# Bisphosphonates for steroid induced osteoporosis (Review)

**Homik J, Cranney A, Shea B, Tugwell P, Wells GA, Adachi J, Suarez-Almazor ME**


This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2010, Issue 7

http://www.thecochranelibrary.com

## TABLE OF CONTENTS

[Intervention Review]

# Bisphosphonates for steroid induced osteoporosis

Joanne Homik[1], Ann Cranney[2], Beverley Shea[3], Peter Tugwell[4], George A Wells[5], Jonathan Adachi[6], Maria E Suarez-Almazor[7]

[1]Deparment of Medicine, University of Alberta, Edmonton, Canada. [2]Division of Rheumatology, Ottawa Hospital, Ottawa, Canada. [3]Institute of Population Health, University of Ottawa, Ottawa, Canada. [4]Centre for Global Health, Institute of Population Health, Department of Medicine, Ottawa Hospital, Ottawa, Canada. [5]Cardiovascular Research Reference Centre, University of Ottawa Heart Institute, Ottawa, Canada. [6]St Joseph's Hospital, Hamilton, Canada. [7]General Internal Medicine, Ambulatory Treatment and Emergency Care, The University of Texas, M.D. Anderson Cancer Center, Houston, Texas, USA

Contact address: Joanne Homik, Deparment of Medicine, University of Alberta, 562 Heritage Medical Research Centre, Edmonton, Alberta, T6G 2S2, Canada. joanne.homik@ualberta.ca.

**Editorial group:** Cochrane Musculoskeletal Group.
**Publication status and date:** Edited (no change to conclusions), published in Issue 7, 2010.
**Review content assessed as up-to-date:** 16 November 1998.

**Citation:** Homik J, Cranney A, Shea B, Tugwell P, Wells GA, Adachi J, Suarez-Almazor ME. Bisphosphonates for steroid induced osteoporosis. *Cochrane Database of Systematic Reviews* 1999, Issue 1. Art. No.: CD001347. DOI: 10.1002/14651858.CD001347.



## ABSTRACT

### Background

Corticosteroids are widely used in inflammatory conditions as an immunosuppressive agent. Diseases treated with corticosteroids include connective tissue diseases, asthma, inflammatory bowel disease and organ transplantation. Bone loss is a serious side effect of this therapy. Several studies have examined the use of bisphosphonates as a treatment for corticosteroid-induced osteoporosis and have reported varying magnitudes of effect. The best estimate of the magnitude of efficacy regarding bisphosphonate prevention of corticosteroid-induced bone loss is needed, before their use is advocated.

### Objectives

To assess the effects of bisphosphonates for the prevention and treatment of corticosteroid-induced osteoporosis.

### Search methods

We searched the Cochrane Musculoskeletal Group trials register, MEDLINE up to 1997 and EMBASE 1988-1997), and selected hand searching of reference lists was conducted. Hand searching of scientific abstracts from relevant meetings for the last five years was also done. An electronic search in Current Contents was done for the last six months. The Cochrane Controlled Trials Register (CCTR) will be searched for future updates.

All languages were included in the search. For practical reasons only those in English were included, but all languages will be retrieved and translated for future updates.

### Selection criteria

All controlled clinical trials (CCTs) dealing with prevention or treatment of corticosteroid-induced osteoporosis with bisphosphonates of any type and reporting the outcomes of interest were assessed. Trials had to involve adults only, and subjects had to be taking a mean steroid dose of 7.5 mg/day or more.

**Data collection and analysis**

All data extraction was performed by two independent reviewers. Outcomes of interest included change in bone mineral density (BMD) at the lumbar spine and femoral neck at six and 12 months. If present, data on number of new fractures and withdrawals due to adverse effects were also extracted. All data extraction was performed by two independent reviewers.

Both continuous and dichotomous data were analyzed using fixed effects models. When significant heterogeneity was present, a random effects model was used.

**Main results**

A total of 13 trials, including 842 patients are included in this meta-analysis. Results are reported as a weighted mean difference of the percent change in BMD between the treatment and placebo groups, with trials being weighted by the inverse of their variance. The 95% confidence intervals (95% CI) are presented. At the lumbar spine, the weighted mean difference of BMD between the treatment and placebo groups was 4.3% (95% CI 2.7, 5.9). At the femoral neck, the weighted mean difference was 2.1% (95%CI 0.01, 3.8). Although there was a 24% reduction in odds of spinal fractures [OR 0.76 (95%CI 0.37, 1.53)], this result was not statistically significant.

**Authors' conclusions**

Bisphosphonates are effective at preventing and treating corticosteroid-induced bone loss at the lumbar spine and femoral neck. Efficacy regarding fracture prevention cannot be concluded from this analysis, although bone density changes are correlated with fracture risk.

## PLAIN LANGUAGE SUMMARY

**Bisphosphonates for treating osteoporosis caused by the use of steroids**

Corticosteroids are widely used to treat inflammation. Bone loss (osteoporosis) is a serious side effect of this therapy. We reviewed a total of 13 trials which included 842 patients. We found that the bone mineral density of the lumbar spine of patients taking bisphosphonate therapy improved 4.3% more than patients who had no treatment. At the femoral neck (top of the thigh bone), the bone mineral density improved 2.1% more in the treatment group. There was no difference in the number of spinal fractures between the the two groups. We found that bisphosphonates are effective at preventing and treating corticosteroid-induced bone loss at the lumbar spine and femoral neck. We do not have enough evidence to say whether or not bisphosphonates prevent fractures.

## BACKGROUND

Corticosteroids are widely used in inflammatory conditions as an immunosuppressive agent. Diseases treated with corticosteroids include connective tissue diseases, asthma, inflammatory bowel disease and organ transplantation. Bone loss is a serious side effect of this therapy. There is some controversy in the literature regarding the dose and duration of corticosteroids required to produce bone loss. Cohort studies have shown that treatment with low dose corticosteroids (<7.5 mg/day) is not associated with clinically significant osteoporosis (Sambrook 1989, Leboff 1991). On the other hand bone loss rates ranging from 0% to 13.9% per year have been reported in patients on >7.5 mg/day prednisone (Montemurro 1990, Nordberg 1993, Als 1985, Pons 1995). Bone loss is likely mediated through a variety of mechanisms. Studies have provided evidence for decreased calcium absorption and increased calcium excretion (Jennings 1991, Gennari 1993), decreased serum concentration of sex hormones (Montecucco 1992), and direct inhibition of bone formation (Dempster 1989) as evidenced by decreased serum osteocalcin levels (Montecucco 1992, Meeran 1995, Prummel 1991).

