Statins and cognition: what can we learn from existing randomized trials?

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CRD summary
The authors concluded that there is insufficient evidence for the use of statins solely for the prevention of dementia, but that the results from current ongoing trials will help provide a more definitive answer. The limited search, lack of a validity assessment and poorly structured synthesis mean it is difficult to assess the reliability of these conclusions.

Authors' objectives
To determine the efficacy and safety of statins on cognitive function.

Searching
MEDLINE was searched from January 1966 to 1 July 2004; the search terms were reported. Bibliographic references were also checked.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. Crossover and parallel-group RCTs were included in the review.

Specific interventions included in the review
Studies that compared statins with placebo were eligible for inclusion. The included studies evaluated lovastatin (20 to 40 mg/day), pravastatin (40 mg/day) and simvastatin (20 to 40 mg/day). Some studies compared two different statins with placebo. In most studies the duration of treatment ranged from 3 to 6 weeks; three longer term studies were 6 months to 5 years in duration.

Participants included in the review
No a priori criteria were reported. Where reported, the studies included healthy participants with and without hypercholesterolaemia, and individuals with coronary artery disease, peripheral vascular disease, diabetes mellitus, vascular disease, or hypertension. The participants were aged between 18 and 82 years old.

Outcomes assessed in the review
Studies that included primary or secondary outcomes of cognitive measures were eligible for inclusion. A variety of cognitive measures covering a number of different cognitive areas and measures of mood and daily function were assessed. The review also mentioned other outcomes including stroke, transient ischaemic attacks, dementia and sleep problems.

How were decisions on the relevance of primary studies made?
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 validity.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.
Methods of synthesis
How were the studies combined?
The studies were combined in a narrative, grouped by treatment comparator or disease. Two large studies in patients with cardiovascular disease were discussed separately.

How were differences between studies investigated?
Study differences were described in the body of the text.

Results of the review
Nine RCTs (n=26,783) were included in the study. The sample size ranged from 22 to 20,000.

Lovastatin versus pravastatin (4 RCTs with 22 to 80 participants; study duration 3 to 6 weeks).
The review included some results for comparisons with placebo under this heading.
Three trials found no significant difference between treatment groups (lovastatin versus pravastatin versus placebo) on cognitive tests or daily function. One trial found a significant decline from baseline in divided attention and vigilance in the lovastatin group and no significant changes from baseline in the pravastatin or placebo group.

Simvastatin versus pravastatin (2 RCTs, n=25 and n=24; study duration 4 weeks).
The review included some results for comparisons with placebo under this heading.
One trial found that individuals treated with simvastatin performed less well on the hit reaction time component of the choice reaction time test and a worsening on the fatigue/inertia dimension of the Profile of Mood States questionnaire, but found no other significant differences between the treatment groups (simvastatin versus pravastatin versus placebo) on cognitive tests or mood. The other trial found no significant differences between the treatment groups (simvastatin versus pravastatin versus placebo) on cognitive test.

Lovastatin versus placebo (5 RCTs).
The reviewers only described one study under this heading.
One trial (n=209) found a 'slight' improvement in the placebo group on tests of attention and psychomotor speed at 6 months, and an improvement in the lovastatin group for memory retrieval.

Simvastatin and pravastatin in cardiovascular disease (2 RCTs).
One study (n=20,536) reported no difference between simvastatin and placebo in the Telephone Interview for Cognitive Status-m after an average of 5 years' follow-up.
One study (n=5,805) reported no difference between pravastatin and placebo in cognitive tests between last observation and second baseline values after an average of 3.2 years' follow-up.

Pravastatin versus placebo (7 RCTs).
No significant differences between treatment groups were found on cognitive tests, or measures of mood or daily function. In one long-term trial no significant differences were found in cardiovascular events, although a trend for decreased incidence of transient ischaemic attack was found for pravastatin.

Simvastatin versus placebo (3 RCTs).
No significant differences between treatment groups were found. One trial reported more difficulty in sleeping in the simvastatin group, while another found a reduction in risk of stroke in the simvastatin group.
Authors' conclusions
There is insufficient evidence for the use of statins solely for the prevention of dementia. The results from current ongoing trials will help provide a more definitive answer.

CRD commentary
The review question was supported by clear inclusion criteria in terms of the intervention, outcome and study design. Since only one database was searched, it is possible that relevant papers were not included in the review. No attempt to assess publication bias was made. In addition, the inclusion of only placebo-controlled trials might have resulted in the omission of other studies that compared two or more different statins. The authors did not describe methodologies for the study selection or data extraction processes, thus it is not possible to assess the likelihood of error or bias being introduced at these stages. The methodological quality of the included studies does not appear to have been systematically assessed.

A narrative synthesis was appropriate given the differences between the studies in terms of their populations, duration of treatment and outcomes. Not all studies that reported comparisons of interest were discussed under the appropriate headings. The lack of reporting of actual values for most outcomes meant it was not possible to verify the reviewers' reported results; in addition, some results were reported as changes from baseline rather than differences between treatments, which made it difficult to interpret the evidence. The limited search, lack of a validity assessment and poorly structured synthesis meant it was difficult to assess the reliability of the conclusions.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.
Research: The authors stated that the results from several prospective ongoing trials looking at long-term effects will help provide a clearer picture on the use of statins as antidementia agents, as well as their safety.

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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.