Anti-hip fracture efficacy of bisphosphonates: a Bayesian analysis of clinical trials

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CRD summary
The authors concluded that bisphosphonates are associated with a reduction in the risk of hip fractures in postmenopausal women with osteoporosis or low bone mineral density. The data appear to support the authors’ conclusions, but it is difficult to assess the reliability of these conclusions given the limited search and lack of an adequate quality assessment of the included studies.

Authors’ objectives
To evaluate the effects of bisphosphonates on the risk of hip fractures in postmenopausal women.

Searching
PubMed and the Cochrane Controlled Trials Register were searched from inception to March 2004 for studies published in English in peer-reviewed journals; the search terms were reported.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with a minimum follow-up of 12 months were eligible for inclusion. The duration of the included studies ranged from 1 to 4.2 years: most lasted 3 years.

Specific interventions included in the review
Studies that compared any bisphosphonate with no bisphosphonate were eligible for inclusion. About half of the included studies evaluated alendronate; other studies evaluated etidronate, risedronate and clodronate (the doses used in the individual studies were reported). In some of the included studies calcium and/or vitamin D were given to all participants.

Participants included in the review
Studies of postmenopausal women were eligible for inclusion. The participants in the included studies either had at least one atraumatic vertebral fracture or low bone mineral density. The mean age of the participants ranged from 63 to 79 years.

Outcomes assessed in the review
Studies that reported the incidence of hip fractures were eligible for inclusion. The primary review outcome was new hip fracture.

How were decisions on the relevance of primary studies made?
Two reviewers selected studies for inclusion in the review. It was not reported whether the study selection process was performed independently.

Assessment of study quality
The authors did not state that they assessed validity. However the level of blinding in each study was reported in the data extraction tables.

Data extraction
Two reviewers independently checked the consistency of the extracted data. Outcome data were extracted into 2x2 tables and used to calculate the relative risk (RR) of hip fracture.
Methods of synthesis
How were the studies combined?
The studies were combined using classical random-effects and Bayesian random-effects meta-analyses; only the results of the Bayesian meta-analysis were presented. Pooled RRs with 95% credibility intervals (CrIs) were calculated. For the Bayesian analysis, the parameter theta (mean of the distribution of log RR) was assigned a prior normal distribution (mean 0, variance 10), while tau-squared (variance of the distribution of log RR) was assumed to be uniformly distributed with parameters (0, 10). These parameters were estimated using the Markov Chain Monte Carlo (MCMC) method. Bayesian analysis using the MCMC method was also used to calculate an absolute risk reduction for studies with a 3-year follow-up.

The potential for publication bias was assessed using a funnel plot and tested statistically using regression analysis (standardised effect size plotted against sample size).

How were differences between studies investigated?
Statistical heterogeneity was assessed using the Cochran Q statistic and the I-squared statistic. Each individual drug that was evaluated in two or more trials was analysed separately. A cumulative meta-analysis was performed to examine changes in the results over time. Three additional Bayesian meta-analyses were conducted using different parameters for between-study variance: uniform distribution with parameters (0, 2) and gamma distributions with parameters (0.1, 0.1) and (3.0, 0.1). The probability of efficacy of bisphosphonates was also calculated for different risk reductions.

Results of the review
Twelve RCTs (n=18,667) were included.

Nine of the studies were double-blind and one additional study was double-blind in its third year.

No statistically significant heterogeneity was detected (Cochran Q, p=0.998; I-squared 0.88%). The regression analysis showed no evidence of publication bias (p=0.116).

The meta-analysis showed that bisphosphonates were associated with a statistically significant reduction in the risk of hip fracture compared with control (RR 0.58, 95% CrI: 0.42, 0.80). Analyses of individual drugs showed no significant difference in hip fracture between individual bisphosphonates and control.

The absolute risk reduction for studies with a 3-year follow-up was 0.0052 (95% CrI: 0.0004, 0.011); this represented a reduction of 52 hip fractures per 10,000 women (95% CrI: 4, 110).

Sensitivity analyses.
For all types of prior distributions examined, the results were statistically significant in favour of bisphosphonates.

After the first three studies were included in the cumulative analysis, the addition of other studies did not influence the results.

Authors' conclusions
Bisphosphonates are associated with a reduction in the risk of hip fractures in postmenopausal women with osteoporosis or low bone mineral density.

CRD commentary
The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. Limiting the search to peer-reviewed reports published in English might have resulted in the omission of other relevant studies, also and raises the possibility of language and publication bias. The reviewers acknowledged the possibility of publication bias but tests showed no evidence of it. Methods were used to minimise reviewer errors and bias in the extraction of data, but it was unclear whether similar steps were taken at the study selection stage (it was not reported if two reviewers independently selected the studies). Although only RCTs were included, validity was not
adequately assessed and so the results from these studies and any synthesis may not be reliable.

Statistical heterogeneity was assessed and the studies were appropriately pooled using meta-analysis. A sensitivity analysis was used to examine the robustness of the results when using different prior distributions. The data appear to support the authors' conclusions, but the limited search and lack of adequate assessment of quality of the included studies meant it was difficult to assess the reliability of these conclusions.

**Implications of the review for practice and research**
The authors did not state any implications for practice or further research.

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