Patients who develop significant osteoporosis or fractures are treated, but the routine use of prophylactic therapy to prevent bone loss is uncommon. Two studies have examined the prescription rate for osteoporosis therapy in patients who are receiving long term corticosteroids (Peat 1995, Walsh 1996). One study showed a 5.6% prevalence of co-prescription, and another showed a 14% prevalence.

There are several retrospective and prospective cohort studies in the literature regarding the treatment of corticosteroid-induced osteoporosis with bone sparing agents, but these studies are open

to more types of bias than are controlled trials. There are a small number of controlled clinical trials, and those utilizing bisphosphonates have shown some of the best evidence for reducing bone loss. The magnitude of effect, however shows considerable variation across studies. Efficacy, measured as percent change in bone mineral density (BMD) over one year, ranges from -10% to +19% in the bisphosphonate studies. Where studies show such a wide variability of efficacy, techniques such as meta-analysis can be used to pool results, providing a more precise estimate of efficacy. The best estimate of the magnitude of efficacy regarding bisphosphonate prevention of corticosteroid-induced bone loss is needed, before their use is advocated.

# OBJECTIVES

To determine the efficacy of bisphosphonates in the prevention of steroid induced osteoporosis.

# METHODS

## Criteria for considering studies for this review

### Types of studies

Initially all controlled clinical trials were selected for further assessment.

### Types of participants

We chose studies where participants were men and/or women over the age of 18, with underlying inflammatory disorders, initiating treatment or currently being treated with systemic corticosteroids (primary or secondary prevention), and who had not received bisphosphonates in the six months prior to the start of the study. Primary prevention was defined by bisphosphonate treatment starting within three months of initiating corticosteroids. Due to controversy in the literature regarding low dose steroids and the risk of osteoporosis, only those trials where the mean corticosteroid dose was 7.5 mg/day or higher were used.

### Types of interventions

Controlled clinical trials that included any of the first or second generation bisphosphonates, alone or in combination with calcium and/or vitamin D, with the control group taking placebo, alone or in combination with calcium and/or vitamin D were included.

### Types of outcome measures

The primary outcome assessed and required for inclusion in the meta-analysis was percent change in BMD at one year at the lumbar spine or femoral neck. Data regarding number of new vertebral fractures was collected if present.

## Search methods for identification of studies

MEDLINE and EMBASE were used to identify all clinical trials relating to the treatment of osteoporosis. We used the MEDLINE search strategy developed by Dickersin et al at the Baltimore Cochrane Centre (Dickersin 1994) with the addition of the clinical keywords listed in appendix one, and searched the years 1966 to 1997. Similar strategies were developed for searching EMBASE, and the years 1988 to 1997 were included. Clinical keywords used in this database are listed in appendix two. All foreign language journals were included in the search. An electronic search in Current Contents was done for the last six months. The Cochrane Controlled Trials Register will be searched for future updates.
The reference lists of studies included in the meta-analysis were manually searched to add any citations missed by the electronic searches. Abstracts for the last five years from the following scientific meetings were manually checked and included if sufficient information was available in the body of the abstract: American Society for Bone and Mineral Research, American College of Rheumatology, Canadian Rheumatology Association, and the European Symposium on Calcified Tissues. For practice reasons, only studies published in English were included. Other languages will be retrieved and translated for future updates.
APPENDIX 1
1. exp “osteoporosis”/
2. exp “adrenal cortex hormones”/
3. exp “anabolic steroids”/
4. exp “bone density”/
5. exp “anti-inflammatory agents, steroidal”/
6. 1 or 4
7. 2 or 3 or 5
8. 6 and 7
9. exp “diphosphonates”/
10. 9 and 6
11. exp “osteoporosis”/ci
12. 8 or 10 or 11
13. limit 12 to human
14. limit 13 to English language
15. exp osteoporosis/dt
16. exp bone diseases/
17. 16 and 7
18. limit 17 to human
19. limit 18 to English language
20. 14 or 15 or 19
APPENDIX 2
1. exp bone demineralization/

2. exp bone density/
3. exp bone disease/
4. bone demineralization/
5. osteopenia/
6. osteoporosis/
7. postmenopause osteoporosis/
8. posttraumatic osteoporosis/
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. exp corticosteroid/
11. exp antirheumatic agent/
12. antiinflammatory agent/
13. exp antiinflammatory agent/
14. exp nonsteroid antiinflammatory agent/
15. 13 not 14
16. 10 or 11 or 12 or 15
17. exp bisphosphonic acid derivative/
18. 9 and 17
19. 9 and 16
20. exp bone demineralization/si
21. exp osteopenia/si
22. exp bone demineralization/dt
23. 18 or 19 or 20 or 21 or 22

## Data collection and analysis

Selection of trials:
After fulfilling the initial criteria, the following criteria were also met:
Randomized or quasi-randomized (alternate) allocation of patients into treatment groups. We looked for the words "random" and "randomized" in the methods of allocation of the trial.
Blinding of the study participants and or investigators to the treatment. There had to be an adequate description of the intervention medications in terms of dosage schedule and administration.
Adequate documentation of withdrawals and dropouts.
Assessment of methodological quality:
Methodological quality of the trials was assessed by two observers (MSA, JH), using the criteria of Jadad 1996.
Methods used to collect data from included trials:
Data were extracted from the trials by two independent observers (AC, JH). Agreement between the two was assessed using the kappa statistic. In the case of disagreements, the two observers would discuss the issue and attempt to reach a consensus. If necessary, a third observer was used as an adjudicator (BS, MSA).
Data were extracted for the following time points and outcomes:
Time Points:
Six months
Twelve months
Outcomes:
Efficacy:
Percent change in bone mineral density at the lumbar spine and femoral neck
Fracture incidence (if present)
Toxicity:
Number of withdrawals due to side-effects
Methods to synthesize data
Analysis was conducted separately for bone loss at the femoral and lumbar sites, because of the differential effects of corticosteroids on cortical and trabecular bone mass (Rickers 84). Results at six and 12 months were analyzed separately. The outcome measurement of interest was the mean difference in change of BMD and the corresponding standard deviation. That is, the percent change in BMD (treatment group) minus the percent change in BMD (placebo group). When standard error of the mean (SEM) was reported, standard deviation was calculated as standard deviation equals the product of the standardized error of the mean and the square root of n, where n is the number of subjects in the group. Where no error measurement was reported, the standard deviation was estimated using the mean coefficient of variation of the other trials, weighted by the sample size of each study. Where number of patients completing was not reported, the number of patients randomized was used as n. Each trial was weighted taking into account sample size and variance in the outcome variable. The overall treatment effect of the combined trials was calculated as a weighted mean difference between the two treatment groups.
The results for each trial was tested for heterogeneity using the chi square statistic. Effect estimates were analyzed using a fixed effects model. If heterogeneity was present, a random effects model was applied. Pooled analysis for fractures and adverse events (dichotomous variables) was conducted for those trials reporting those outcomes using the Peto odds ratio.

