JAMA Clinical Evidence Synopsis

Statin Therapy for Primary Prevention of Cardiovascular Disease

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CLINICAL QUESTION Do statins reduce rates of cardiovascular events when used for primary prevention?

BOTTOM LINE When used for primary prevention, statins are associated with lower rates of all-cause mortality, major vascular events, and revascularizations compared with placebo. Statin therapy is not associated with increased rates of life-threatening adverse effects such as cancer.

Statins lower rates of cardiovascular events in patients both with and without clinically evident cardiovascular disease (CVD).[1,2] Statin use has increased from 16 million Americans in 2000 to 30 million in 2005. Over that same period, outpatient statin expenditure increased from $7.7 billion to $19.7 billion.[3] In England, the number of prescriptions for statins rose 5-fold to 61 million annually from 2001 to 2011 with a cost of £544 million (US $870 million).[4] Given such wide use and increasing costs, it is important to summarize the benefits and any associated harms of statin use for primary prevention, particularly among people at low risk of a CVD event.

Editorial

Summary of Findings in Primary Prevention

Pravastatin was most commonly used in trials that ran from 2 to 5 years. The overall quality of the studies was high, and all were funded by a pharmaceutical company. Three trials, accounting for 47% of the recruited population, were stopped prematurely due to a significant reduction in the primary outcome.

Statins compared with placebo/control reduced low-density lipoprotein (LDL) cholesterol levels by 39 mg/dL (to convert to millimoles per liter, multiply by 0.0259) and were associated with lower rates of all-cause mortality (relative risk [RR], 0.86 [95% CI, 0.79-0.94]; number needed to treat for 5 years [NNT_5], 138), combined fatal and nonfatal CVD (RR, 0.75 [95% CI, 0.70-0.81]; NNT_5, 49), combined fatal and nonfatal coronary heart disease (CHD) events (RR, 0.73 [95% CI, 0.67-0.80]; NNT_5, 88), and combined fatal and nonfatal stroke (RR, 0.78 [95% CI, 0.68-0.89]; NNT_5, 155) (**Figure**). Statins were associated with reduced coronary revascularization (percutaneous coronary intervention and coronary bypass surgery) rates (RR, 0.62 [95% CI, 0.54-0.72]; NNT_5, 96). In these trials the median control group CVD event rate was 15% over 10 years. The NNT_5 at a lower level of CVD risk of 10% over 10 years would be 75; and at a higher level of 30%, 25.

The incidence of cancers, myalgia, rhabdomyolysis, liver enzyme elevation, renal dysfunction, or arthritis did not differ between the groups, although not all trials reported fully on these outcomes. Rates of adverse events (17%) and stopping treatment (12%) were similar in statin and placebo/control groups. An increased risk of incident diabetes was found in 1 of the 2 trials reporting this outcome (RR, 1.18 [95% CI, 1.01-1.39]; NNT_5, 198). Hemorrhagic stroke may be increased by statins but none of the individual studies provided any results for this. Overall, results suggest that the benefits of statin therapy outweigh serious life-threatening hazards.

Discussion

Benefits of statins are consistent with the recent Cholesterol Treatment Trialists' Collaboration report using individual patient data covering both primary and secondary prevention trials.[2] Their findings demonstrated benefits of statins in people with levels of risk lower than current eligibility criteria used by US, current UK,[5] and European guidelines,[6] and by previous US guidelines.[7]

Limitations

Some trials included participants with CVD, but rather than exclude these trials, we included trials that contained 10% or fewer participants with documented CVD. A recent primary prevention trial of 6-month statin treatment found increased self-reporting of reduced energy and fatigue on exertion,[8] but none of

Evidence Profile

No. of randomized clinical trials: 18 (19 cohorts)

Study years: Conducted, 1994 to 2008; Published, 2011 to 2013

No. of participants: 56 934, including some with specific conditions (elevated lipids, diabetes, hypertension, and microalbuminuria)

Men: 60.3% **Women:** 39.7%

Race/ethnicity: 85.9% white

Age, mean (range): 57 (28-97) years

Setting: Primary care

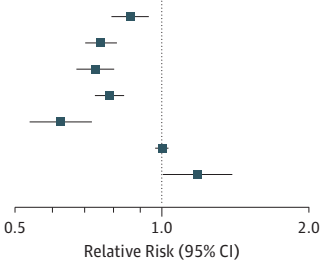
Countries: 17 trials: Japan, United States, Europe; 1 trial: South America, Israel, South Africa, and Russia

Primary outcomes: All-cause mortality; fatal and nonfatal CHD, CVD, and stroke events

