Effects of statins on stroke prevention in patients with and without coronary heart disease: a meta-analysis of randomized controlled trials

Briel M, Studer M, Glass T R, Bucher H C

CRD summary
This review assessed the effectiveness of a variety of lipid-lowering treatments in preventing stroke. The authors concluded that statins reduce the risk of stroke in people with and without coronary heart disease. No other lipid-lowering agents appeared to have this effect. The review was well conducted and the authors' conclusions are supported by the data presented.

Authors' objectives
To assess the effects of lipid-lowering agents in preventing stroke in people with or without coronary heart disease (CHD).

Searching
MEDLINE, EMBASE, Pascal, Index Medicus and the Cochrane Library were searched to August 2002. No language restrictions were applied. The reference lists of relevant reviews and identified studies were checked for any additional publications to June 2003.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with a minimum follow-up of 6 months were eligible for inclusion.

Specific interventions included in the review
Studies that compared any lipid-lowering treatment (pharmacological or dietary) with placebo or usual diet were eligible for inclusion. Studies of interventions with obvious adverse events, such as hormone replacement therapy or outdated interventions (e.g. ileal bypass surgery), were excluded. The treatments in the included studies were statins (pravastatin, lovastatin, simvastatin, fluvastatin, atorvastatin), fibrates (clofibrate, bezafibrate, gemfibrozil, fenofibrate), resins (colestipol, cholestyramine), n-3 fatty acids (fish oil, linolenic acid), diet (diet, soya bean oil), others (niacin, policosanol, garlic), or a combination of these.

Participants included in the review
Studies on people with or without CHD were eligible for inclusion. Studies restricted to people with previous strokes were excluded. The mean age of participants in the included studies ranged from 45 to 75 years, and in most studies the majority of the participants were men (between 20 and 100%). Where reported, just over half of the included studies contained only patients with CHD, the proportion of patients with diabetes ranged from 0 to 35%, and 0 to 100% had hypertension. Baseline total cholesterol levels ranged from 4.5 to 8.5 mmol/L.

Outcomes assessed in the review
To be included, the studies had to report on nonfatal and fatal stroke and total mortality. The primary outcomes of interest were ischaemic and haemorrhagic stroke (fatal or nonfatal). The secondary outcomes were nonfatal or fatal myocardial infarction (MI).

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed studies for inclusion. Any disagreements were resolved by consensus.

Assessment of study quality
The quality of studies was assessed on the following criteria: concealment of allocation, blinding and the proportion of
participants with complete follow-up. Two reviewers independently assessed study quality. Any disagreements were resolved by consensus.

**Data extraction**

The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Investigators of included studies were contacted for additional information, when required. Risk ratios were calculated for the individual studies. The percentage change in total cholesterol in each trial was calculated as the difference in the mean change in cholesterol level from baseline to follow-up between the intervention and control groups. Where no exact levels were available, information was extracted from graphs.

**Methods of synthesis**

How were the studies combined?

A random-effects model was used to estimate pooled weighted risk ratios (RRs). A funnel plot was used to assess for publication bias. The number-needed-to-treat (NNT) was calculated by multiplying the averaged weighted mean annual baseline risk with the mean relative risk reduction. Meta-regression was used to assess any association between nonfatal and fatal stroke and changes in cholesterol levels and type of cholesterol-lowering treatment.

How were differences between studies investigated?

Heterogeneity was assessed using the Breslow-Day test and the I-squared statistic. Differences between the studies were investigated using subgroup analyses based on drug class (statins, fibrates, resins, n-3 fatty acids and dietary interventions), the presence or absence of CHD, and studies that did or did not differentiate between stroke and transient ischaemic attack. Sensitivity analyses were performed to investigate the influence of study quality.

**Results of the review**

Sixty-five RCTs (200,607 participants) were included.

Lipid-lowering interventions were associated with a statistically significant reduction in nonfatal and fatal stroke (RR 0.89, 95% confidence interval, CI: 0.83, 0.96). There was no evidence of significant heterogeneity (P=0.24, I-squared 10%, 95% uncertainty interval, UI: 0%, 34%). Statins statistically significantly reduced the risk of fatal or nonfatal stroke (RR 0.82, 95% CI: 0.76, 0.90), whereas non-statin interventions did not (RR 0.98, 95% CI: 0.90, 1.07).

Neither all lipid-lowering interventions, nor statins alone, appeared to affect the incidence of haemorrhagic stroke (RR 1.21, 95% CI: 0.78, 1.89 and RR 1.03, 95% CI: 0.49, 2.16, respectively). There was no evidence of significant heterogeneity (P=0.3, I-squared 15%, 95% UI: 0%, 57% and P=0.13, I-squared 46%, 95% UI: 0%, 82%, respectively).

In the subgroup of trials of people without CHD, statins statistically significantly reduced the risk of nonfatal and fatal stroke (RR 0.77, 95% CI: 0.62, 0.95). There was no evidence of significant heterogeneity (P=0.6, I-squared 0%, 95% UI: 0%, 75%). The reduction was similar in trials of people with CHD (RR 0.75, 95% CI: 0.65, 0.87; heterogeneity, P=0.9, I-squared 0%, 95% UI: 0%, 51%). Subgroup analyses showed that trial quality did not significantly alter the results. The NNT per year with statins, to prevent fatal or nonfatal stroke, was 617 (95% CI: 463 to 1,111) in high-risk populations with established CHD and 2,778 (95% CI: 2,083 to 5,000) in low-risk populations without established CHD. All other pooled data suggested that no other lipid-lowering treatments were statistically significantly beneficial in reducing stroke in people with or without CHD.

**Authors' conclusions**

The results suggested that statins reduce the risk of stroke in people with and without CHD.

**CRD commentary**
This review had clearly stated aims and inclusion criteria. A number of relevant databases were searched without language restrictions. The study selection and quality assessment processes were carried out in duplicate, which helps reduce the potential for reviewer error or bias. The studies were quality assessed using appropriate criteria, and the results of the quality assessment exercise were used to perform subgroup analyses. Adequate details of the included studies were tabulated. The statistical methods for pooling data appeared appropriate, and the authors used subgroup analyses to investigate the effects of differences between the included studies. The review appears to have been well conducted and the authors’ conclusions are likely to be reliable.

Implications of the review for practice and research
The authors did not state any implications for practice or further research.

Bibliographic details

PubMedID
15465509

DOI
10.1016/j.amjmed.2004.04.022

Other publications of related interest
This additional published commentary may also be of interest. Kingsbury KJ. Review: statins reduce non-fatal and fatal strokes in patients with and without coronary heart disease. Evid Based Nurs 2005;8:86.

Indexing Status
Subject indexing assigned by NLM

MeSH
Aged; Confidence Intervals; Coronary Disease /complications; Female; Humans; Hydroxymethylglutaryl-CoA Reductase Inhibitors /therapeutic use; Hypolipidemic Agents /therapeutic use; Male; Middle Aged; Randomized Controlled Trials as Topic; Stroke /complications /mortality /prevention & control

AccessionNumber
12004001867

Date bibliographic record published
30/11/2006

Date abstract record published
30/11/2006

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.