Initially all trials reporting data for an outcome were pooled together. Subsequently, sensitivity analyses or subgroup analysis were performed for: a) heterogeneity, excluding those trials with methodological differences; b) primary vs. secondary prevention trials; c) quality, using the median quality score of two as a cut off value defining higher and lower quality trials; and d) BMD measurement method, excluding studies that did not use DEXA.

# RESULTS

## Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.
After review of the abstracts in the search, a total of 26 controlled studies were found assessing the treatment of corticosteroid induced osteoporosis with a bisphosphonate. Some were retrospective analyses and were excluded. The reason for the exclusion of 13 of the studies are outlined in the table of excluded studies. The

13 remaining controlled clinical trials reported data on 842 participants. Two of the included trials, presented in abstract form, did not report the mean dose of prednisone in the study groups (Worth 94, Jenkins 97), but were still included. Another two only reported two year data (Pitt 97, Eastell 96), and these studies were included in an analysis of all trials along with a study reporting only six month data (Worth 94). Two trials reported two treatment groups (same drug, different dose), as well as the control group, and the treatment arm representing the most frequently used dosage regimen in clinical practice was used.

Most trials used etidronate, administered in a cyclic fashion. There was one trial each that used daily etidronate, oral risedronate, oral alendronate and one using daily oral pamidronate. Eight out of 13 studies used dual energy xray absorptiometry (DEXA), one used dual photon absorptiometry (Worth 94), one used quantitative computed tomography (QCT) (Reid 88) and three did not specify the method used to measure BMD. Six studies involved primary prevention of osteoporosis and seven with secondary prevention or a mixed group. In one study the control but not the treatment group received vitamin D supplementation (VanCleemput 96).

All 13 trials reported data on bone loss at the lumbar spine, while only eight reported changes at the femoral neck. Twelve studies reported a significant improvement in lumbar BMD in the treatment group as compared to controls, while one study, performed in cardiac transplant patients, showed continued bone loss in the bisphosphonate group (VanCleemput 96), even over the control group. Four studies reported a significant improvement over controls in femoral neck BMD, while the other four reported no significant difference between the two groups.

Four studies reported on the incidence of new vertebral fractures. These were mostly defined radiologically by an increase in vertebral deformity. One trial that was presented in abstract form, referred to new vertebral fractures reported (Roux 97). It is unclear whether this refers to symptomatic fractures. One study found an increased number of new fractures in the treatment group (VanCleemput 96), and three found a decreased number (Worth 94, Adachi 97, Roux 97).

## Risk of bias in included studies

The agreement between the two investigators regarding the methodological quality of the trials was substantial, as indicated by a kappa statistic of 0.73 (Sackett 1991). Where scores differed, the average was used. Scores ranged from one to four with eight trials scoring equal or higher than the median rating of two, and five scoring lower than average. Six of the 13 trials were double blinded studies. Nine studies were randomized, three used alternate allocation and one abstract did not specify the method of patient allocation.

## Effects of interventions

Pooled analysis for lumbar and femoral neck BMD:

Results for lumbar spine and femoral neck at six and 12 months were analyzed separately. The analysis of all trials reporting BMD at the lumbar spine after 12 months of therapy showed statistically significant heterogeneity. A random effects model was used, which resulted in a weighted mean difference of 4.3%(95% CI 2.7, 5.9). That is, on average, the treatment and placebo groups had a percent change in bone density that differed by four percentage points. Analysis of trials reporting lumbar BMD at six months resulted in a weighted mean difference of 3.4%(95% CI 1.1, 5.8).

Results at the femoral neck for all trials reporting data at twelve months just reached statistical significance. The weighted mean difference was 2.1%(95% CI 0.01, 4.3). The data for change in BMD at six months resulted in a non significant weighted mean difference of 0.6 (95% CI -10.4, 11.7).

Sensitivity analysis for heterogeneity:

Sensitivity analyses were performed excluding those trials that were methodologically different from the rest and were felt to contribute to the majority of the heterogeneity in the analysis. These included the trial involving cardiac transplant patients (VanCleemput 96), the trial where QCT measurements were used (Reid 88), and the trial where extremely osteoporotic patients were enrolled [Struy 95]. For the twelve month analysis at the lumbar spine, this resulted in a weighted mean difference of 4.2% (95%CI 3.1, 5.3). For the six month analysis, the resulting weighted mean difference was 4.7% (95%CI 2.6, 6.7). Analysis of the twelve month femoral neck data were re-analyzed excluding the same heterogeneous trials, resulting in a weighted mean difference of 1.1% (95%CI 0.02, 2.1). In the six month analysis, there were only two studies ( Struys 95, VanCleemput 96), both of which were excluded in the sensitivity analysis.

Sensitivity analysis for primary vs. secondary prevention:

Sensitivity analysis was also used to compare primary versus secondary prevention in trials reporting data on lumbar spine at 12 months. Excluding the heterogeneous trials as before, the primary prevention trials showed a weighted mean difference of 4.4% (95%CI 3.0, 5.8). The secondary prevention trials had a weighted mean difference of 3.2% (95%CI 2.0, 4.5).

Sensitivity analysis for methodologic quality, BMD technique and study duration:

A sensitivity analysis comparing those trials with higher median vs. lower median methodologic quality was performed for change in lumbar BMD at 12 months. There were only two trials in the high quality subgroup, one of which was the trial utilizing QCT to measure BMD, and the analysis resulted in a skewed estimate. An analysis was performed, pooling the 12 month data at the lumbar spine, excluding those studies that did not utilize DEXA to measure BMD. Of the eight trials using DEXA, one was excluded as it only reported two year data (Eastell 96), and another two were excluded for methodological differences (Struys 95, VanCleemput 96). The remaining trials (Adachi 97, Jenkins 97, Mulder 94,

Skingle 94, Wolfhagen 97) resulted in a weighted mean difference of 4.8 (95%CI 3.7, 6.0).
In another analysis of lumbar BMD, all trials were pooled, including two studies reporting two year data (Pitt 97, Eastell 96) and one study only reporting 6 month data (Worth 94), with the one year trials. This resulted in a weighted mean difference of 4.2%(95%CI 3.0, 5.4), using a random effects model.

