Statins and fracture risk: a systematic review
Toh S, Hernandez-Diaz S

CRD summary
The authors concluded that current evidence does not support the use of statins to prevent fractures. Although these conclusions appear to be well supported by the evidence presented, they require some caution in interpretation given the uncertainties and weaknesses in the review process, lack of prospective randomised evidence and differences between the primary studies.

Authors' objectives
To investigate the association between statin use and risk of fracture.

Searching
MEDLINE, EMBASE, the Cochrane CENTRAL Register and the Cochrane Database of Systematic Reviews were searched to January 2006; the search terms were reported. The reference lists of retrieved articles and relevant reviews were checked. The search was limited to articles in English.

Study selection
Randomised controlled trials (RCTs) and observational studies of fracture risk in statin users were eligible for inclusion. The primary review outcome was overall fractures. Studies that provided insufficient data for the calculation of effect estimates were excluded.

In the included studies, the mean age of the participants ranged from 59 to 82 years and nearly half of them included only female participants. The statins used were atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin and simvastatin. The majority of studies included only one statin type. The definition and method of ascertaining both statin use and fracture outcomes varied widely. The most commonly studied fracture sites were the hip and spine. The mean or median follow-up time, where stated, varied from 1.9 to 6.5 years. All of the included studies compared fracture rates between statin users and non-users; several studies also compared statin users with other non-statin lipid-lowering drugs.

The included studies used the following study designs (listed in frequency order): case-control, prospective cohort, randomised controlled and retrospective cohort. Fractures were not a pre-specified outcome in the RCTs in the review, so the RCT data were post hoc analyses of fractures reported spontaneously as adverse events. The included studies adjusted for a diverse range of potential confounders (e.g. age, gender, menopausal status, body mass index) by various means (e.g. restricted inclusion criteria, matching, statistical modelling).

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
Odds ratios (ORs), with 95% confidence intervals (CIs), comparing event rates in statin users versus non-users were extracted or calculated. Where multiple adjusted effect estimates were reported, the most adjusted estimate was used. Studies focusing on a specific fracture site were included in the primary analysis. When an estimate for overall fractures was not reported, it was calculated from site-specific data in the study.

Two reviewers independently extracted the data from the included studies. Study authors were not contacted for additional data.

Methods of synthesis
Study findings were combined using both the DerSimonian and Laird random-effects model (main analysis) and a fixed-effect model. The results were stratified by study design. Statistical heterogeneity was assessed using the \( \chi^2 \) statistic and a Galbraith plot. When heterogeneity was detected it was explored using qualitative techniques and meta-regression. Differences between the studies were investigated by sub-grouping studies by fracture site (hip/spine/other), statin used and gender, and by a sensitivity analysis excluding each study individually. Publication bias was assessed visually using Begg's funnel plot and statistically by Egger's asymmetry test, and also by excluding studies with large relative standard errors from the analysis.

**Results of the review**

Fifteen articles describing 18 studies were included (n=522,507): 4 RCTs (n=34,991), 6 prospective (n=119,707) and 2 retrospective (n=125,636) cohort studies, and 6 case-control studies (n=242,173).

Statin users versus non-users (18 studies): there was no statistically significant difference between the groups when the RCTs were pooled, and no significant heterogeneity (OR 1.03, 95% CI: 0.91, 1.16; 4 studies). When cohort studies, case-control studies and all studies were pooled, fracture rates were significantly lower in statin users: OR 0.77 (95% CI: 0.59, 1.00; 8 studies), OR 0.62 (95% CI: 0.45, 0.85; 6 studies) and OR 0.77 (95% CI: 0.66, 0.90; 18 studies), respectively. There was statistically significant heterogeneity for these three analyses (p<0.01).

Statin users versus other lipid-lowering drug users (3 studies): there was no statistically significant difference between the groups (OR 0.96, 95% CI: 0.67, 1.37).

Although Egger's test was not statistically significant for most analyses, Begg's funnel plot suggested possible publication bias. Further investigation suggested that small studies were more likely to be published if they were positive.

The results of subgroup and meta-regression analyses were also reported in the review.

**Authors' conclusions**

Current evidence does not support the use of statins for the prevention of fractures.

**CRD commentary**

The review objective was clear and relevant sources were searched for studies, although the restriction to studies in English means that studies might have been missed. There was no attempt to locate unpublished studies and the authors' analysis into the potential for publication bias suggests that some small studies may have been missed. As the authors noted, they did not search for all statin trials or request fracture data from authors, so it is possible that the RCTs in the review may be a biased subset of RCTs in terms of fractures. Steps were taken to minimise bias and subjectivity in the data extraction by having more than one reviewer make decisions independently. However, it is unclear whether this also applied to the study selection process, and there is no indication that study validity was systematically assessed; these factors make it difficult to determine the reliability of the data presented. Suitable statistical methods were used to combine the studies and to assess and explore statistical heterogeneity and publication bias. Potential sources of heterogeneity and bias were well addressed in the text. In drawing conclusions, the authors appropriately prioritised the better quality evidence while emphasising that even the randomised evidence was suboptimal as it derived from post hoc analyses. Although the authors’ conclusions appear to be well supported by the evidence presented, they require some caution in interpretation given the possibility that some studies were missed, uncertainties about the review process and the reliability of the results, the lack of prospective randomised evidence and heterogeneity among the primary studies.

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

Practice: The authors stated that until more conclusive evidence becomes available, currently approved medications should be used to treat patients at high risk of fracture.

Research: The authors stated that the possible role of statins in preventing fractures should be assessed in RCTs designed to evaluate fracture risk.
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