CRD summary
The review evaluated the risk of atrial fibrillation associated with biphosphonate use in patients with osteoporosis or fractures and provided evidence for a risk of serious atrial fibrillation. In view of some potential limitations arising from the review process and the limited evidence available, the authors’ own reservations about the reliability of the evidence are justified.

Authors' objectives
To evaluate the risk of atrial fibrillation associated with biphosphonate use in patients with osteoporosis or fractures.

Searching
MEDLINE was searched to May 2008 for publications in English. The authors registered with PubMed to receive electronic updates on any new relevant articles. Websites regulatory authorities in USA and Europe, manufacturers' product information sheets and pharmaceutical companies' clinical trial registers were searched for unpublished articles. Bibliographies of each retrieved article were handsearched. Science Citation Index was used to identify cited and citing articles. Search terms were reported.

Study selection
Parallel-group randomised controlled trials (RCTs) of any biphosphonate compared to placebo in patients with either osteoporosis or fractures were eligible for inclusion. Studies needed to be of at least three months duration and provide numerical data on atrial fibrillation adverse events. Case control and prospective or retrospective cohort studies in patients with osteoporosis that reported on the association between biphosphonate exposure and atrial fibrillation were also eligible for inclusion.

Interventions in the included RCTs included zoledronic acid 5mg once a year, alendronate 5 to 10 mg/day and risedronate 5mg/day. Interventions in the included case control studies were mostly alendronate or etidronate. Mean duration of included RCTs ranged from 22 to 50 months. There were both osteoporosis and hip fracture patients in the included RCTs. Most patients were women with postmenopausal osteoporosis (range 76.1% to 100%). Mean age ranged from 69 to 74.5 years. Patients in the included case control studies were women with atrial fibrillation and flutter; both studies used matched population controls without atrial fibrillation.

Primary outcomes were atrial fibrillation adverse events and atrial fibrillation serious adverse effects (defined as life threatening or leading to death, prolongation of hospitalisation or disability, or that required interventions to prevent permanent damage). Secondary outcomes were stroke and cardiovascular mortality in studies that reported on atrial fibrillation.

The authors stated neither how the papers were assessed for validity nor how many reviewers performed the validity assessment. Two independent researchers were involved in the literature search and study selection. Any disagreements were resolved following discussion with a third reviewer.

Assessment of study quality
Criteria used for RCTs included: allocation concealment; blinding of participants and assessors; loss to follow-up; and methods used to detect and confirm adverse events. Criteria used for case control studies were: representativeness of case/controls; comparability of case/controls; ascertainment of exposure or outcomes; and adequacy of follow-up and duration.

The authors did not report how many reviewers performed the validity assessment.

Data extraction
Two reviewers independently extracted data on the number of events for each outcome in order to calculate odds ratios (OR) and 95% confidence intervals (CI). If data were available for more than one period of follow-up, the most recent data were extracted. Authors of articles were contacted for further details of studies when required.

Methods of synthesis
Odds ratios and 95% CIs for RCTs were pooled using a random-effects model. Between-study heterogeneity was determined using the $I^2$ statistic. Sensitivity analyses were planned to explore individual study characteristics if heterogeneity was greater than 60%. A narrative synthesis was performed for the two case-control studies.

Results of the review
Eleven studies were included (n=109,677): nine RCTs (n=26,352), which comprised three individual RCTs and one pooled analysis of six RCTs provided by a pharmaceutical company; and two case control studies (n=83,325). All of the RCTs were double-blind. Allocation concealment was adequate in three RCTs. Loss to follow-up was reported for three RCTs (range 1.9% to 6.7%).

Biphosphonates significantly increased risk of serious adverse events for atrial fibrillation compared to placebo (OR 1.47, 95% CI 1.01 to 2.14; nine RCTs). There was moderate heterogeneity ($I^2=46\%$). The risk was not significant when serious and nonserious events for atrial fibrillation were combined. Biphosphonates did not significantly increase risk of stroke or cardiovascular mortality (three RCTs).

One case-control study found that patients with atrial fibrillation were more likely to have used biphosphonates than control patients (adjusted OR 1.86, 95% CI 1.09 to 3.15, $I^2=46\%$). The second case-control study found no association. Neither study found a greater likelihood of current use of biphosphonates among patients with atrial fibrillation. Adjustments were made for age, hypertension, year of osteoporosis diagnosis and cardiovascular disease.

An additional unpublished pooled analysis of 28 alendronate trials was available from the manufacturers website, but did not report sufficient detail for inclusion in the meta-analysis.

Authors' conclusions
Biphosphonates were associated with serious atrial fibrillation, but heterogeneity of the existing evidence and a paucity of information on some agents precluded any definitive conclusions with respect to risk.

CRD commentary
The review addressed a well-defined question in terms of participants, interventions, study design and relevant outcomes. Relevant databases were searched, but further databases could have been used. Unpublished studies were considered. Publication bias was not assessed. Only publications in English were considered, so some relevant studies may have been missed. Study quality was assessed using suitable criteria and some relevant data were reported. Efforts were made to reduce error and bias; it was unclear whether this process applied to validity assessment. Relevant study details were reported. The statistical method used for meta-analysis of RCTs seemed appropriate, but already combined data were used for six of the nine RCTs in the meta-analysis. Statistical heterogeneity was assessed and there was evidence for heterogeneity with the primary outcome. A sensitivity analysis was carried out. In view of some potential limitations arising from the review process and the limited evidence available, the authors' own reservations about the reliability of the evidence are justified.

Implications of the review for practice and research
Practice: The authors stated that clinicians should consider risk of atrial fibrillation after treatment with biphosphonates in susceptible patients when treating patients with a low risk of fractures and in future report episodes of atrial fibrillation to national pharmacovigilance centres.

Research: The authors identified a need for physicians and future patients in ongoing trials to be vigilant for episodes of atrial fibrillation so that any risk can be identified early.

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