Statin therapy and the risk of intracerebral hemorrhage: a meta-analysis of 31 randomized controlled trials

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CRD summary
The authors concluded that statins were not associated with increased risk of intracerebral haemorrhage and were associated with reduced risk of all stroke and all-cause mortality. This was a generally well-conducted review. There was some inconsistency in direction of effects in individual studies but the authors conclusions are likely to be reliable.

Authors' objectives
To examine the risk of intracerebral haemorrhage due to statin use.

Searching
MEDLINE, Web of Science and The Cochrane Library were searched to January 2012 for publications in English; search terms were reported. Reference lists of included articles and meta-analyses were checked.

Study selection
Randomised controlled trials (RCTs) on primary or secondary prevention with blinded outcome assessment of adults aged at least 18 years were eligible. Eligible control groups were treatment as usual, placebo or lower-dose statins. Trials had to provide data on haemorrhagic stroke or intracerebral haemorrhage.

Mean age was 63 years, 67% of patients were males and 78% were white. Eleven per cent of participants had a history of stroke, 59% had a cardiovascular disease, 53% hypertension, 25% diabetes and 61% were treated with aspirin or an oral anticoagulant. In addition, 21% smoked regularly. Statins used were simvastatin, lovastatin, pravastatin, atorvastatin, rosuvastatin; no regimens were stated.

Studies were selected by two reviewers. Disagreements were resolved through discussion.

Assessment of study quality
Randomisation, allocation concealment, comparison of baseline characteristics, eligibility criteria, type of control group, blinding (participants, investigators, assessors), percentage lost to follow-up and use of intention-to-treat analyses were assessed as part of the critical appraisal.

The authors did not state how many reviewers conducted the quality assessment.

Data extraction
Outcomes (total strokes, intracerebral haemorrhages and all-cause mortality) were extracted from each study to calculate odds ratios and 95% confidence intervals.

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Methods of synthesis
Intention-to-treat data were pooled using a random-effects model. Analyses were presented by type of control, primary or secondary prevention. Heterogeneity was assessed using the Q statistic. A meta-regression was used to assess the association between LDL (low-density lipoprotein) and intracerebral haemorrhage risk. Publication bias was assessed using funnel plots, trim-and-fill method and fail-safe N models. Numbers need to treat (NNT) were calculated.

Three sensitivity analyses were conducted: a study that found zero events in both groups was excluded in the main analysis but was included in the sensitivity analysis with one event in each group imputed; an influence analysis was conducted by examining the impact of removing one study at a time; and a cumulative meta-analysis was conducted to examine the effects of adding progressively larger studies one at a time.

Results of the review
Thirty-one trials (182,803 participants) were included in the review: six trials compared high dose and low dose statins; all other trials compared statins with either placebo or usual care. Median follow up was 46.8 months.

Statin treatment was not associated with greater risk for intracerebral haemorrhage (OR 1.08, 95% CI 0.88 to 1.32; 30 trials) with no evidence of statistical heterogeneity (Q=30.71, p=0.38). Similar results were found when stratifying by control group and primary versus secondary prevention trials. Sensitivity analyses confirmed these findings. There was no evidence of publication bias.

Statin treatment was associated with a small statistically significant reduction in risk of any stroke (OR 0.84, 95% CI 0.78 to 0.91; 31 trials; NNT=200) and there was no evidence of statistical heterogeneity (Q=33.32, p=0.31). There was also a small statistically significant reduction in all-cause mortality (OR 0.92, 95% CI 0.87 to 0.96; 31 trials; NNT=167) with no evidence of statistical heterogeneity (Q=32.27, p=0.31).

Authors' conclusions
Statin therapy was not associated with an increased risk of intracerebral haemorrhage. Statistically significant reductions in all stroke and all-cause mortality were found in association with statin use.

CRD commentary
The review question and inclusion criteria were clear. The search included a reasonable coverage of electronic databases. Only publications in English were included in the review so relevant studies may have been missed. No evidence was found to suggest the presence of publication bias.

Appropriate methods were used to minimise risk of errors in study selection; it was unclear whether this was the case for data extraction and quality assessment. A quality assessment was conducted but results from this were not provided in the paper so it was difficult to draw conclusions concerning the risk of bias associated with the included studies. Studies appeared statistically similar enough to provide valid pooled estimates. Suitable methods were used to assess heterogeneity. Statistical tests did not identify evidence of heterogeneity but there was some inconsistency in direction of effects of individual studies.

This was a generally well-conducted review. There was some inconsistency in direction of effects of individual studies but the authors conclusions are likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that their findings supported current recommendations on the use of statins in appropriate populations. Caution was warranted for statin use in patients with previous intracerebral haemorrhage who may potentially be at increased risk.

Research: The authors stated that further research was needed to assess use of statins in patient with prior intracerebral haemorrhage.

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