Efficacy of statins in combination with interferon therapy in multiple sclerosis: a meta-analysis
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CRD summary
The authors concluded that the addition of statins to interferon therapy did not significantly influence disease progression, the relapse risk, or the Expanded Disability Status Scale scores of patients with relapse-remitting multiple sclerosis. This appears to have been a well-conducted review, but methodological and clinical differences between the trials mean that the reliability of the conclusions is uncertain.

Authors' objectives
To evaluate the efficacy of combined statin and interferon therapy for patients with multiple sclerosis.

Searching
MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science were searched to September 2011; search terms were reported. Reference lists of included articles and ClinicalTrials.gov were searched to locate further studies.

Study selection
Randomised controlled trials (RCTs) that compared statin plus interferon with interferon alone (the control) were eligible for inclusion if they were of patients with multiple sclerosis. At least one of the following outcomes had to be reported: the clinical relapse rate; disease progression; or the Expanded Disability Status Scale (EDSS) score.

In included trials, the mean patient age ranged from 29.3 to 45.1 years and the percentage of male patients ranged from 14.2 to 37.5. All of the trials were of patients with relapsing-remitting multiple sclerosis, and in all but one, patients were already being treated with interferon beta-1a, given once or three times per week. Across all trial groups, the weekly interferon dose ranged from 30 micrograms (μg) to 132μg; half of the trials were of intra-muscular administration and the other half were of subcutaneous administration. The statins were taken orally and were simvastatin or atorvastatin, with daily doses ranging from 20mg to 80mg. Treatment duration ranged from six to 24 months.

Two reviewers independently selected trials for inclusion; it was unclear how any discrepancies were resolved.

Assessment of study quality
Trial quality was assessed using the Jadad Scale, for randomisation, double-blinding, and patient withdrawals. The scale ranged from zero (weak) to five (strong); trials with a score of less than three were considered to be of low quality.

Two reviewers assessed the quality of the trials; it was unclear how any discrepancies were resolved.

Data extraction
Data were extracted to calculate incident risk ratios for the clinical relapse rate, relative risks for relapse and disease progression, and weighted mean differences for the change in EDSS scores from baseline. All estimates were calculated with 95% confidence intervals.

The data were extracted independently by two reviewers; it was unclear how any discrepancies were resolved.

Methods of synthesis
Estimates from individual trials were pooled using the random-effects DerSimonian and Laird method. Statistical heterogeneity was assessed using $I^2$.

Results of the review
Four RCTs were included in the review and meta-analysis, with 463 patients (range 26 to 307 per trial). Duration of
follow-up ranged from nine to 24 months. All four trials had a total Jadad score of three or more. Patient withdrawals and loss to follow-up were adequately reported in all of the trials; three trials used intention-to-treat analyses.

No statistically significant differences were found between the treatment and control groups for all of the outcomes examined: clinical relapse rate (incident RR 0.72, 95% CI 0.17 to 3.11; two trials); risk of relapse (RR 0.99, 95% CI 0.53 to 1.85; three trials; $I^2=54.1\%$); disease progression (RR 1.31, 95% CI 0.73 to 2.36; four trials; $I^2=38.1\%$); and change in EDSS score (WMD -0.06, 95% CI -0.30 to 0.19; three trials; $I^2=0$).

**Authors' conclusions**
The addition of statins to interferon therapy did not significantly influence disease progression, the relapse risk, or the EDSS scores of patients with relapse-remitting multiple sclerosis.

**CRD commentary**
The review question was clear and the inclusion criteria were sufficiently replicable. Relevant databases were searched and efforts were made to find additional relevant literature. It was unclear whether any language restrictions were applied, so the possibility of language bias is unknown. The small number of included trials limited the investigation of publication bias, but the unavailability of data from two completed trials suggested that it could exist. Efforts were made to reduce the risk of reviewer error and bias for study selection and data extraction. This may have been the case for quality assessment, but the authors did not report whether it was conducted independently. The quality of the trials was assessed using a tool with relevant criteria; the individual scores for each criterion were mixed across the trials.

The trial details were presented and the methods of synthesis seem to have been appropriate for the data. The authors acknowledged that the included trials were of different statin and interferon regimens and had small samples, and two trials had a short follow-up of 12 months or less. The mean disease durations and baseline relapse rates differed across the trials.

The authors' conclusions reflected the evidence presented, but methodological and clinical differences between the trials mean that their reliability is uncertain.

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

**Research:** The authors stated that larger trials, with longer follow-up, were required to provide better evidence on the effects of statins in the treatment of multiple sclerosis.

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