Pooled analysis for fractures and adverse effects:
Four studies reported the number of participants with new vertebral fractures. Symptomatic and asymptomatic fractures were combined. The resulting odds ratio for the risk of new fracture in the control group did not reach statistical significance: 0.76 (95%CI 0.37, 1.53).
Six studies reported withdrawals due to adverse effects. Half found an increased number of withdrawals in the treatment group, and half reported no dropouts in either group due to adverse effects. Not all adverse effects were listed, but in those trials that did have information, the major adverse effect was nausea. Odds ratio for withdrawals for side effects could not be accurately estimated due to the three trials reporting no dropouts in either group.
We analyzed the results of only controlled clinical trials. We included studies that were only single blinded (in all cases outcome assessor was blinded), because BMD is an objective measure, measured and calculated by machine, and we felt it unlikely that there would be bias in the measurement on the basis of inadequate blinding. We also included studies that used alternate allocation instead of random allocation. Other investigators have found that non randomized clinical trials can overestimate the magnitude of effect by up to 40% (Schulz 1995). A sensitivity analysis comparing randomized vs. non randomized studies of lumbar BMD resulted in estimates of 4.0%(95%CI 2.9, 5.2) and 3.5%(95%CI 1.5, 5.6) respectively. Excluding the three heterogeneous trials from the above analyses, the point estimates were 3.8% and 4.6%. As the non randomized studies underestimated the effect size in this analysis, we felt it unnecessary to exclude them.

## DISCUSSION

This meta-analysis was performed to evaluate the efficacy of bisphosphonates in corticosteroid-induced osteoporosis. Bisphosphonates have been used successfully in post-menopausal osteoporosis (Storm 1990, Storm 1990), but the mechanisms of bone loss are sufficiently different in corticosteroid-induced osteoporosis to require independent review of their efficacy.

Osteopenia and osteoporosis are defined by the number of standard deviations a person's bone mass differs from sex matched peak bone mass (T score). Reference values for bone mass at the lumbar spine in females, show that a 10% decrease in BMD constitutes a fall by one standard deviation (Hologic Inc., Waltham, Massachusetts, USA). The results of this analysis showed a statistically significant improvement in lumbar BMD in the subjects treated with bisphosphonates, over the control group, with a weighted mean difference of approximately 4%. Interventions that bring about a 4% change in bone density would likely have a significant impact on the T score. In studies of fracture prognosis, a BMD decrease of one standard deviation has been shown to carry a statistically significant increased fracture risk (Marshall 1996).

We were interested in analyzing the primary and secondary prevention trials separately as the two clinical scenarios are distinct. The response to therapy appears to be greater in the primary prevention as compared to secondary prevention trials. In general, the primary prevention trials showed greater bone loss in the placebo arm, with maintenance or small amounts of bone accrual in the treatment arm. In contrast, the secondary prevention trials showed a greater degree of accrual in the treatment arm, with less dramatic bone loss in the placebo arm. This supports the belief that bone loss is more prominent in the early stages of corticosteroid therapy, with a slower rate of loss as therapy continues.

The trials included in this analysis were heterogeneous. Three trials contributed significantly to the chi squared statistic for heterogeneity and were excluded in sensitivity analyses. The study which showed continued rapid bone loss in the treatment group, used a unique study population, (cardiac transplant recipients), in whom other factors may contribute to bone loss [Vancleemput 96]. Several cohort studies have reported high rates of bone loss in the first year after organ transplantation (Thiebaud 1996, Sambrook 1994, McDonald 1991, Julian 1991). Bone loss was related to length of hospital stay in one study, prompting the authors to conclude that immobility may be a contributing factor (Julian 1991). Cyclosporin A, which is routinely used in all transplant recipients, has been shown to increase bone resorption in animal models (Movsowitz 1988), and likely contributes to the excessive bone loss seen in this population. This trial also treated the control group but not the treatment group with vitamin D, which may be another source of its different results. Another trial included in the meta-analysis reported a large percentage of bone accrual in the treatment group compared to other trials (Reid 88). This study is the only one to use quantitative computed tomography to measure bone density in the lumbar spine, which tends to isolate trabecular bone, and may account for the more dramatic results seen. This is also the only study that used pamidronate, and it is possible that this bisphosphonate has greater efficacy than etidronate (used in 9 of the 11 studies), although this cannot be concluded from this analysis. The third study (Struys 95) also reported a moderately high degree of bone accrual, and due to the weight assigned, it figured importantly in the heterogeneity calculations. This study population was very osteoporotic at baseline (T score=-3.75), as compared to all the other trials (T score -1 to -2), and it may be that this population responds more vigorously to treatment, ex-

plaining the magnitude of the effect size. The remaining studies all reported a moderate degree of positive change, and a test of heterogeneity for this subset just fell short of statistical significance. Excluding these studies did not change the magnitude of effect size for changes at the lumbar spine, and the significance of the result remained.

There was a statistically significant difference in femoral neck BMD between the treatment and placebo groups, although the effect size was small (2.1%). If corticosteroids had a minimal osteopenic effect at this site, one would not expect to see as much of a treatment effect. Data from the placebo arms of the trials, however, show a similar magnitude of bone loss at both lumbar and femoral neck. Heterogeneity in this series was prominent and most studies reported bone loss in the treatment groups. After excluding the two heterogeneous trials, the effect size was smaller (1.4%) although still statistically significant. It is generally believed that corticosteroid-induced bone loss is not as prominent in cortical bone [Rickers 84], and efficacy of bisphosphonates is not as dramatic at this site.

We included two studies which had two active treatment groups (same intervention, different dosage). The results of both trials suggest that the higher dosage is more efficacious. Both results were included in the analysis as two separate studies, and this difference in efficacy also contributed to the heterogeneity among trials.

We looked at both fixed and random effects models. Both models often resulted in similar pooled estimate, with the random effects model giving a larger confidence interval. The random effects model is sometimes used when heterogeneity exists, in order to provide a more conservative estimate of effect. All results are reported with the random effects model to reflect our concern with heterogeneity.

It is important to evaluate the effects of these drugs on fracture prevention in these patients. Unfortunately, only four studies reported fracture data, and the result was inconclusive. Since fractures occur at a variable length of time after the onset of osteoporosis, it is not surprising that clinical trials of one year duration are unable to show significant differences between treatment groups. Longer follow-up is required to ascertain the efficacy of bisphosphonates in fracture prevention. A recent meta-analysis of fracture risk for various levels of BMD has shown an increased risk (odds ratio 1.5) for fractures at all sites with a BMD that is only one standard deviation below peak bone mass [Marshall 96]. In the absence of fracture outcome data in most clinical trials of osteoporosis, the intermediate outcome of BMD gives fair information regarding fracture risk. It should be noted that the correlation between BMD and fracture risk has been established in post-menopausal osteoporosis and not corticosteroid-induced osteoporosis. Studies of bone resorbing agents that are able to achieve the results presented here would be expected to have an impact on vertebral fracture prevention.

