Statins in COPD: a systematic review
Janda S, Park K, FitzGerald JM, Etminan M, Swiston J

CRD summary
The review concluded that statins may have a beneficial effect in the treatment of COPD. This conclusion reflected the results of the review, but should be treated with caution due to a limited number of studies and flawed methodology.

Authors' objectives
To systematically review the effects of statin therapy on outcomes of patients with Chronic Obstructive Pulmonary Disease.

Searching
MEDLINE, Excerpta Medica, PapersFirst and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to December 2008. Search terms were reported. Bibliographies of retrieved articles were handsearched for additional material. Searching was limited to English-language articles.

Study selection
Randomised, double-blind, single-blind, placebo-controlled trials (RCTs), observational cohort (retrospective and prospective), case-controlled studies and population-based analyses of statin therapy in patients with chronic obstructive pulmonary disease (COPD) were eligible for inclusion in the review. Experimental and laboratory based studies were excluded.

Eligible outcomes were: exacerbation episodes or time to exacerbation; intubations; mortality (all cause, COPD or COPD hospital); respiratory related emergency department visits; Decline in FEV₁ (forced expiratory volume) or FVC (forced vital capacity); increase in exercise time on treadmill; C-reactive protein levels or changes; COPD hospitalisation.

COPD was diagnosed according to hospital definitions, Health Maintenance Organisation registry coding, International Classification of Diseases, more than two pulmonary function tests six months apart, FEV₁/FVC ratios, prescription patterns and self reporting. Disease severity varied across studies (37.3 to 77.4 FEV₁ or measured by Global Initiative on Obstructive Lung Disease) or was not reported. Statins used were atorvastatin, simvastatin, pravastatin, not recorded or recorded as other statin. Statins were used alone or in combination. Exposure to statins was between three months and more than one year or not recorded. Comparators for use of statins were no use or placebo.

Two reviewers independently assessed studies for inclusion. Disagreements were resolved by consensus with a third reviewer.

Assessment of study quality
Quality of observational studies was measured according to meta-analysis of observational studies in epidemiology (Stroup et al., 2000), which assessed key design components separately and produced a single aggregate score. Quality of cohort studies was assessed with a scale of four questions about exposure definition, clinical outcome, inclusion criteria and adjustment for confounding variables. Each question scored 0 to 2 and 8 represented maximum score.

The authors did not state how many reviewers assessed validity.

Data extraction
Data for relevant outcomes were extracted. The authors did not state how many reviewers extracted data.

Methods of synthesis
The studies were combined in a narrative synthesis, supported by accompanying data tables.
Results of the review

Nine studies (at least 295,875 participants) were included in the review. One study was a randomised controlled trial (randomisation was concealed, blinding was adequate, few withdrawals occurred and analysis was by intention to treat). Six studies were retrospective: one scored 8 points; four scored 7 points; and one scored 5 points. Two studies were population based and quality was not assessed.

Mortality: Four studies were retrospective and compared statin use to non-use. Two studies found that all-cause mortality was significantly lower in statin users. One study reported that all-cause mortality was reduced in statin users, but did not report significance. One study reported a dose-dependent effect for statins that significantly reduced hospital mortality.

Reduction of COPD exacerbations that resulted in hospitalisation: Three studies were retrospective and compared statin use to non-use. All found a significant reduction in hospitalisation, time to exacerbation or intubations, intubations and FEV\textsubscript{1} or FVC decline.

Exercise time: One randomised controlled trial found a 54% increase in exercise capacity in patients receiving statins compared to placebo.

Results of population analyses were reported.

Authors' conclusions

Statins may have a beneficial role in treatment of COPD. However, most published studies had methodological flaws and prospective interventional trials designed specifically to assess the impact of statins on clinically relevant outcomes were required.

CRD commentary

The review question was clear. Inclusion criteria were broadly defined for participants and interventions and detailed for study design or outcomes. Four databases were searched. The search was limited to English-language articles and relevant studies in other languages may have been missed. It appeared that no attempts were made to locate unpublished trials and some trials may have been missed, leading to publication bias. Appropriate methods were used to reduce reviewer error and bias in study selection; it was unclear whether similar methods were used for validity assessment and data extraction. Validity was assessed using published criteria for observational studies and was discussed for the RCT. Relevant details of included studies were provided. A narrative synthesis was appropriate in view of heterogeneity between the included studies. There was considerable clinical heterogeneity between included trials, particularly with regard to the interventions employed, diagnosis of COPD, disease severity and definitions of exposure. Only one included study was an intervention study specifically designed to address the effect of statins in COPD. The other studies were retrospective observational studies and so subject to confounding and bias. The authors' conclusions reflected the evidence presented, but should be treated with caution due to a limited number of included studies and methodological flaws.

Implications of the review for practice and research

Practice: The authors stated that currently there was insufficient evidence to justify a clinical indication for statins therapy in patients with COPD outside of vascular protection.

Research: The authors stated that further well-designed randomised controlled trials were required to evaluate the effect of statins on outcomes of patients with COPD.

Funding

One author was part funded by the National Sanatorium Association.

Bibliographic details

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.