Bisphosphonate use in women and the risk of atrial fibrillation: a systematic review and meta-analysis

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CRD summary
The review concluded that bisphosphonate use was associated with a significant increase in the risk of serious atrial fibrillation in postmenopausal women. The authors’ identified several limitations in their review. Additional concerns with the methods of data analysis mean the conclusions should be viewed with caution.

Authors’ objectives
To determine the risk of atrial fibrillation associated with bisphosphonate therapy.

Searching
EMBASE, PubMed, The Cochrane Library and CINAHL were searched to January 2009 for articles published in English. The related articles feature was used. Search terms were reported. Reference lists of retrieved articles were searched.

Study selection
Studies in participants with osteoporosis or fractures that used bisphosphonates (oral or intravenous) were eligible for inclusion. Studies had to provide data on atrial fibrillation and had to have a clinical follow-up of at least 12 months.

The included trials examined oral alendronate (5mg to 10mg daily), oral risedronate (5mg daily) and intravenous zoledronic acid (5mg once a year), all compared with placebo. The mean age of participants ranged from 69 to 74.5 years. Most participants were women with osteoporosis. Some trials included only postmenopausal women. The included observational studies examined alendronate and etidronate in patients with a mean age of more than 70 years.

The authors did not state how many reviewers were involved in study selection.

Assessment of study quality
Two reviewers independently assessed study quality using criteria developed by the US Preventive Services Task Force. Studies were graded as poor, fair or good quality. Disagreements between reviewers were resolved by discussion and consultation with a third reviewer.

Data extraction
Two reviewers extracted data on atrial fibrillation and used these to calculate relative risks (RRs) and 95% confidence intervals (CIs). Disagreements between reviewers were resolved by discussion and consultation with a third reviewer.

Methods of synthesis
A Mantel-Haenszel fixed-effect meta-analysis was undertaken of randomised controlled trials (RCTs) to calculate pooled relative risks and 95% CIs. Statistical heterogeneity was assessed using the Cochran Q test and I² statistic. Non-RCTs were synthesised narratively.

Results of the review
Four RCTs (26,342 participants) and three observational studies (130,710 participants) were included in the review. The quality of RCT and observational studies were both deemed good. Trials were double-blinded. Trial duration ranged from 22 to 50 months.

The RCTs showed a statistically significantly greater risk of atrial fibrillation with bisphosphonates compared with placebo (RR 1.525, 95% CI 1.166 to 1.997, I² = 53%; four RCTs).

Two out of three observational studies showed a statistically significant increase in the risk of atrial fibrillation with
bisphosphonate therapy. One study showed no difference. There was some evidence that alendronate had a greater risk of atrial fibrillation compared with etidronate (one study).

**Authors' conclusions**
Bisphosphonate use was associated with a significant increase in the risk of serious atrial fibrillation in postmenopausal women.

**CRD commentary**
Inclusion criteria for the review were clearly defined and several relevant data sources were searched. There was potential for language bias, as only articles in English were included. The authors acknowledged potential for publication bias. Attempts were made to reduce reviewer error and bias during data extraction and quality assessment; it was unclear whether the same methods were used for study selection. Quality assessment was undertaken using a standard tool, which indicated that the included studies were good quality, although full results were not presented and this made identifying potential study biases difficult. Trials were pooled using fixed-effect meta-analysis. Statistical heterogeneity was assessed. There was moderate evidence of clinical and statistical heterogeneity and so a random-effects meta-analysis may have been more appropriate. The authors did not present any sensitivity analysis, which made determining the robustness of results difficult. A narrative synthesis of observational data was presented. The authors noted some limitations with the review and urged a degree of caution when interpreting the data.

Limitations of the synthesis mean that the pooled results and conclusions should be interpreted with caution.

**Implications of the review for practice and research**
**Practice:** The authors stated that physicians and patients must carefully weigh the risks and benefits of bisphosphonate therapy before starting treatment, especially when considering zoledronic acid or alendronate. The results may not be applicable to men.

**Research:** The authors stated that future and current trials of bisphosphonate therapy must carefully monitor for atrial fibrillation. A randomised trial to specifically monitor for atrial fibrillation was needed.

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