Do statins improve outcomes and reduce the incidence of vasospasm after aneurysmal subarachnoid hemorrhage: a meta-analysis

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CRD summary
This review evaluated the effectiveness of statins in preventing cerebral vasospasm in patients who have had aneurysmal subarachnoid haemorrhage (SAH). The evidence suggested that statins may be promising, but the authors’ conclusions appear over-optimistic given the limited evidence available.

Authors’ objectives
To evaluate the effectiveness of statins in preventing cerebral vasospasm in patients who have had aneurysmal subarachnoid haemorrhage (SAH).

Searching
Two independent reviewers searched MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials to 2007 with no language restrictions. Search terms used were reported. Not only peer-reviewed articles but also studies published only as abstracts were included. In addition, the bibliographies of review articles were checked and authors were contacted for unpublished trial data.

Study selection
Randomised controlled trials (RCTs) and controlled clinical trials of statins in patients after aneurysmal SAH were eligible for inclusion. Trials were required to administer a statin medication to patients in one arm of the trial. The primary outcome was the incidence of clinical cerebral vasospasm, which was defined as the clinical manifestation of vasospasm (a neurologic deficit not associated with a re-bleed, hydrocephalus or infection) that had been radiographically determined with an imaging modality such as transcranial Doppler or cerebral angiography. Secondary outcomes included mortality and incidence of vasospasm-related delayed ischaemic deficits.

Two studies used 80 mg simvastatin daily. One study used 40 mg pravastatin daily. Follow up duration was 14 days in two studies. One study looked at length of ICU stay. All included trials compared a statin to placebo. Two reviewers independently selected studies for inclusion. Disagreements were resolved by consensus.

Assessment of study quality
Methodological quality was assessed by two independent reviewers using the Jadad scale, a 5-point scale evaluating randomisation, blinding and intention to treat. Studies were considered high quality if they scored ≥3.

Data extraction
Two independent reviewers extracted data into standard data extraction forms. Data on numbers of events in each group were used to derive the relative risk (RR) for outcomes, which were all dichotomous, and the number needed to treat (NNT).

Methods of synthesis
The pooled relative risk (RR) and corresponding 95% CIs were calculated using a fixed-effect model. Statistical heterogeneity was assessed using a $X^2$ test, visual inspection of studies in forest plots and the $I^2$ test. Publication bias was assessed using funnel plots.

Results of the review
Three double-blind RCTs (n=158) were included in the review. Two trials included 39 participants and one trial included 80 participants. All studies were considered to be of high quality: two trials scored 3 and one trial scored 5 on the Jadad scale.

The incidence of vasospasm was significantly less in patients who received statin therapy compared with placebo (three
trials, RR 0.73, 95%CI: 0.54, 0.99). The number needed to treat for this outcome was reported as 6.1 in the text (the abstract quoted 6.25). The incidence of vasospasm-related delayed ischemic deficits (two trials, RR 0.38, 95%CI: 0.17, 0.83) and mortality (two trials, RR 0.22, 95%CI: 0.06, 0.82) were significantly lower in patients who received statin therapy. The number needed to treat for vasospasm-related delayed ischemic deficits was 5.0 and for mortality 6.7. No significant heterogeneity was found for any of the analyses.

Authors' conclusions
The use of statin therapy decreased the incidence of vasospasm, delayed ischemic deficits and mortality after aneurysmal SAH, although larger RCTs were necessary to confirm safety and efficacy.

CRD commentary
This review addressed a clear question supported by appropriate inclusion criteria. A number of relevant electronic databases were searched without language restrictions. Efforts were made to retrieve unpublished data. Suitable methods were used throughout the review process to minimise the risks of reviewer error and bias. In terms of the generalisability of this review to different clinical situations, it would have been useful if some patient characteristics had been reported.

Results were pooled using meta-analysis. The authors reported that they assessed heterogeneity using the $X^2$ and $I^2$ tests. Reporting the results for these analyses may have helped avoid discrepancies: the results report no significant heterogeneity for the primary outcome (data not reported), however, the discussion reports significant heterogeneity for the primary outcome and authors report that it may not have been appropriate to combine studies. This has quite important implications for a review of this size, as there were only three studies included and all had small study numbers.

In terms of methodology, this review was carried out robustly. But, without reporting patient characteristics and results it was difficult to interpret. The authors' conclusions appeared to be over-optimistic given the limited evidence available and should be interpreted with some caution.

Implications of the review for practice and research
Practice: The authors stated that physicians should consider initiating statin therapy immediately after diagnosis of SAH.

Research: The authors identified three trials in progress evaluating the use of statin therapy following SAH. The authors suggested that further research into the optimal dose and duration of therapy should be considered.

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