⚖ Cochrane for Clinicians

Putting Evidence into Practice

Statins for Primary Cardiovascular Prevention

DEAN A. SEEHUSEN, MD, MPH, *DeWitt Army Community Hospital, Fort Belvoir, Virginia*

Clinical Scenario

A 54-year-old man presents for a health maintenance visit. He has no significant medical history, has never smoked, and takes no medications. Other than a body mass index of 26 kg per m^2, his examination is unremarkable. He has no family history of cardiovascular disease (CVD). A recent lipid panel revealed a total cholesterol level of 256 mg per dL (6.63 mmol per L), a high-density lipoprotein level of 51 mg per dL (1.32 mmol per L), and a low-density lipoprotein level of 162 mg per dL (4.20 mmol per L). You consider starting him on a statin to lower his cholesterol level and wonder if it is likely to reduce his risk of a cardiovascular event.

Clinical Question

Do statins reduce cardiovascular events in persons without known coronary artery disease?

Evidence-Based Answer

Trials to date have found that statins reduce all-cause mortality, composite cardiovascular outcomes, and revascularization. However, most trials included large numbers of persons with known CVD. Clear evidence of the effectiveness of statins to prevent a first cardiovascular event is lacking. (Strength of Recommendation: B, based on inconsistent or limited-quality patient-oriented evidence.)

Practice Pointers

Statins are potent reducers of serum cholesterol levels. Their ability to reduce morbidity and mortality in patients with known CVD is well established. However, some authors have started to question the effectiveness of statins for the primary prevention of cardiovascular outcomes.[1] To examine this specific body of evidence, the authors of this Cochrane review chose studies in which no more than 10 percent of participants had a history of CVD. This criterion eliminated several large trials that showed reductions in cardiovascular outcomes.[2]

A total of 16 arms from 14 clinical trials were included in the analysis. Trials typically reported on composite end points because of an overall small number of events. A few trials were stopped early, which can overestimate treatment effects. Other weaknesses included poor reporting of randomization techniques in several studies, and evidence of incomplete or selective outcome reporting. Trial participants were mostly middle-aged white men, calling into question the generalizability of the findings. All but one of the trials were at least partially industry supported.

Eight trials including more than 28,000 participants reported mortality data. Pooled analysis favored statin use with a relative risk (RR) of 0.83 (95% confidence interval [CI], 0.73 to 0.95). Pooled analysis of nine trials showed a reduction in coronary heart disease events with statin use (RR = 0.72; 95% CI, 0.65 to 0.79). Pooled analysis of six trials showed a reduction in fatal and nonfatal CVD events with statin use (RR = 0.74; 95% CI, 0.66 to 0.85). Pooled analysis of seven trials showed that statin use reduced combined fatal and nonfatal stroke events (RR = 0.78; 95% CI, 0.65 to 0.94).

Three trials with a combined 17,452 participants reported composite fatal and nonfatal coronary heart disease, CVD, and stroke events. All three trials showed statistically significant reductions; pooled analysis revealed an RR of 0.70 (95% CI, 0.61 to 0.79). Of more than 18,000 participants in the five trials reporting on revascularization, 1.7 percent underwent percutaneous transluminal coronary angioplasty or coronary artery bypass grafting. Pooled analysis showed a statistically significant reduction in the statin groups (RR = 0.66; 95% CI, 0.53 to 0.83).

Cochrane Abstract

Background: Reducing high blood cholesterol, a risk factor for cardiovascular disease (CVD) events in persons with and without a history of coronary heart disease (CHD), is an important goal of pharmacotherapy. Statins are the first-choice agents. Previous reviews of the effects of statins have highlighted their benefits in persons with coronary artery disease. The case for primary prevention, however, is less clear.

Objectives: To assess the effects, both harms and benefits, of statins in persons with no history of CVD.

Search Strategy: To avoid duplication of effort, we checked reference lists of previous systematic reviews. We searched the Cochrane Central Register of Controlled Trials (Issue 1, 2007), Medline (2001 to March 2007), and EMBASE (2003 to March 2007). There were no language restrictions.

