Preventing fractures in postmenopausal women with osteoporosis: a review of recent controlled trials of antiresorptive agents

Hochberg M

Authors' objectives
To review and summarise the evidence from randomised controlled trials (RCTs), of the ability of antiresorptive treatments to reduce the risk of fractures in postmenopausal women with osteoporosis.

Searching
A previous systematic review to October 1998 (see Other Publications of Related Interest) was updated by searching MEDLINE and Current Contents from October 1998 to December 1999. The reference lists of retrieved articles and review articles were considered. Conference proceedings published in the Journal of Bone and Mineral Research, Osteoporosis International, Calcified Tissue International, Bone and Arthritis and Rheumatism between January 1998 and December 1999 were searched manually.

Study selection
Study designs of evaluations included in the review
Double-blind RCTs with fracture as a predefined end point were eligible for inclusion. The author also included observational studies for background information, although these were not systematically sought.

Specific interventions included in the review
Studies of antiresorptive treatment were eligible for inclusion in the review. The included studies were of bisphosphonates with or without calcium supplements; oestrogen replacement therapy with or without vitamin D; selective oestrogen receptor modulators (SERMs); calcitonin (50 to 200 IU/day for 2 years); or calcium plus vitamin D, calcium monotherapy and vitamin D monotherapy. All interventions were compared with placebo. The bisphosphonates studied were alendronic acid (5 to 10 mg/day for at least 12 months), risedronic acid (2.5 to 5mg/day for 3 years), etidronic acid (5 mg/day for 2 weeks every 13 weeks for 2 to 3 years), pamidronic acid (dose not stated), tiludronic acid (50 or 200 mg/day for 7 days per month for 2 to 3 years) and clodronic acid (800 mg/day for 3 years). The SERMs studied were raloxifene (60 to 120 mg/day for 3 years with calcium and vitamin D) and tamoxifen (20 mg/day for 4 years).

Participants included in the review
Postmenopausal osteoporosis. Studies of women with postmenopausal osteoporosis were eligible for inclusion. Studies that included both men and women with osteoporosis were included in the review. Studies of patients with glucocorticoid-induced osteoporosis, or that were conducted only in men with osteoporosis, were excluded.

Outcomes assessed in the review
Fracture. To be eligible for inclusion in the review, studies had to count fracture events as the number of patients with at least one new fractures, rather than the total number of new fractures.

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

Assessment of study quality
The author does not report the method used to assess validity, or how the validity assessment was performed. However, he does state that greater consideration was given to larger studies, full-length peer-reviewed publications (rather than conference abstracts), and studies with high patient retention and low drop-out rates.
**Data extraction**
The author does not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

Statistically-significant reductions in fracture incidence from qualified RCTs were taken as evidence of antifracture efficacy; point estimates of the relative risk (RR) were calculated where possible, along with the 95% confidence interval (CI). Data appear to have been extracted in the following categories: study identification, sample size, diagnosis, intervention, control, outcome definition, and results.

**Methods of synthesis**

*How were the studies combined?*
The studies were combined narratively for each intervention. The reports of full-length published studies were reported first, then conference abstracts, then observational studies.

*How were differences between studies investigated?*
Differences between the studies in terms of the participants, interventions and outcomes were mentioned briefly in the text.

**Results of the review**

Thirty-eight RCTs involving more than 57,308 participants (n not reported for some trials) met the inclusion criteria. However, the results of several RCTs that did not meet the inclusion criteria were also reported, as were 5 meta-analyses and 8 observational studies.

Only the results from full publications of RCTs that met the stated inclusion criteria are reported here (except where the interventions were only reported in conference abstracts).

**Bisphosphonates, alendronic acid.**

One trial showed a reduction in the incidence of women with new radiographic or symptomatic vertebral fractures, hip or any symptomatic fracture at 3 years in women who had at least one radiographic vertebral fracture at baseline. In the same trial, alendronic acid was also associated with a reduction in fracture risk in women with low bone mineral density (BMD) or established osteoporosis. Two more RCTs were also reported to show significant reductions in the incidence of women with new radiographic vertebral fractures and in the cumulative incidence of symptomatic nonvertebral fractures. The trials were reported to be of a high quality.

**Bisphosphonates, risedronic acid plus calcium.**

Two large RCTs reported statistically-significant reductions in the risk of radiographic vertebral fractures in women with either 2 or more radiographic vertebral fractures at baseline or one radiographic vertebral fracture and low BMD (T score of less than -2.0).

**Bisphosphonates, etidronic acid.**

Two small trials reported significant reductions in radiographic vertebral fracture incidence during 2 to 3 years’ treatment. A small 4-year RCT of etidronic acid alone and in combination with hormone replacement therapy (HRT) showed no significant reduction in radiographic vertebral fracture risk.

**Bisphosphonates, pamidronic acid.**

One very small RCT (n=48) showed no difference in the incidence of fractures or height loss.

**Bisphosphonates, tiludronic acid plus calcium.**

Four RCTs showed no statistically-significant effect of intermittent cyclical tiludronic acid (50 or 200 mg) on the
incidence of radiographic vertebral fractures, compared with placebo.

Bisphosphonates, clodronic acid.

