Review: Cholesterol-lowering treatment with statins reduces all-cause mortality in persons at risk

Baigent C, Keech A, Kearney PM, et al. **Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90, 056 participants in 14 randomised trials of statins.** Lancet. 2005;366:1267-78. Epub 2005 Sep 27.

Clinical impact ratings: GIM/FP/GP ★★★★★☆☆ Cardiology ★★★★★☆☆

QUESTION

In persons at risk, do cholesterol-lowering interventions reduce mortality?

METHODS

Data sources: {Computer databases, relevant journals, bibliographies of relevant articles, lists of conference abstracts, the trial register of the International Committee on Thrombosis and Haemostasis, researchers in the field, and manufacturers of lipid-modifying drugs}*.

Study selection and assessment: Unconfounded randomized controlled trials (RCTs) that compared a statin with a control condition (placebo or usual care) for ≥ 2 years, and enrolled ≥ 1000 participants.

Outcomes: All-cause mortality, coronary heart disease (CHD) mortality, and non-CHD mortality. Secondary outcomes included major coronary events (a composite outcome of nonfatal myocardial infarction [MI] or CHD death), major vascular events (a composite outcome of major coronary events, nonfatal or fatal stroke, or coronary revascularization), and incidence of cancer.

MAIN RESULTS

14 RCTs (n = 90 056, age range 18 to 82 y, 76% men) met the selection criteria. Meta-analyses assessed the effects on clinical outcome in each trial weighted by the absolute low-density lipoprotein (LDL) cholesterol difference in that trial at the end of the first year of follow-up. The rates of all-cause and CHD mortality were lower in the statin group than in the control group (Table), without a difference in nonvascular mortality. The rates of major coronary events and major vascular events were lower in the statin group than in the control group (Table). The groups did not differ for incidence of cancer (Table).

CONCLUSIONS

Cholesterol-lowering treatment with statins reduces all-cause and coronary heart disease mortality without an increase in nonvascular mortality. Furthermore, statin therapy reduces major coronary events relatively by 23% and major vascular events by 21% for each mmol/L reduction in low-density lipoprotein cholesterol.

Source of funding: UK-Medical Research Council; British Heart Foundation; Australian NHMRC.

For correspondence: Dr. C. Baigent, Radcliffe Infirmary, Oxford, England, UK. E-mail ctt@ctsu.ox.ac.uk.

*__Cholesterol Treatment Trialists' Collaboration.__ Am J Cardiol. 1995;75:1130-4. 7762499

Hydroxymethylglutaryl-CoA reductase inhibitors (statins) vs control (e.g., placebo or usual care) in persons at risk at 5 years†

Outcomes	Statins	Control	RRR‡ (95% CI)	NNT (CI)
All-cause mortality	8.5%	9.7%	12% (9 to 16)	87 (65 to 115)
Coronary heart disease (CHD) mortality	3.4%	4.4%	19% (15 to 24)	121 (96 to 154)
Non-CHD vascular mortality	1.2%	1.3%	7% (–3 to 7)	Not significant
Nonvascular mortality	3.8%	4.0%	5% (–1 to 10)	Not significant
Any major coronary event	7.4%	9.8%	23% (20 to 26)	45 (40 to 51)
Any major vascular event	14.1%	17.8%	21% (19 to 23)	27 (25 to 30)
Cancer incidence	6.4%	6.4%	0% (–6 to 5)	

†Any major coronary event = nonfatal myocardial infarction or CHD mortality; any major vascular event = a major coronary event, nonfatal or fatal stroke, or coronary revascularization. Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.
‡RRRs are weighted to correspond to a reduction in rate per 1 mmol/L low-density lipoprotein cholesterol achieved by treatment at 1 year after randomization.

COMMENTARY

The meta-analysis by the Cholesterol Treatment Trialists' Collaboration confirms that lowering LDL cholesterol with statins significantly reduces CHD mortality, MI stroke, and coronary revascularization without increasing nonvascular mortality or cancer incidence.

Statins had a good toxic-to-therapeutic ratio: For every patient with a statin-induced excess case of rhabdomyolysis, 174 persons did not die and 361 people did not have an MI or coronary death.

Regardless of starting LDL cholesterol level, the authors found that each 39 mg/dL (1.0 mmol/L) statin-induced reduction in LDL cholesterol was associated with a one-eighth relative reduction in all-cause mortality and a one-fifth relative reduction in major vascular events. While this was true for relative risk, it was not true for absolute risk. The absolute risk reduction (ARR) for MI or coronary death was 3.8% for LDL cholesterol > 173 mg/dL (> 4.47 mmol/L) (number needed to treat [NNT] = 28), 2.3% for LDL cholesterol 135 to 173 mg/dL (3.49 to 4.47 mmol/L) (NNT = 43), and 1.9% for LDL cholesterol < 135 mg/dL (< 3.49 mmol/L) (NNT = 53), suggesting diminishing, although still important, benefits at lower LDL cholesterol levels.

When LDL cholesterol is high, statins are clearly indicated. The question is how to treat patients with atherosclerosis and lower LDL cholesterol levels—that is, those who typically have lower HDL cholesterol and denser LDL cholesterol, both responsive to fibrates or niacin. Clinical trials showing that statins are superior to other lipid-lowering therapies do not exist. Intriguingly, the HIT trial (1), with a mean LDL cholesterol of about 115 mg/dL (2.97 mmol/L), showed that fibrate therapy (gemfibrozil) produced a 4.3% 5.1-year ARR for MI or coronary death (NNT = 22). In the CPD trial (2), niacin therapy was associated with a 4.4% 6-year ARR for MI or coronary death (NNT = 22). These results suggest that fibrates or niacin have benefits that are at least comparable to statins in patients with atherosclerosis and low LDL cholesterol. Head-to-head comparisons with these agents and statins would be required to test this assertion.

Christopher Rembold, MD
University of Virginia
Charlottesville, Virginia, USA

References

1. **Robins SJ, Collins D, Wittes JT, et al.** Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomized controlled trial. JAMA. 2001;285:1585-91.
2. Clofibrate and niacin in coronary heart disease. JAMA. 1975;231:360-81.