Selection Criteria: Randomized controlled trials of statins with minimum duration of one year and follow-up of six months, in adults with no restrictions on their total low-density lipoprotein or high-density lipoprotein cholesterol levels, and where 10 percent or less had a history of CVD, were included.

Data Collection and Analysis: Two authors independently selected studies for inclusion and extracted data. Outcomes included all-cause mortality, fatal and nonfatal CHD, CVD and stroke events, combined end points (fatal and nonfatal CHD, CVD, and stroke events), change in blood total cholesterol concentration, revascularization, adverse events, quality of life, and costs. Relative risk (RR) was calculated for dichotomous data, and for continuous data pooled weighted mean differences (with 95% confidence intervals [CIs]) were calculated.

Main Results: Fourteen randomized controlled trials (16 trial arms; 34,272 participants) were included. Eleven trials recruited patients with specific conditions (raised lipids, diabetes mellitus, hypertension, microalbuminuria). All-cause mortality was reduced by statins (RR = 0.83; 95% CI, 0.73 to 0.95), as were combined fatal and nonfatal CVD end points (RR = 0.70; 95% CI, 0.61 to 0.79). Benefits were also seen in the reduction of revascularization rates (RR = 0.66; 95% CI, 0.53 to 0.83). Total cholesterol and low-density lipoprotein cholesterol levels were reduced in all trials but there was evidence of heterogeneity of effects. There was no clear evidence of any significant harm caused by statin prescription or of effects on patient quality of life.

Authors' Conclusions: Although reductions in all-cause mortality, composite end points, and revascularizations were found with no excess of adverse events, there was evidence of selective reporting of outcomes, failure to report adverse events, and inclusion of persons with CVD. Only limited evidence showed that primary prevention with statins may be cost-effective and improve patient quality of life. Caution should be taken in prescribing statins for primary prevention in persons at low cardiovascular risk.

A population-based cohort study with more than 2 million participants found statin use to be statistically associated with moderate to severe liver dysfunction, moderate to serious myopathy, acute renal failure, and cataracts.[3] However, adverse event reporting was irregular in the trials included in this analysis. Eight trials did not report on adverse events at all. Pooled data showed no difference between intervention and control groups for myalgia, rhabdomyolysis, or any types of cancer.

Published guidelines include near-term risk, calculated with validated scoring systems, as a factor to determine when to start lipid-lowering therapy. The National Cholesterol Education Program, Adult Treatment Panel III, guidelines and the American Heart Association Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women use calculated risk as one factor to consider when starting lipid-lowering therapy.[4,5] There is evidence that many patients who do not meet these criteria are being prescribed statins. One British study found that only 14 percent of patients being treated for primary prevention would be considered at high risk of CVD using an established risk score.[6]

Although this review does not prove that statins are ineffective for primary prevention of cardiovascular events, it highlights notable gaps in the literature concerning statin use in patients without a history of CVD. When determining whether to prescribe a statin to prevent a first cardiovascular event, a patient's overall cardiovascular risk should be estimated using a validated score, such as the Framingham risk score (calculator available at http://hp2010.nhlbihin.net/atpiii/calculator.asp). For those at highest risk, statins are likely to be beneficial. Because it is less certain whether patients at moderate or low risk will benefit from statin use, physicians should inform these patients of the gaps in the evidence, and assist them in weighing the potential cardiovascular benefits with the inconvenience, expense, and adverse effects of statins.

REFERENCES

1. 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.

2. Taylor F, Ward K, Moore TH, et al. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev.* 2011;(1): CD004816.

3. Hippisley-Cox J, Coupland C. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. *BMJ*. 2010;340:c2197.

4. National Heart, Lung, and Blood Institute. Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). NIH publication no. 02-5215. September 2002. http://www.nhlbi.nih.gov/guidelines/cholesterol/. Accessed August 15, 2011.

5. Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update: a guideline from the American Heart Association [published correction appears in *Circulation*. 2011;123(22):e624]. *Circulation*. 2011;123(11)1243-1262.