One issue that is not addressed by any of the studies is the possible physiologic increase in BMD that may occur after cessation of corticosteroid therapy. Cohort studies in patients with Cushing's disease suggest that bone metabolism may return to normal after treatment of corticosteroid excess (Lufkin 1988). A randomized controlled trial of adjunct prednisone therapy in 40 rheumatoid arthritis patients showed that after discontinuation of prednisone at six months, there was bone accrual at a rate of 5.3% in the following six months (Laan 1993). A case series of six corticosteroid treated sarcoid patients reported that bone loss reversed after exogenous steroids were discontinued (Rizzato 1993). One must consider, however, that patients experience significant bone loss and increased risk of fractures while on corticosteroid therapy even if their condition improves following discontinuation of corticosteroids. The above three studies do suggest, however, that anti-resorptive therapy does not need to be continued beyond the duration of corticosteroid therapy.

# AUTHORS' CONCLUSIONS

## Implications for practice

Bisphosphonates appear to be efficacious at preventing and treating corticosteroid-induced bone mineral loss at the lumbar spine. There is a statistically significant treatment effect of bisphosphonates on femoral BMD, although the magnitude is smaller than that seen at the lumbar spine. At this time long term effects regarding efficacy beyond one year, or efficacy against spinal fractures cannot be adequately established, except by extrapolation.

Despite these cautions, bisphosphonates remain a promising therapy for preventing the significant osteoporosis associated with corticosteroid use. The data suggests that primary prevention is more efficacious than secondary prevention.

## Implications for research

Efficacy of bisphosphonates in the primary and secondary prevention of corticosteroid-induced osteoporosis is well established. More research needs to be conducted into prevention of corticosteroid-induced osteoporosis in organ transplant recipients.

Recommendations regarding the routine use of these medications in patients on corticosteroids requires further research to answer questions regarding cost-effectiveness.

# ACKNOWLEDGEMENTS

The authors would like to thank David Henry, Vivian Welch, Norma Davies and Jim Davies for their time and effort in reviewing this document.

# REFERENCES

## References to studies included in this review


**Adachi 97** *{published data only}*

Adachi JD, Bensen WG, Brown J, Hanley D, Hodsman A, Josse R, Kendler DL, Lentle B, Olszynski W, Ste-. -Marie L, Tenenhouse A, Chines AA. Intermittent etidronate therapy to prevent corticosteroid-induced osteoporosis. *N Engl J Med* 1997;**337**:382–7.

**Eastell 96** *{published data only}*

Eastell R, Devogelaer JP, Peel NFA, Gill C, Bax DE, Nagant de Deuxchaisnes C, Russell RGG. A double-blind placebo-controlled study to determine the effects of risedonate on bone loss in glucocorticoid-treated rheumatoid arthritis patients. *J Bone Miner Res* 1996;**11**:1812.

**Jenkins 97** *{published data only}*

Jenkins EA, Walker-Bone KE, Wood A, McCrae FC, Cooper C, Cawley MID. The prevention of corticosteroid induced osteoporosis with intermittent cyclical etidronate. *Bone* 1997;**20**(Suppl 4):103S.

**Mulder 94** *{published data only}*

Mulder H, Struys A. Intermittent cyclical etidronate in the prevention of corticosteroid-induced bone loss. *Br J Rheumatol* 1994;**33**(4):348–50.

**Pitt 97** *{published data only}*

Pitt P, Li F, Bloom B, Todd P, Pack S, Hughes G, Moniz C. A double-blind placebo controlled study to determine the effects of intermittent cyclical etidronate on bone mineral density in patients on long term corticosteroid treatment. *Bone* 1997;**20**(Suppl 4):100S.

**Reid 88** *{published data only}*

Reid IR, King AR, Alexander CJ, Ibbertson HK. Prevention of steroid-induced osteoporosis with (3-amino-1-hydroxypropylidene)-1,1-bisphosphonate (APD). *Lancet* 1988;**1**(8578):143–6.

**Roux 97** *{published data only}*

Roux C. , Oriente P, Laan R, Hughes RA, Ittner J, Kaufman JM, Di Munno O, Pouilles JM, Horlait S, Cortet B. Etidronate in the prevention of corticosteroid induced bone loss: A randomized placebo-controlled prospective study. *J Bone Min Res* 1997;**12**(Supp1):S509.

**Saag 97** *{published data only}*

Saag K, Emkey R, Gruber B, Tesser J, Lane N, Yanover M, Dubois C, Freedholm D, Carofano W, Daifotis A. Alendronate for the management of glucocorticoid-induced osteoporosis: results of the multicenter U.S. study. *Arthritis Rheum* 1997;**40**(supp):S136.

**Skingle 94** *{published data only}*

Skingle SJ, Crisp AJ. Increased bone density in patients on steroids with etidronate. *Lancet* 1994;**344**(8921):543–4.

**Struys 95** *{published data only}*

Struys A, Snelder AA, Mulder H. Cyclical etidronate reverses bone loss of the spine and proximal femur in patients with established corticosteroid-induced osteoporosis. *Am J Med* 1995;**99**(3):235–42.

**VanCleemput 96** *{published data only}*

Van Cleemput J, Daenen W, Geusens P, Dequeker P, Van De Werf F, VanHaecke J. Prevention of bone loss in cardiac transplant recipients. A comparison of biphosphonates and vitamin D. *Transplantation* 1996;**61**(10):1495–9.

**Wolfhagen 97** *{published data only}*

Wolfhagen F, van Buuren H, den Ouden J, Hop W, van Leeuwen J, Schalm S, Pols H. Cyclical etidronate in the prevention of bone loss in corticosteroid-treated primary biliary cirrhosis. *J Hepatol* 1997;**26**:325–30.

**Worth 94** *{published data only}*

Worth H, Stammen D, Keck E. Therapy of steroid-induced bone loss in adult asthmatics with calcium, vitamin D, and a diphosphonate. *Am J Resp & Crit Care Med* 1994;**150**(2): 394–7.


## References to studies excluded from this review


**Adachi 94** *{published data only}*

Adachi J, Cranney A, Goldsmith CH, Bensen WG, Bianchi F, Cividino A, Craig GL, Kaminska E, Sebaldt RJ, Papaioannou A, et al.Intermittent cyclic therapy with etidronate in the prevention of corticosteroid induced bone loss. *J Rheumatol* 199 4;**21**(10):1922–6.

