Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention
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CRD summary
The review concluded that lipid lowering with statins was effective in reducing both initial and recurrent stroke. Limitations relating to review methodology and reporting mean the authors' conclusions should be interpreted with caution.

Authors' objectives
To determine the effect of statins and low-density lipoprotein cholesterol reduction on stroke prevention. This is an update review; for previous review see Other Publications of Related Interest.

Searching
PubMed was searched for studies published in English (or translated) from September 2003 to December 2008; search terms were reported. Conference abstracts from the 2008 American Heart Association meeting, and reference lists of retrieved articles and previous reviews were also searched.

Study selection
Randomised controlled trials (RCTs) of statin treatment in adults (aged 18 years and over) that recorded data on stroke events (brain infarction and haemorrhage) using blinded assessment of outcomes were eligible for inclusion. To be eligible, trials had to recruit at least 1,000 adults. Trials of specific patient groups (e.g. renal transplant recipients, or patients receiving haemodialysis) were excluded.

Included trials were of patients at high-risk of stroke, treated with simvastatin, atorvastatin, pravastatin, lovastatin, and rosuvastatin. In most trials the majority of participants were male, with mean ages that ranged from 55 to 75 years. Mean baseline low-density lipoprotein cholesterol ranged from 2.5 to 5.0mmol/L. Most trials appeared to be placebo-controlled; a quarter compared different statins or doses. The mean duration of follow-up ranged from 0.3 to 6.7 years.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed trial quality.

Data extraction
Intention-to-treat data were extracted in order to calculate relative risks (RR) and 95% confidence intervals (CI). For trials with no events in one group, a pseudo-count of 0.5 was added to each cell.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Pooled relative risks were calculated using a random-effects model. Heterogeneity was assessed using the $I^2$ statistic. Linear regression was used to assess the effect of cholesterol changes. Sensitivity analyses excluded specific studies based on cerebrovascular disease status and also explored the effect of statin dose (intensive versus standard).

Results of the review
Twenty-four RCTs (n=165,792) were included in the review.

Statin treatment reduced incidence of all strokes by 18% (RR 0.82, 95% CI 0.77 to 0.87; $I^2=7%$; 24 RCTs) and reduced incidence of fatal stroke by 13% (p=0.10; 14 RCTs); pooled results of the four trials treating for secondary
The incidence of haemorrhagic stroke did not increase (p=0.88; 10 RCTs). Meta-regression suggested that each 1 mmol/L decrease in low-density lipoprotein cholesterol equated to a relative risk reduction for stroke of 21% (p=0.009). No increase in haemorrhagic stroke was seen when all trials were pooled, but an increase was seen for two trials treating for secondary prevention (RR 1.73, 95% CI 1.19 to 2.50; I²=0%).

Further results were presented.

**Authors' conclusions**
Lipid lowering with statins was effective in reducing both initial and recurrent stroke.

**CRD commentary**
The review aims were implied, rather than being expressly stated. The inclusion criteria appeared appropriate, although the authors excluded studies of fewer than 1,000 patients (which was not done in the original review). Only one database was searched and this, coupled with restriction of the search to English only articles, meant that some relevant studies may have been missed. The authors did not report using methods which could minimise the risk of reviewer error and bias (such as independent duplicate study selection and data extraction). No assessment of study quality was made, which made it difficult to assess the strength of the evidence (although to be included trials had to use blinded outcome assessors).

Some trial details were provided, but the limited reporting of population type, statin dose, and comparator treatment details, made it difficult to assess the generalisability of the pooled results. Appropriate methods were used to pool data and assess heterogeneity.

Although this review included very large trials, limitations relating to review methodology and reporting mean the authors' conclusions should be interpreted with caution.

**Implications of the review for practice and research**

**Practice**: The authors recommended caution when considering statin therapy in patients with prior cerebral haemorrhage (due to the increased incidence of haemorrhagic stroke).

**Research**: The authors stated the need for a trial of two strategies to lower low-density lipoprotein cholesterol concentrations (target less than 1.8 mmol/L versus a standard dose of statin), in the secondary prevention of stroke. Use of triglyceride-lowering therapy with fibric acid compounds, or their combination with statins, and treatments to raise high-density lipoprotein cholesterol concentrations, should be investigated in RCTs. New strategies of care need to be investigated, such as prevention clinics with nurse practitioners trained in the prevention of vascular disease to monitor patients closely to ensure they are treated to target.

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