feyter P, Macaya C, et al.; Lescol Intervention Prevention Study (LIPS) Investigators. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. *JAMA*. 2002;287(24):3215-3222.
40. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360(9326):7-22.
41. Zhou Z, Rahme E, Pilote L. Are statins created equal? Evidence from randomized trials of pravastatin, simvastatin, and atorvastatin for cardiovascular disease prevention. *Am Heart J*. 2006;151(2):273-281.
42. Afilalo J, Majdan AA, Eisenberg MJ. Intensive statin therapy in acute coronary syndromes and stable coronary heart disease: a comparative meta-analysis of randomised controlled trials. *Heart*. 2007;93(8):914-921.
43. Marchioli R, Barzi F, Bomba E, et al. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. *Circulation*. 2002;105(16):1897-1903.
44. Burr ML, Ashfield-Watt PA, Dunstan FD, et al. Lack of benefit of dietary advice to men with angina: results of a controlled trial. *Eur J Clin Nutr*. 2003;57(2):193-200.
45. Singh RB, Dubnov G, Niaz MA, et al. Effect of an Indo-Mediterranean diet on progression of coronary artery disease in high risk patients (Indo-Mediterranean Diet Heart Study): a randomised single-blind trial. *Lancet*. 2002;360(9344):1455-1461.
46. Morantz C, Torrey B. Practice guideline briefs. Benefits of omega-3 fatty acids. *Am Fam Physician*. 2005;71(2):387.
47. Manktelow BN, Potter JF. Interventions in the management of serum lipids for preventing stroke recurrence. *Cochrane Database Syst Rev*. 2003;(3):CD002091.
48. Lampl Y, Lorberboym M, Gilad R, et al. Early outcome of acute ischemic stroke in hyperlipidemic patients under atorvastatin versus simvastatin. *Clin Neuropharmacol*. 2010;33(3):129-134.
49. Amarenco P, Bogousslavsky J, Callahan A III, et al.; Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med*. 2006;355(6):549-559.
50. Aung PP, Maxwell HG, Jepson RG, Price JF, Leng GC. Lipid-lowering for peripheral arterial disease of the lower limb. *Cochrane Database Syst Rev*. 2007;(4):CD000123.
51. Ferguson CD, Clancy P, Bourke B, et al. Association of statin prescription with small abdominal aortic aneurysm progression. *Am Heart J*. 2010;159(2):307-313.
52. Van Kuijk JP, Flu WJ, Witteveen OP, Voute M, Bax JJ, Poldermans D. The influence of statins on the expansion rate and rupture risk of abdominal aortic aneurysms. *J Cardiovasc Surg (Torino)*. 2009;50(5):599-609.
53. Grundy SM. Should women be offered cholesterol lowering drugs to prevent cardiovascular disease? Yes. *BMJ*. 2007;334(7601):982.
54. Kendrick M. Should women be offered cholesterol lowering drugs to prevent cardiovascular disease? No. *BMJ*. 2007;334(7601):983.
55. Walsh JM, Pignone M. Drug treatment of hyperlipidemia in women. *JAMA*. 2004;291(18):2243-2252.
56. Afilalo J, Duque G, Steele R, Jukema JW, de Craen AJ, Eisenberg MJ. Statins for secondary prevention in elderly patients: a hierarchical bayesian meta-analysis. *J Am Coll Cardiol*. 2008;51(1):37-45.
57. Petersen LK, Christensen K, Kragstrup J. Lipid-lowering treatment to the end? A review of observational studies and RCTs on cholesterol and mortality in 80+-year olds. *Age Ageing*. 2010;39(6):674-680.