**Boutsen 97** *{published data only}*

Boutsen Y, Jamart J, Esselinckx W, Stoffel M, Devogelaer J-P. Primary prevention of glucocorticoid-induced osteoporosis with intermittent intravenous pamidronate: a randomized trial. *Calcif Tissue Int* 1997;**61**:266–71.

Boutsen Y, Jamart J, Esselinckx W, Stoffel M, Devogelaer J-P. Primary prevention of glucocorticoid-induced osteoporosis with intermittent intravenous pamidronate: a randomized trial. *Calcif Tissue Int* 1997;61:a randomized trial. Calcif Tissue Int 1997;61;266-271.

**Braun 83** *{published data only}*

Braun JJ, Birkenhager-Frenkel DH, Rietveld AH, Juttmann JR, Visser TJ, Birkenhager JC. Influence of 1 alpha-(OH)D3 administration on bone and bone mineral metabolism in patients on chronic glucocorticoid treatment; a double blind controlled study. *Clinical Endocrinology* 1983;**19**(2):265–73.

**Condon 78** *{published data only}*

Condon JR, Nassim JR, Dent CE, Hilb A, Stainthorpe EM. Possible prevention and treatment of steroid-induced osteoporosis. *Postgrad Med J* 1978;**54**(630):249–52.

**Diamond 95** *{published data only}*

Diamond T, McGuigan L, Barbagallo S, Bryant C. Cyclical etidronate plus ergocalciferol prevents glucocorticoid-induced bone loss in postmenopausal women. *Am J Med* 1995;**98**(5):459–63.

**Eggelmeijer 96** *{published data only}*

Eggelmeijer F, Papapoulos SE, van Paassen HC, Dijkmans BA, Valkema R, Westedt ML, Landman JO, Pauwels EK, Breedveld FC. Increased bone mass with pamidronate

treatment in rheumatoid arthritis. Results of a three-year randomized, double-blind trial. *Art hritis & Rheum* 1996; **39**(3):396–402.

**Gallacher 92** ***{published data only}***

Gallacher SJ, Fenner JA, Anderson K, Bryden FM, Banham SW, Logue FC, Cowan RA, Boyle IT. Intravenous pamidronate in the treatment of osteoporosis associated with corticosteroid dependent lung disease: an open pilot study. *Thorax* 1992;**47**(11):932–6.

**Geusens 97** ***{published data only}***

Geusens P, Vanhoof J, Stalmans R, Joly J, Dequeker J, Nijs J, Raus J. Cyclic etidronate increases bone density in the spine and hip in postmenopausal women on chronic corticosteroid treatment. A double-blind controlled study. *Bone* 1997;**20**(Supp 4):9S.

**Gonelli 97** ***{published data only}***

Gonnelli S, Rottoli P, Cepollaro C, Pondrelli C, Cappiello V, Vagliasindi M, Gennari C. Prevention of corticosteroid-induced osteoporosis with alendronate in sarcoid patients. *Calcif Tissue Int* 1997;**61**:382–85.

**Krieg 96** ***{published data only}***

Krieg MA, Thiébaud D, Gillard-berguer D, Goy JJ, Burckhardt P. Intermittent intervenous pamidronate prevents the dramatic bone loss after heart transplantation. *J Bone Miner Res* 1996;**11**:S345.

**Reid 90** ***{published data only}***

Reid IR, Schooler BA, Stewart AW. Prevention of glucocorticoid-induced osteoporosis. *J Bone & Min Res* 1990;**5**(6):619–23.

**Reid letter 88** ***{published data only}***

Reid IR, Heap SW, King AR, Ibbertson HK. Two-year follow-up of biphosphonate (APD) treatment in steroid osteoporosis. *Lancet* 1988;**2**(8620):1144.

**Sebaldt 96** ***{published data only}***

Sebaldt RJ, Adachi JD, Bensen WG, Bianchi F, Cividano A, Craig GL, Cranney A, Kaminska E, Gordon M, Steele M, et al.Intermittent cyclic therapy with etidronate prevents corticosteroid-induced bone loss: two years of follow-up. *Scand J Rheumatol* 1996;**103**(Suppl):91–3.

## References to studies awaiting assessment

**Roux** ***{published data only}***

**Saag** ***{published data only}***

## Additional references

**Als 1985**

Als OS, Gotfredsen A, Christiansen C. The effect of glucocorticoids on bone mass in rheumatoid arthritis patients. Influence of menopausal state. *Arthritis Rheum* 1985;**28**:369–75.

**Black 1996**

Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, Bauer DC, Genant HK, Haskell WL, Marcus R, Ott SM, Torner JC, Quandt SA, Reiss TF, Ensrud KE. Randomized trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. *Lancet* 1996;**348**:1535–41.

**Dempster 1989**

Dempster DW. Bone histomorphometry in glucocorticoid-induced osteoporosis. *J Bone Min Res* 1989;**4**:137–41.

**Diamond 1995**

Diamond T, McGuigan L, Barbagallo S, Bryant C. Cyclical etidronate plus ergocalciferol prevents glucocorticoid-induced bone loss in postmenopausal women. *Am J Med* 1995;**98**:459–63.

**Dickersin 1994**

Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. *BMJ* 1994;**309**:1286–91.

**Gallacher 1992**

Gallacher SJ, Fenner JA, Anderson K, Bryden FM, Banham SW, Logue FC, Cowan RA, Boyle IT. Intravenous pamidronate in the treatment of osteoporosis associated with corticosteroid dependent lung disease: an open pilot study. *Thorax* 1992;**47**:932–6.

**Gennari 1993**

Gennari C. Differential effect of glucocorticoids on calcium absorption and bone mass. *Br J Rheumatol* 1993;**32**(Suppl 2):11–4.

**Jadad 1996**

Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary?. *Control Clin Trials* 1996;**17**:1–12.

**Jennings 1991**

Jennings BH, Andersson KE, Johansson SA. The assessment of the systemic effects of inhaled glucocorticosteroids. The effects of inhaled budesonide vs oral prednisolone on calcium metabolism. *Eur J Clin Pharmacol* 1991;**41**:11–6.

**Julian 1991**

Julian BA, Laskow DA, Dubovsky J, Dubovsky EV, Curtis JJ, Quarles LD. Rapid loss of vertebral mineral density after renal transplantation. *N Engl J Med* 1991;**325**:544–50.

