Prevention of nonvertebral fractures by alendronate: a meta-analysis


Authors' objectives
To evaluate the effect of treatment with alendronate sodium, an aminobisphosphonate, on the incidence of nonvertebral fractures in post-menopausal women with osteoporosis.

Searching
Studies were sought from published data and data on file at Merck Research Laboratories. No search details were provided.

Study selection
Study designs of evaluations included in the review
The studies evaluated were all randomised, prospective double-blind placebo controlled trials of at least two years duration that evaluated the efficacy of treatment with daily oral alendronate.

Specific interventions included in the review
Daily treatment with various doses of at least 2.5 mg oral alendronate for at least two years. All participants received, in addition, 500 mg of calcium carbonate daily during the study. The control group received oral placebo.

Participants included in the review
Women with osteoporosis between the ages of 42 and 85 years who had been menopausal for at least 4 years were included. Women studied had lumbar spine bone mineral density using dual-energy X-ray absorptiometry (DXA) at least 2 or 2.5 standard deviations below the mean for young adult women. All participants were screened for vitamin D deficiency. Women who had a previous fracture were included. Excluded were women with secondary causes of osteoporosis, active gastrointestinal disease, other significant health problems such as cancer or renal or hepatic dysfunction and those receiving current treatment with other osteoporosis therapies.

Outcomes assessed in the review
The main outcome assessed was the number of women with a nonvertebral fracture. The participants were instructed to report all symptomatic fractures which were confirmed either by radiography or, in the case of some fractures, such as ribs or digits, examination by a physician. The other outcomes assessed were bone mineral density and number of women with specific nonvertebral osteoporotic fractures.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The authors do not state that they assessed validity.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction.

Methods of synthesis
How were the studies combined?
Cumulative nonvertebral fracture-free proportions were calculated, using the life table for the pooled populations. The
relative risk (RR) of nonvertebral fracture for those on alendronate versus placebo was computed from the Cox proportional hazards model with study as a stratification factor. Fractures of the wrist and hip were analysed using the Cochran-Mantel-Haenzel method, stratified by study.

How were differences between studies investigated?
Heterogeneity across the studies was assessed by evaluating the interaction of treatment and study in a Cox protocol. The RR across the studies was computed after omitting each study in turn.

Results of the review
Five randomised controlled trials (RCTs; 1,602 women) were included.

Nonvertebral fractures: the RR for nonvertebral fracture for those on alendronate versus placebo was 0.71 (95% CI: 0.502, 0.997, P=0.048). The estimated cumulative incidence of nonvertebral fracture after 3 years was 9.0% in the alendronate group and 12.6% in the placebo group.

For women younger than 65, the nonvertebral fracture rate per 100 patient years was 3.66 in the placebo group and 2.99 in the alendronate group. For women over 65, the nonvertebral fracture rate per 100 patient years was 5.34 in the placebo group and 3.57 in the alendronate group.

Point estimates for RR across studies ranged from 0.61 to 0.76 when any one trial was omitted.

The Cox model including treatment, study and their interaction showed no evidence of heterogeneity (P=0.77).

After 3 years, the risk reduction for fractures of the hip was estimated to be 54% (95% CI: 85% reduction, 36% increase, P=0.15) and the risk reduction for fractures of the wrist was estimated to be 61% (95% CI: 22% reduction, 81% reduction, P=0.006).

Bone mineral density: over 3 years, 10 mg alendronate increased bone mineral density compared to placebo. The bone mineral density increased by the following amounts at the following sites: spine 8.8%, trochanter 7.8%, femoral neck 5.9%. Total body calcium increase by 2.5%.

Treatment with 20 mg daily produced comparable effects, whereas 5 mg daily was only about 70% as effective as 10 mg. 2.5 mg was approximately half as effective as the 5 mg dose.

Authors' conclusions
In post-menopausal women with osteoporosis, treatment with alendronate reduces the risk of nonvertebral fracture over at least three years.

CRD commentary
The authors defined inclusion criteria for primary studies, data were analysed on an intention-to-treat basis, reference was made to the baseline comparability of the treatment groups with regards to fracture risk and previous fracture and the discussion includes mention of some of the limitations of the review, such as the reliance on self-reporting of the main outcome measure used.

Heterogeneity among studies was assessed and the influence of each study on the pooled results assessed. The results are clearly presented with relevant graphical illustrations.

No details are given of the literature search and bias in the selection of studies cannot, therefore, be excluded. The methods used to select articles and to extract the data are not stated. There is no evaluation of the validity of the primary studies. The decision to analyse nonvertebral fractures was taken post hoc and no reasons are given for this. It is unclear why the participants in the studies had investigation of bone density, and hence were included, and such information may have been helpful in assessing the relevant population who may benefit from treatment. It would have been appropriate to include mention of adverse events of treatment and perhaps to include an economic assessment of
the intervention.

In view of the omission of details of the literature search, lack of assessment of the validity of the primary studies and omission of details of the methods used to select articles or extract data, it is not possible to support the conclusions of this review.

**Funding**
Merck Research Laboratories, Rahway, NJ.

**Bibliographic details**

**PubMedID**
9087473

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adult; Aged; Aged, 80 and over; Alendronate /therapeutic use; Bone Density; Female; Fractures, Bone /prevention & control; Humans; Middle Aged; Osteoporosis, Postmenopausal /drug therapy; Proportional Hazards Models; Randomized Controlled Trials as Topic

**AccessionNumber**
11997008299

**Date bibliographic record published**
30/11/1998

**Date abstract record published**
30/11/1998

**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.