Secondary outcomes: Change in total and LDL cholesterol concentration, coronary revascularization, adverse events, quality of life, and costs

Figure. Summary of Relative Risks and Numbers Needed to Treat for 5 Years for Outcomes in Primary Prevention Trials of Statins

Outcome	Trials, No.	Statin Events, No.	Statin Total No. of Participants	Placebo/Control Events, No.	Placebo/Control Total No. of Participants	Relative Risk (95% CI)	No. Needed to Treat for 5 Years (95% CI)
All-cause mortality	13	1077	24408	1223	23652	0.86 (0.79-0.94)	138 (92-321)
Total CVD events	9	1103	11892	1444	11913	0.75 (0.70-0.81)	49 (40-66)
Total CHD events	14	820	24217	1114	23832	0.73 (0.67-0.80)	88 (72-119)
Total stroke events	10	345	20302	442	19993	0.78 (0.68-0.89)	155 (106-309)
Revascularization	7	286	21166	461	21237	0.62 (0.54-0.72)	96 (78-129)
Any adverse event[a]	12	5748	20718	5090	19998	1.00 (0.97-1.03)	Not applicable
Type 2 diabetes	2	342	12205	290	12202	1.18 (1.01-1.39)	99 (46-1778)



CVD indicates cardiovascular disease; CHD, coronary heart disease.
[a] Adverse events included cancer, myalgia and rhabdomyolysis, arthritis, and increased liver enzyme.

the long-term primary prevention trials have reported health-related quality-of-life outcomes. There was limited evidence to suggest that statin use for primary prevention in low-risk people is cost-effective.

Comparison of Findings With Current Guidelines

The recently released 2013 American College of Cardiology/American Heart Association (ACC/AHA) guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults[9] recommends moderate- to high-intensity statin therapy for primary prevention for the following groups (class I recommendations): (1) persons with low-density lipoprotein (LDL) cholesterol levels of 190 mg/dL or higher; (2) persons aged 40 to 75 years with type 1 or 2 diabetes; or (3) persons aged 40 to 75 years with LDL cholesterol levels between 70 and 189 mg/dL and 7.5% or higher estimated 10-year risk of atherosclerotic cardiovascular disease. The committee also recommends that it is reasonable to offer moderate-dose statin treatment in individuals with an estimated 10-year risk of 5% to less than 7.5% (class IIa recommendation), though the level of evidence supporting this recommendation is graded as B by the ACC/AHA criteria and as weak by the National Institutes of Health criteria.

Areas in Need of Study

Cost-effectiveness estimates for statins in low-risk people are needed to inform guidelines in light of new evidence of benefits. New studies of the cost-effectiveness of alternative nonpharmacological CVD prevention strategies are needed. Further evidence on unintended adverse effects of statins from large-scale observational data and from unreported trial data is required to evaluate potential hazards of type 2 diabetes, adverse quality of life, and hemorrhagic stroke.

ARTICLE INFORMATION

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Submissions: We encourage authors to submit papers for consideration as a JAMA Clinical Evidence Synopsis. Please contact Dr McDermott at mdm608@northwestern.edu.

REFERENCES

1. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2013;(1):CD004816.

2. Cholesterol Treatment Trialists (CTT) Collaboration. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease. *Lancet*. 2012;380(9841):581-590.

3. National Institute for Health and Clinical Excellence (NICE). Technology Appraisal TA94. http://www.nice.org.uk/TA094. 2006. Accessed October 23, 2013.

4. Stagnitti MN. Trends in statins utilization and expenditures for the US civilian noninstitutionalized population, 2000 and 2005. http://meps.ahrq.gov/mepsweb/data_files/publications/st205/stat205.pdf. Accessed October 23, 2013.

5. The Health and Social Care Information Centre. Prescriptions dispensed in the community. https://catalogue.ic.nhs.uk/publications/prescribing/primary/pres-disp-com-eng-2001-11/pres-disp-com-eng-2001-11-rep.pdf. Accessed October 23, 2013.

6. Graham I, Atar D, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice. *Eur J Cardiovasc Prev Rehabil*. 2007;14(suppl 2):S1-S113.

7. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the 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). *JAMA*. 2001;285(19):2486-2497.

8. Golomb BA, Evans MA, Dimsdale JE, White HL. Effects of statins on energy and fatigue with exertion. *Arch Intern Med*. 2012;172(15):1180-1182.

9. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults [published online ahead of print November 12, 2013]. *Circulation*. 2013. doi:10.1161/01.cir.0000437738.63853.7a.