6. Garg P, Raju P, Sondej E, Rodrigues E, Davis G. Use of the Joint British Society cardiovascular risk calculator before initiating statins for primary prevention in hospital medicine: experience from a large university teaching hospital. *Int J Gen Med*. 2010;3:379-382.

Cochrane Briefs

Nicotine Receptor Partial Agonists for Smoking Cessation

Clinical Question

Does varenicline (Chantix) use improve smoking cessation rates, and how does its effectiveness and safety compare with other medications?

Evidence-Based Answer

Compared with placebo, varenicline more than doubles the chances of successful long-term smoking abstinence. In head-to-head trials, varenicline appears to be at least as effective as nicotine replacement therapy and bupropion (Zyban). The most common adverse effect is nausea, which decreases over time; a large cohort study found no increase in the likelihood of depression or suicidality. (Strength of Recommendation = A, based on consistent, good-quality patient-oriented evidence.)

Practice Pointers

The 2008 U.S. Public Health Service guideline on treating tobacco use and dependence recommended combining cessation counseling with nicotine replacement therapy, bupropion, and/or varenicline for nonpregnant adult smokers.[1] Varenicline is a nicotine receptor partial agonist that was highly effective and well-tolerated in initial trials that led to U.S. Food and Drug Administration (FDA) approval.[2] However, postmarketing reports of depressed mood, agitation, and suicide attempts in patients using varenicline led the FDA to require a boxed warning in July 2009.[3] In June 2011, the FDA also warned of a link between varenicline use and increased risk of myocardial infarction in smokers with cardiovascular disease.[4]

In this Cochrane review, the authors searched multiple electronic databases for randomized controlled trials with a minimum follow-up period of six months that compared varenicline with placebo or other medications for smoking cessation. Fourteen trials were identified, containing more than 10,000 total participants. The pooled risk ratio (RR) for six-month smoking abstinence for varenicline versus placebo was 2.3 (95% confidence interval [CI], 2.0 to 2.7). In five head-to-head trials, varenicline was statistically more effective at one year than bupropion (RR = 1.5; 95% CI, 1.2 to 1.9) and as effective at six months as nicotine replacement therapy (RR = 1.1; 95% CI, 0.9 to 1.4). Although up to one-third of all patients taking varenicline initially reported mild to moderate nausea, only 1 to 8 percent discontinued the drug for this reason.

A cohort study of more than 80,000 adults in primary care practices in the United Kingdom found no association between varenicline use and depression, suicidal thoughts, or self-harm.[5] Nonetheless, physicians should generally avoid prescribing varenicline for smokers with poorly controlled psychiatric disorders or a history of suicidality, and carefully weigh risks and benefits in smokers with known cardiovascular disease. If patients who use varenicline experience agitation or mood changes, they should be counseled to immediately report these conditions to their physician, discontinue the drug, and seek prompt medical evaluation.

KENNETH W. LIN, MD

REFERENCES

1. A clinical practice guideline for treating tobacco use and dependence: 2008 update. A U.S. Public Health Service report. *Am J Prev Med*. 2008; 35(2):158-176.

2. Love BL, Merz T. Varenicline (Chantix) for smoking cessation. *Am Fam Physician*. 2007;76(2):279-280.

3. U.S. Food and Drug Administration. Information for healthcare professionals: varenicline (marketed as Chantix) and bupropion (marketed as Zyban, Wellbutrin, and generics). http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm169986.htm. Accessed March 8, 2011.

4. U.S. Food and Drug Administration. FDA Drug Safety Communication: Chantix (varenicline) may increase the risk of certain cardiovascular adverse events in patients with cardiovascular disease. http://www.fda.gov/Drugs/DrugSafety/ucm259161.htm. Accessed July 6, 2011.

5. Gunnell D, Irvine D, Wise L, Davies C, Martin RM. Varenicline and suicidal behaviour: a cohort study based on data from the General Practice Research Database. *BMJ*. 2009;339:b3805. ∎