An interim analysis of 1-year data from a planned 3-year trial showed no statistically-significant difference between clodronic acid and placebo, with regard to the incidence of new radiographic vertebral fractures.

Oestrogen replacement therapy.

One RCT showed no significant reduction in incidence of symptomatic fractures; however, the effect on radiographic vertebral fractures could not be determined. Another RCT found that the incidence of nonspine fracture in the HRT plus vitamin D group was significantly lower than in the placebo group (RR 0.29, 95% CI: 0.10, 0.90). However, approximately one third of the participants dropped out of the HRT groups in this trial; this was three times the rate in the placebo or vitamin D groups. One small RCT showed no significant difference between the groups (RR 0.6, p>0.17). Another small RCT also showed no significant difference between the groups.

SERMs, raloxifene.

One large RCT reported a significant reduction in the incidence of radiographic vertebral fractures with raloxifene in 60 mg (RR 0.7, 95% CI: 0.5, 0.8) and 120 mg doses (RR 0.6, 95% CI: 0.4, 0.7), and in the incidence of clinically diagnosed vertebral fractures (RR 0.4, 95% CI: 0.3, 0.7, both groups pooled). No significant difference between the groups was found in the incidence of women with nonvertebral fractures (RR 0.9, 95% CI: 0.8, 1.1) or hip fractures (RR 1.1, 95% CI: 0.6, 1.9). A much smaller RCT found no significant effect of raloxifene on the incidence of either nonvertebral fractures or radiographic vertebral fractures.

SERMs, tamoxifen.

A large RCT designed to assess the incidence of breast cancer also reported outcomes for hip, wrist and symptomatic vertebral fractures. No significant differences were found.

Calcitonin.

One small trial found a significant reduction in the incidence of both radiographic vertebral fractures and peripheral fractures. However, there were several methodological limitations to this trial.

Calcium plus vitamin D.

One large study reported that calcium (1,200 mg daily) plus vitamin D (800 IU daily) significantly reduced the incidence of hip (RR 0.73, 95% CI: 0.23, 0.99) and nonvertebral fractures (RR 0.72, 95% CI: 0.60, 0.84) in a population with a high prevalence of vitamin D deficiency and a low calcium intake.

Calcium.

One RCT of calcium (1,200 mg/day) found no significant differences from placebo.

Vitamin D.

Two RCTs found no effect of vitamin D on the incidence of hip or nonvertebral fractures. Three small RCTs found no effect of calcitriol on vertebral fracture risk or nonvertebral fractures. Two small trials of alfacalcidol found no significant reductions in fracture risk. A third trial did report a significant reduction in vertebral fracture risk, but the trial was of only 6 months' duration.

**Cost information**

One conference abstract reported that health care utilisation was reduced by approximately 25% among alendronic acid users, compared with placebo recipients, and that the costs associated with hip fracture care were significantly reduced by US$172 per person (averaged over all women, not only those with fractures; year of costing not stated).
Authors' conclusions
Alendronic acid and risedronic acid are the only agents that have demonstrated a consistent reduction in the risk of multiple fractures across trials, including a reduction in the incidence of both radiographic vertebral fractures and nonspine fractures, in postmenopausal women. Raloxifene has demonstrated evidence of a reduction in the risk of both radiographic and clinical vertebral fractures, but not nonvertebral fractures. There was limited evidence of antifracture efficacy for calcium and vitamin D, primarily in a nursing home setting or in elderly individuals with low intakes of these nutrients. Furthermore, since both the placebo and active treatment groups received calcium and vitamin D in most trials, it appears that the other agents provided benefits beyond those of calcium and vitamin D. There was insufficient evidence from RCTs to support the antifracture efficacy of other agents, such as intranasal calcitonin, oestrogen replacement therapy and other bisphosphonates (e.g. etidronic acid), in postmenopausal women. Nevertheless, data from observational studies in this population suggest that oestrogen and etidronic acid may have antifracture efficacy.

CRD commentary
This review presented clear inclusion criteria but did not apply them consistently. It was stated that only RCTs were to be included in the review, but the results from meta-analyses and observational studies were also reported. Further inclusion criteria relating to the definition of study outcomes were stated, but the results of RCTs that did not meet these criteria were then reported (and dismissed). The review only had one author, which could be a further limitation since it suggests that aspects of the review process, such as study selection and data extraction, were not double-checked. The literature search may have been adequate, with attempts to identify grey literature, but there were insufficient detail to be sure. It is also not possible to tell whether language restrictions were applied to the literature search.

Some attempt was made to discuss the validity of the studies in the text, but the results of the validity assessment were not presented systematically. Details of the included studies are hard to find; it would have been better if they had been tabulated. This would also have made it easier to be certain of the number of RCTs included and the number of participants in each. A narrative discussion seems appropriate, but there could probably have been a greater attempt at a 'synthesis'.

Despite the limitations highlighted, the review does give an overview of the topic. However, this may not be comprehensive and the author's conclusions should, therefore, be treated with caution.

Implications of the review for practice and research
The author did not state any implications for research and practice.

Bibliographic details
Hochberg M. Preventing fractures in postmenopausal women with osteoporosis: a review of recent controlled trials of antiresorptive agents. Drugs and Aging 2000; 17(4): 317-330

PubMedID
11087009

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
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.