**Laan 1993**

Laan RF, van Riel PL, van de Putte LB, van Erning LJ, van't Hof MA, Lemmens JA. Low-dose prednisone induces rapid reversible axial bone loss in patients with rheumatoid arthritis. A randomized, controlled study. *Ann Intern Med* 1993;**119**:963–8.

**Leboff 1991**

LeBoff MS, Wade JP, Mackowiak S, El-Haji Fuleihan G, Zangari M, Liang, MH. Low dose prednisone does not affect calcium homeostasis or bone density in postmenopausal women with rheumatoid arthritis. *J Rheumatol* 1991;**18**: 339–44.

**Lufkin 1988**

Lufkin EG, Wahner HW, Bergstralh EJ. Reversibility of steroid-induced osteoporosis. *Am J Med* 1988;**85**:887–8.

**Marshall 1996**
Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *BMJ* 1996;**312**:1254–9.

**McDonald 1991**
McDonald JA, Dunstan CR, Dilworth P, Sherbon K, Sheil AGR, Evans RA, McCaughan GW. Bone loss after liver transplantation. *Hepatology* 1991;**14**:613–9.

**Meeran 1995**
Meeran K, Hattersley A, Burrin J, Shiner R, Ibbertson K. Oral and inhaled corticosteroids reduce bone formation as shown by plasma osteocalcin levels. *Am J Respir Crit Care Med* 1995;**151**:333–6.

**Montecucco 1992**
Montecucco C, Caporali R, Caprotti P, Caprotti M, Notario A. Sex hormones and bone metabolism in postmenopausal rheumatoid arthritis treated with two different glucocorticoids. *J Rheumatol* 1992;**19**:1895–900.

**Montemurro 1990**
Montemurro L, Fraioli P, Riboldi A, Delpiano S, Zanni D, Rizzato G. Bone loss in prednisone treated sarcoidosis: a two-year follow-up. *Ann Ital Med Int* 1990;**5**:164–8.

**Movsowitz 1988**
Movsowitz C, Epstein S, Fallon M, Ismail F, Thomas S. Cyclosporin-A in vivo produces severe osteopenia in the rat: effect of dose and duration of administration. *Endocrinology* 1988;**123**:2571–7.

**Nordberg 1993**
Nordborg E, Hansson T, Jonson R, Szucs J, Bengtsson BA. Bone mineral content of the third lumbar vertebra during 18 months of prednisolone treatment for giant cell arteritis. *Clin Rheumatol* 1993;**12**:455–60.

**Peat 1995**
Peat ID, Healy S, Reid DM, Ralston SH. Steroid induced osteoporosis: An opportunity for prevention?. *Ann Rheum Dis* 1995;**54**:66–8.

**Pons 1995**
Pons F, Peris P, Guanabens N, Font J, Huguet M, Espinosa G, Ingelmo, M, Munoz-Gomez J, Setoain J. The effect of systemic lupus erythematosus and long-term steroid therapy on bone mass in pre-menopausal women. *Br J Rheumatol* 1995;**34**:742–6.

**Prummel 1991**
Prummel MF, Wiersinga WM, Lips P, Sanders GT, Sauerwein HP. The course of biochemical parameters of bone turnover during treatment with corticosteroids. *J Clin Endocrinol Metab* 1991;**72**:382–6.

**Rickers 1984**
Rickers H, Deding A, Christiansen C, Rodbro P. Mineral loss in cortical and trabecular bone during high-dose prednisone treatment. *Calcified Tissue Int* 1984;**36**(3): 269–73.

**Rizzato 1993**
Rizzato G, Montemurro L. Reversibility of exogenous corticosteroid-induced bone loss. *Eur Respir J* 1993;**6**: 116–9.

**Sackett 1991**
Sackett D, Haynes R, Guyatt G, Tugwell P. Clinical Epidemiology: A Basic Science for Clinical Medicine. (2nd ed. **1991**:19–49.

**Sambrook 1989**
Sambrook PN, Cohen ML, Eisman JA, Pocock NA, Champion GD, Yeates MG. Effects of low dose corticosteroids on bone mass in rheumatoid arthritis: a longitudinal study. *Ann Rheum Dis* 1989;**48**:535–8.

**Sambrook 1994**
Sambrook PN, Kelly PJ, Keogh AM, Macdonald P, Spratt P, Freund J, Eisman JA. Bone loss after heart transplantation: a prospective study. *J Heart Lung Transplant* 1994;**13**: 116–20.

**Schulz 1995**
Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**:408–12.

**Storm 1990**
Storm T, Thamsborg G, Steiniche T, Genant HK, Sorensen OH. Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. *N Engl J Med* 1990;**322**:1265–71.

**Thiebaud 1996**
Thiebaud D, Krieg MA, Gillard-Berguer D, Jacquet AF, Goy JJ, Burckhardt P. Cyclosporine induces high bone turnover and may contribute to bone loss after heart transplantation. *Eur J Clin Invest* 1996;**26**:549–55.

**Walsh 1996**
Walsh LJ, Wong CA, Pringle M, Tattersfield AE. Use of oral corticosteroids in the community and the prevention of secondary osteoporosis: A cross sectional study. *BMJ* 1996; **313**:344–6.

* *Indicates the major publication for the study*

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies *[ordered by study ID]*

**Adachi 97**

| | |
|---|---|
| Methods | Randomized clinical trial |
| Participants | 116 patients with rheumatoid arthritis and polymyalgia rheumatica |
| Interventions | Cyclic etidronate<br>400 mg |
| Outcomes | Percent change in BMD at 12 months |
| Notes | BMD measured by DEXA<br>Primary prevention |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Yes | A - Adequate |

**Eastell 96**

| | |
|---|---|
| Methods | Controlled clinical trial, allocation of patients not specified |
| Participants | 80 patients with rheumatoid arthritis |
| Interventions | Risedronate<br>2.5 mg/day |
| Outcomes | Percent change in BMD at 24 months |
| Notes | BMD measurement technique not specified<br>Secondary prevention |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Jenkins 97**

| | |
|---|---|
| Methods | Randomized clinical trial |
| Participants | 28 patients with rheumatoid arthritis and polymyalgia rheumatica |
| Interventions | Cyclic etidronate<br>400 mg |
| Outcomes | Percent change in BMD at 6 and 12 months |
| Notes | BMD measured by DEXA<br>Primary prevention |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Yes | A - Adequate |

**Mulder 94**

| | |
|---|---|
| Methods | Controlled clinical trial |
| Participants | 20 patients with temporal arteritis |
| Interventions | Cyclic etidronate<br>400 mg |
| Outcomes | Percent change in BMD at 6 and 12 months |
| Notes | BMD measured by DEXA<br>Primary prevention |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | No | C - Inadequate |

