Meta-analysis of the efficacy of alendronate for the prevention of hip fractures in postmenopausal women

Papapoulos S E, Quandt S A, Liberman U A, Hochberg M C, Thompson D E

CRD summary
This review assessed alendronate for preventing hip fractures in postmenopausal women. The authors concluded that alendronate was associated with reductions in hip fracture rates in women with postmenopausal osteoporosis. The evidence presented in the review appears to support the authors' conclusions, but poor reporting of the review methods means that the reliability of the conclusions is unclear.

Authors' objectives
To evaluate the effects of alendronate for preventing hip fractures in postmenopausal women, and to examine the consistency of effects among different populations.

Searching
MEDLINE, EMBASE and the Cochrane CENTRAL Register were searched using the reported keywords. In addition, the Merck database was searched for unpublished studies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. The duration of the included studies ranged from 1 to 4.5 years.

Specific interventions included in the review
Studies of alendronate were eligible for inclusion. Most of the included studies compared between 5 and 20 mg/day alendronate with placebo; one of the included studies compared alendronate plus calcium with calcium alone.

Participants included in the review
Studies of postmenopausal women with a T-score of -2.0 or less, or with a vertebral fracture, were eligible for inclusion. The majority of the included studies were in women with a T-score of -2.0 or less at the femoral neck or lumbar spine, with and without prevalent vertebral fracture. One study included women with a prevalent vertebral fracture and a T-score of -1.6 or less at the femoral neck. One of the included studies was in women in a long-term care facility. Most of the participants were Caucasian and ages ranged between 39 and 91 years.

Outcomes assessed in the review
Studies that presented sufficient data to permit calculation of the relative risk (RR) of hip fracture were eligible for inclusion.

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. However, they did report on double-blinding and use of intention-to-treat analysis.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data.
extraction. For each study, the number of hip fractures was extracted and the number of hip fractures per 10,000 person-years at risk (PYR) was calculated for each treatment group; the exact number of PYR was estimated where required.

Methods of synthesis

How were the studies combined?
The data were combined in two separate meta-analyses: studies evaluating women with either a T-score of -2.0 or less or a vertebral fracture, and studies evaluating women with a T-score of -2.5 or less or a vertebral fracture. Pooled RRs and relative risk reductions were calculated. Ninety-five per cent confidence intervals (CIs) and levels of statistical significance were calculated using the log likelihood function.

How were differences between studies investigated?
Statistical heterogeneity in the relative risk reduction across studies was assessed and quantified using a Poisson regression analysis. The influence of each study was assessed by repeating the analysis of RR after omitting each study in turn. The influence of the mean age of the participants in individual studies on the absolute risk reduction (ARR) was also examined using simple and weighted (by PYR) regression analysis.

Results of the review

Six RCTs (n=9,023) were included in the review.

Five of the 6 RCTs were double-blinded. All of the studies used intention-to-treat analysis.

For women with either a T-score of -2.0 or less or a vertebral fracture, alendronate was associated with a significant reduction in the risk for hip fracture (RR 0.55, 95% CI: 0.36, 0.84, p=0.007; based on data from 9,023 women). The results were consistent across studies (p=0.898). The RRs were similar after excluding each study in turn.

For women with either a T-score of -2.5 or less or a vertebral fracture, alendronate was associated with a significant reduction in the risk for hip fracture (RR 0.45, 95% CI: 0.28, 0.71, p=0.0008; based on data from 6,804 women). The results were consistent across studies (p=0.981). The RRs were similar after excluding each study in turn.

ARRs ranged from 10 to 65 events per 10,000 PYR for women with either a T-score of -2.0 or less or a vertebral fracture, and from 22 to 76 events per 10,000 PYR for women with either a T-score of -2.5 or less or a vertebral fracture. For both groups of women, there was a trend towards greater ARR with increasing age (p<0.05).

Authors' conclusions
Alendronate was associated with significant and clinically important reductions in the rate of hip fracture in women with postmenopausal osteoporosis. The overall reduction was consistent across different patient populations.

CRD commentary
The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. Several relevant sources were searched but the search strategy was not described in full (dates searched were not reported). Attempts were made to identify unpublished studies but it was unclear whether any language restrictions had been applied, thus the potential for language bias could not be assessed. The methods used to select studies and extract the data were not described, so it is not known whether any efforts were made to reduce reviewer errors and bias. The authors did not report any formal assessment of validity.

Statistical heterogeneity was assessed and the studies appear to have been appropriately combined using meta-analysis. The influence of each study was assessed and a potential cause of heterogeneity among studies for the ARR was examined. The evidence presented in the review appears to support the authors' conclusions, but the lack of reporting of review methods means that the reliability of the conclusions is unclear.

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 of the meta-analysis should not undermine the need for large clinical trials.

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