Statins and intracerebral hemorrhage: collaborative systematic review and meta-analysis


CRD summary
This review found no evidence that statins were associated with intracerebral haemorrhage, and if there was a risk, it was small and outweighed by the cardiovascular benefits of treatment. Based on the presented evidence, these conclusions appear to be reliable.

Authors' objectives
To determine the association between statin use and intracerebral haemorrhage, using randomised and observational data.

Searching
The authors searched 17 electronic databases, including MEDLINE, The Cochrane Library and ClinicalTrials.gov, from inception to June 2011. Search terms were reported. They searched conference proceedings and the bibliographies of relevant publications, and they contacted experts to identify other studies. The search was not restricted by language or publication status.

Study selection
Studies were eligible for inclusion if they were randomised controlled trials (RCTs) or observational studies that included data on the frequency of intracerebral haemorrhage and statin exposure.

Included studies had a variety of patient populations on statin treatment, including patients with coronary artery disease, type 2 diabetes, hypercholesterolaemia, recent myocardial infarction, hypertension plus other coronary heart disease risk factors, and a history of stroke or transient ischaemic attack.

Two reviewers independently selected studies for inclusion, with disagreements resolved through discussion and consensus.

Assessment of study quality
Methodological quality was assessed using the Jadad criteria for RCTs (up to five points, based on randomisation, concealment of allocation, blinding, and description of withdrawals), and using the Downs and Black checklist for observational studies (up to 32 points based on quality of reporting, internal and external validity, and statistical power).

The authors did not state how many reviewers performed the assessment.

Data extraction
Data were extracted on key study characteristics, with risk ratios and related 95% confidence intervals for dichotomous outcomes. Confidence intervals were converted to standard errors using standard formulae.

Double data entry suggests that two reviewers performed the extraction.

Methods of synthesis
Pooled risk ratios and 95% confidence intervals were calculated using the DerSimonian and Laird random-effects model. The degree of statistical inconsistency between pooled studies was assessed using $I^2$. Pooled risk ratios were calculated separately for RCTs, cohort studies and case-control studies.

Sensitivity analyses were conducted by recalculating the pooled values without one study at a time, by using a fixed-effect model, and by assessing the relationship between outcome and study characteristics, including length of follow-up, methodological quality, trial dates, disease incidence, statin efficacy, statin type, ethnicity and prevention status, using a random-effects meta-regression.
Publication bias was assessed using funnel plots and the Begg and Mazumdar rank correlation test.

**Results of the review**

Twenty-three RCTs, with 130,443 participants, were included in the review (median follow-up 3.9 years, IQR 2.8 to 5.0). Twenty-one trials had Jadad scores of three or more. The pooled risk ratio indicated a non-significant association between statin use and intracerebral haemorrhage (RR 1.10, 95% CI 0.86 to 1.41; $I^2=30\%$).

Nineteen observational studies, with 117,948 participants, were included in the review (median follow-up 3.0 years, IQR 1.4 to 4.1). The median Downs and Black score was 21 points and the interquartile range was 18 to 22. The pooled risk ratios indicated that statins were not associated with an increased risk of intracerebral haemorrhage, both in cohort studies (RR 0.94, 95% CI 0.81 to 1.10; $I^2=0$) and in case-control studies (RR 0.60, 95% CI 0.41 to 0.88; $I^2=66\%$).

Sensitivity analyses did not substantially alter these results. There was no obvious evidence publication bias.

**Authors' conclusions**

The authors found no evidence that statins were associated with intracerebral haemorrhage. If there was a risk, it was small and outweighed by the cardiovascular benefits of treatment.

**CRD commentary**

This review addressed a broadly defined question that was supported by appropriate inclusion criteria. The authors made efforts to identify all the relevant published and unpublished evidence, and combined this evidence using relevant accepted statistical methods. It was unclear whether attempts were made to minimise the risk of errors and bias for some stages of the review process. The meta-analyses included a large numbers of patients, and the authors took appropriate steps to investigate the quality and consistency of the evidence they presented.

The authors interpreted the results of their analyses as relative and absolute risks, and their conclusions appear to be reliable.

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

**Practice:** The authors stated that clinicians should continue to base statin treatment initiation on each person’s global risk of cardiovascular events.

**Research:** They did not state any implications for research.

**Funding**

Funded by a grant from the Physicians' Services Incorporated Foundation, Canada.

**Bibliographic details**


**PubMedID**

22007076

**DOI**

10.1161/CIRCULATIONAHA.111.055269

**Original Paper URL**

http://circ.ahajournals.org/content/124/20/2233.abstract

**Indexing Status**

Subject indexing assigned by NLM
MeSH
Animals; Case-Control Studies; Cerebral Hemorrhage /chemically induced /epidemiology; Cohort Studies; Humans; Hydroxymethylglutaryl-CoA Reductase Inhibitors /adverse effects /therapeutic use; Randomized Controlled Trials as Topic /methods /trends

AccessionNumber
12011007453

Date bibliographic record published
08/03/2012

Date abstract record published
06/11/2012

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.