CRD summary
This review concluded that effective treatments for fracture prevention in osteoporosis reduced mortality in older, frailer individuals with osteoporosis who were at high risk of fracture. Weaknesses in the review methods and reporting and interpretation of results mean that these conclusions should be viewed cautiously.

Authors' objectives
To determine whether effective osteoporosis treatment reduced mortality.

Searching
MEDLINE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to September 2008. Search terms were reported. Bibliographies of recent meta-analyses of treatment for osteoporosis and retrieved articles were screened for additional studies. Conference abstracts of American Society for Bone and Mineral Research annual meetings were searched (2000 to 2008).

Study selection
Randomised double-blind placebo-controlled trials of agents with proven vertebral and non-vertebral anti-fracture efficacy at currently approved dosages (alendronate 10mg daily, risedronate 5mg daily, zoledronic acid 5mg annually, teriparatide 20μg daily, strontium ranelate 2g daily, denosumab 60mg six-monthly and clodronate 800mg daily) in patients with osteoporosis were eligible for inclusion. Trials of oestrogen, selective oestrogen receptor modulators, etidronate, ibandronate, pamidronate, calcitonin, calcium, vitamin D and PTH 1–84 were excluded. Included trials had to be conducted in patients with a mean baseline age of more than 50 years over a study duration of more than one year. Included studies had to use intention-to-treat analyses and report more than 10 deaths. Trials in which most participants had a major pathology other than osteoporosis and trials in which participants had secondary osteoporosis (such as glucocorticoid-induced) were excluded.

Most of the included trials were conducted over three years. Primary endpoints were vertebral or non-vertebral fracture, hip fracture and clinical endpoints. All except one of the included studies were carried out in postmenopausal patients with low bone mineral density and/or a history of fractures. Treatments assessed by included studies were alendronate 5mg to 10mg daily (secondary analysis only), risedronate 5mg daily, zoledronic acid 5mg annually, strontium ranelate 2g daily and denosumab 60mg six-monthly

The authors did not state how many reviewers selected studies for inclusion.

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

Data extraction
Mortality rates were extracted from the text of the article. Where these data were not reported, they were sought from company websites, published meta-analyses and the Food and Drug Administration website. These data were used to calculate relative risks (RR) of mortality, with 95% confidence intervals (CIs), in treatment versus control groups.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Pooled estimates of relative risks, with 95% CI, were calculated using either a fixed-effect model (no significant heterogeneity) or a random-effects model (significant heterogeneity $I^2>50\%$) was determined. Meta-regression using the co-variables of age, hip and non-vertebral fracture rate in the placebo group and vertebral and non-vertebral fracture
risk reduction and mortality rate in the placebo group was undertaken to establish whether these markers of frailty and disease severity modified the impact of osteoporosis treatment on mortality. Sensitivity analyses (not specified a priori) were performed.

Between-study heterogeneity was assessed using Cochran’s Q statistic and the $I^2$ statistic.

Publication bias was assessed using Funnel plots and Egger’s regression model.

**Results of the review**

Ten studies (39,549 participants and 1,417 deaths) were included in the review. Two studies used 5mg of alendronate daily for the first two years of the trial and 10mg daily for the remainder; approved dose for treatment of osteoporosis is 10 mg daily, so these studies were included only in secondary analyses.

Osteoporosis treatment was associated with an 11% reduction in mortality (RR 0.89, 95% CI 0.80 to 0.99, p=0.036, $I^2=37\%$; eight studies). When the analysis was restricted to the five studies of bisphosphonates there was no significant reduction in mortality associated with treatment. Sensitivity analyses showed that results were non-significant when the one study conducted after hip fracture (or any one of four other studies) was excluded. Results were similar when random-effects models were used and when the two alendronate studies were included in analyses.

Mortality rate in the placebo group was the only significant variable in the meta-regression (p=0.030). Studies with higher mortality rates (>10 per 1,000 patient years) showed a significant reduction in mortality associated with treatment (RR 0.83, 95%CI 0.72 to 0.94, p=0.0052; four studies). Studies with mortality rates below 10 per 1,000 patient years showed no significant treatment effect.

There was no evidence of publication bias for any of the analyses performed.

**Authors’ conclusions**

Treatments for osteoporosis with established vertebral and non-vertebral fracture efficacy reduced mortality in older, frailer individuals with osteoporosis at high risk of fracture.

**CRD commentary**

The review addressed a clearly stated research question. Appropriate inclusion criteria were defined. The search strategy included sources of unpublished studies (conference proceedings). A formal assessment of publication bias was reported. It was unclear whether any language restrictions were applied to searches. Reporting of the review process was limited and no assessment of the methodological quality of the included studies was reported; potential for error and bias in the review process and the possible effects of weaknesses in the included studies on the results of the review could not be assessed.

The authors’ conclusions appeared strong relative to reported data; regression analyses did not appear to support the conclusion for older, frailer individuals at high risk of fracture. Overall, given the weaknesses in the review methods and reporting and the nature of the results reported, the authors conclusions should be viewed cautiously.

**Implications of the review for practice and research**

**Practice:** The authors stated that the reduction in mortality with effective osteoporosis treatment (when added to the established reduction in morbidity from such treatment) provided another reason for vigorously intervening in frail elderly patients with osteoporosis at high risk of fracture.

**Research:** The authors stated that mortality should be included as a prespecified endpoint in future studies of osteoporosis therapies.

**Funding**

Health Research Council of New Zealand.