Statin therapy in stroke prevention: a meta-analysis involving 121,000 patients
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CRD summary
The authors concluded that statin therapy provided high levels of protection for all-cause mortality and non-haemorrhagic strokes, which reinforced consideration of prolonged statins for patients at high risk of major vascular events; caution remained for patients at risk of bleeds. The authors’ conclusions reflect the review findings, although the unclear quality of included trials should be borne in mind.

Authors’ objectives
To assess the effects of statin therapy on stroke prevention and to determine differences in stroke risk reduction based upon variety of statins, dosing strategy and types of stroke.

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), AMED, CINAHL, PsycINFO, Web of Science, TOXNET, Development and Reproductive Toxicology and Hazardous Substances Databank were searched without language or publication restrictions from inception to December 2006. Search terms were not reported. Bibliographies of published trials, systematic reviews, health technology assessments and a previous meta-analysis were searched for additional studies.

Study selection
Randomised controlled trials (RCTs) of any duration that compared statins to placebo or no treatment were eligible for inclusion; eligible statins included atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin. Studies had to report on the outcomes: all-cause mortality; all-stroke incidence; fatal strokes; and haemorrhagic or ischaemic strokes. Studies that reported only surrogate outcomes were excluded.

Average doses for each statin varied in the included studies and were reported as: atorvastatin (10 to 80), fluvastatin (40 to 80), lovastatin (20 to 73), pravastatin (10 to 40) and simvastatin (20 to 40). Both placebo and standard care trials were included. Low-density lipoprotein (LDL) change between groups ranged from -0.110% to -0.430%. Average patient age ranged from 47 to 75 years. The proportion of females ranged from zero to 68.4%. The proportion of patients with diabetes ranged from zero to 100%. The proportion of patients with hypertension ranged from 12.2% to 100%. The proportion of smokers ranged from 8.1% to 84.3%.

Two authors independently selected studies for inclusion in the review.

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

Data extraction
Two authors independently extracted data to enable calculation of relative risks (RR) and 95% confidence intervals (CI). The Haldane method of adding 0.5 to each trial group was applied in the case of zero events. Study authors and authors of previous reviews were contacted for additional information, where necessary.

Methods of synthesis
Relative risks and 95% CI were pooled in a random-effects meta-analysis (DerSimonian and Laird). To assess the association between statin treatment and risk of mortality or stroke a weighted meta-regression for study characteristics was undertaken using an unrestricted maximum likelihood model. Sensitivity analyses were used to assess the impact of a priori identified covariates that included: specific within-class effects; underlying conditions and patient characteristics; dosage; lipid changes; and length of follow-up. Statistical heterogeneity was assessed using the I² statistic. Publication bias was assessed using funnel plots.
Results of the review
Forty-two RCTs were included (n=121,285, range 71 to 20,536). Follow-up duration ranged from one to 6.1 years.

Patients who received statin therapy showed significant reductions for: all strokes (RR 0.84, 95% CI 0.79 to 0.91; n=121,285, I²=0%); all-cause mortality (RR 0.88, 95% CI 0.83 to 0.93; n=116,080, I²=25%); cardiovascular deaths (RR 0.81, 95% CI 0.74 to 0.90; n=57,599, I²=21%) and non haemorrhagic cerebrovascular events (RR 0.81, 95% CI 0.69 to 0.94; n=58,604, I²=49%).

Each unit increase in low-density lipoprotein (LDL) resulted in a 0.3% increased risk ratio of death (p=0.02).

Authors’ conclusions
Statin therapy provided high levels of protection for all-cause mortality and non haemorrhagic strokes. This overview reinforced the need to consider prolonged statin treatment in patients at high risk of major vascular events; caution remained for patients at risk of bleeds.

CRD commentary
The review question and the inclusion criteria were clear. Study details were adequately provided, but the dose unit used for statins was unclear. The authors searched a number of relevant databases and additional sources without language restrictions; the lack of language or publication restrictions reduced the chance of relevant studies being omitted and bias being introduced. The authors reported that there was no evidence of publication bias, but the funnel plots were not shown. Study selection and data extraction were carried out with sufficient attempts to minimise error and bias. The absence of any formal quality assessment of included trials limited interpretation of the reliability of the findings. It appeared that appropriate methods were used to pool the trials. Reasonable measures were used to assess and explore heterogeneity between studies.

The authors’ conclusions reflected the results of the review and appear likely to be reliable, although the the unclear quality of the included trials should be borne in mind.

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

Research: The authors stated that there was a need for direct trials of individual statins to assess whether they offered protection from clinically important events and for trials that assessed secondary prevention.

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