Pravastatin was not better than usual care in reducing all-cause mortality or CHD events

Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA. 2002;288:2998-3007.

QUESTION

In older patients with well-controlled hypertension and moderately elevated low-density lipoprotein cholesterol (LDL-C), is pravastatin better than usual care in reducing all-cause mortality and coronary heart disease (CHD) events?

DESIGN

Randomized (allocation concealed*), unblinded,* controlled trial with mean 4.8-year follow-up (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial [ALLHAT-LLT]).

SETTING

513 clinical centers in the United States, Canada, Puerto Rico, and the U.S. Virgin Islands.

PATIENTS

10 355 patients (mean age 66 y, 51% men) who were enrolled in the ALLHAT (age ≥ 55 y and stage 1 or 2 hypertension with ≥ 1 additional risk factor for CHD; fasting LDL-C level 3.1 to 4.9 mmol/L for those with no known CHD, or 2.6 to 3.3 mmol/L for those with known CHD; and fasting triglyceride levels < 3.9 mmol/L). Patients were excluded if they were receiving lipid-lowering therapy, large doses of niacin, or probucol; were intolerant of statins; or had liver or kidney disease, other contraindications for statin therapy, or a known secondary cause of hyperlipidemia. Follow-up was 97%. All randomized patients were included in the analysis.

INTERVENTION

Patients were allocated to open-label pravastatin, 40 mg/d (n = 5170), or usual care (LDL-C lowering at the discretion of the primary care physician) (n = 5185).

MAIN OUTCOME MEASURES

All-cause mortality. Secondary outcomes included a composite of fatal CHD or nonfatal myocardial infarction (MI) (CHD events), cause-specific mortality, and total and site-specific cases of cancer.

MAIN RESULTS

Analysis was by intention to treat. Pravastatin and usual-care groups did not differ for all-cause mortality (Table). Groups also did not differ for CHD events (Table) or for any other secondary outcomes.

CONCLUSION

In older patients with well-controlled hypertension and moderately elevated low-density lipoprotein cholesterol, pravastatin was no better than usual care in reducing all-cause mortality and CHD events.

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*See Glossary.

Pravastatin vs usual care for well-controlled hypertension and moderately elevated low-density lipoprotein cholesterol at 6 years†

Outcomes	Pravastatin	Usual care	RRR (95% CI)	NNT
All-cause mortality	14.9%	15.3%	1% (–11 to 11)	Not significant
CHD events	9.3%	10.4%	9% (–4 to 21)	Not significant

†CHD events = a composite of fatal coronary heart disease or nonfatal myocardial infarction. Other abbreviations defined in Glossary.

COMMENTARY

Unlike the ALLHAT hypertension treatment trial, in which negative results justified a firm endorsement of a drug of first choice, the negative results of the companion ALLHAT lipid-lowering trial (ALLHAT-LLT) are unimportant.

The negative results probably reflect flaws in study design and thus do not challenge beliefs about statins, especially in light of the positive results from the larger and more rigorous Heart Protection Study (HPS) (1). The design flaw that sets it apart from the 9 other large, long-term statin trials—including HPS—is the open-label, unblinded design that allowed nearly 30% of the control group to "drop-in" on lipid-lowering therapy. By year 6, the absolute difference in the reduction in LDL-C between the intervention group (28%) and control group (16%) was only 12%.

At the start of ALLHAT-LLT in 1994, the value of statins for primary prevention among patients with only moderately elevated cholesterol and other cardiovascular risk factors was uncertain. Subsequent publication of several positive, blinded, placebo-controlled, randomized trials provided convincing supporting evidence. Thus, only a meticulously designed, large, negative trial with minimal crossover could have challenged this conclusion. We agree with the authors' concluding advice to ignore the results and continue prescribing statins for patients with elevated risk for cardiovascular disease.

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Reference

1. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002;360:7-22.