**Pitt 97**

| | |
|---|---|
| Methods | Randomized clinical trial |
| Participants | 49 patients with asthma, lupus and polymyalgia rheumatica |
| Interventions | Cyclic etidronate<br>400 mg |

**Pitt 97** (*Continued*)

| | | |
|---|---|---|
| Outcomes | Percent change in BMD at 24 months | |
| Notes | BMD measured by DEXA<br>Secondary prevention | |
| ***Risk of bias*** | | |
| **Item** | **Authors' judgement** | **Description** |
| Allocation concealment? | Yes | A - Adequate |

**Reid 88**

| | | |
|---|---|---|
| Methods | Randomized clinical trial | |
| Participants | 35 patients with asthma and collagen vascular disease | |
| Interventions | Pamidronate<br>150 mg/day | |
| Outcomes | Percent change in BMD from chart at 12 months | |
| Notes | BMD measure by quantitative CT<br>Secondary prevention | |
| ***Risk of bias*** | | |
| **Item** | **Authors' judgement** | **Description** |
| Allocation concealment? | Yes | A - Adequate |

**Roux 97**

| | | |
|---|---|---|
| Methods | Randomized clinical trial | |
| Participants | 107 patients with rheumatoid arthritis and polymyalgia rheumatica | |
| Interventions | Cyclic etidronate<br>400 mg | |
| Outcomes | Percent change in BMD at 12 months | |
| Notes | BMD measurement technique not specified<br>Primary prevention | |
| ***Risk of bias*** | | |

**Roux 97** (*Continued*)

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Yes | A - Adequate |

**Saag 97**

| | |
|---|---|
| Methods | Randomized clinical trial |
| Participants | 136 patients with rheumatic diseases |
| Interventions | Alendronate<br>10 mg/day |
| Outcomes | Percent change in BMD at 12 months |
| Notes | BMD measurement technique not specified<br>Secondary prevention |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Yes | A - Adequate |

**Skingle 94**

| | |
|---|---|
| Methods | Randomized clinical trial |
| Participants | 38 patients with polymyalgia rheumatica, temporal arteritis and chronic obstructive pulmonary disease (COPD) |
| Interventions | Cyclic etidronate<br>400 mg |
| Outcomes | Percent change in BMD at 12 months |
| Notes | BMD measured by DEXA<br>Secondary prevention |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Yes | A - Adequate |

**Struys 95**

| | |
|---|---|
| Methods | Controlled clinical trial |
| Participants | 39 patients with asthma, COPD and temporal arteritis |
| Interventions | Cyclic etidronate<br>400 mg |
| Outcomes | Percent change in BMD at 6 and 12 months |
| Notes | BMD measured by DEXA<br>Secondary prevention |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | No | C - Inadequate |

**VanCleemput 96**

| | |
|---|---|
| Methods | Controlled clinical trial |
| Participants | 41 patients undergoing cardiac transplantation |
| Interventions | Cyclic etidronate<br>400 mg |
| Outcomes | Percent change in BMD at 6 and 12 months |
| Notes | BMD measured by DEXA<br>Primary prevention |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | No | C - Inadequate |

**Wolfhagen 97**

| | |
|---|---|
| Methods | Randomized clinical trial |
| Participants | 12 patients with primary biliary cirrhosis participating in a trial of prednisone azathioprine vs placebo |
| Interventions | Cyclic etidronate<br>400 mg |

**Wolfhagen 97** (*Continued*)

| | | |
|---|---|---|
| Outcomes | Percent change in BMD at 12 months | |
| Notes | BMD measured by DEXA<br>Primary prevention | |
| ***Risk of bias*** | | |
| **Item** | **Authors' judgement** | **Description** |
| Allocation concealment? | Yes | A - Adequate |

**Worth 94**

| | | |
|---|---|---|
| Methods | Randomized clinical trial | |
| Participants | 33 patients with asthma | |
| Interventions | Etidronate<br>7.5 mg/day | |
| Outcomes | Percent change in BMD from chart at 6 months | |
| Notes | BMD measured by DPA<br>Secondary prevention | |
| ***Risk of bias*** | | |
| **Item** | **Authors' judgement** | **Description** |
| Allocation concealment? | Yes | A - Adequate |

## Characteristics of excluded studies *[ordered by study ID]*

| Study | Reason for exclusion |
|---|---|
| Adachi 94 | cohort study |
| Boutsen 97 | poor accountability (<50%) of study participants; did not meet the inclusion criteria |
| Braun 83 | bone biopsy data |
| Condon 78 | cohort study |

(*Continued*)

| | |
|---|---|
| Diamond 95 | prospective cohort |
| Eggelmeijer 96 | no subjects on steroids |
| Gallacher 92 | cohort study |
| Geusens 97 | low mean dose of corticosteroid |
| Gonelli 97 | peripheral bone density measurement only |
| Krieg 96 | not a controlled clinical trial |
| Reid 90 | same study as Reid 1988, only biochemical data |
| Reid letter 88 | biochemical data only |
| Sebaldt 96 | retrospective cohort |

## DATA AND ANALYSES

### Comparison 1. bisphosphonates vs placebo

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 % change in femoral BMD at 6 months - all trials | 2 | 80 | Mean Difference (IV, Fixed, 95% CI) | 3.94 [1.87, 6.01] |
| 2 % change in femoral BMD at 12 months - all trials | 7 | 489 | Mean Difference (IV, Fixed, 95% CI) | 0.78 [0.26, 1.30] |
| 3 % change in femoral BMD at 12 months - homogeneous | 5 | 408 | Mean Difference (IV, Fixed, 95% CI) | 0.52 [-0.01, 1.05] |
| 4 % change in lumbar BMD at 12 months - all trials | 10 | 572 | Mean Difference (IV, Fixed, 95% CI) | 4.14 [3.54, 4.75] |
| 5 % change in lumbar BMD at 12 months - homogeneous trials | 7 | 457 | Mean Difference (IV, Fixed, 95% CI) | 4.08 [3.45, 4.71] |
| 6 % change lumbar BMD 12 months - quality high | 2 | 151 | Mean Difference (IV, Fixed, 95% CI) | 4.03 [2.45, 5.60] |
| 7 % change lumbar BMD 12 months - quality low | 5 | 274 | Mean Difference (IV, Fixed, 95% CI) | 4.39 [3.62, 5.15] |
| 8 % change in lumbar BMD 12 months - primary prevention - all trials | 6 | 324 | Mean Difference (IV, Fixed, 95% CI) | 4.06 [3.25, 4.86] |
| 9 % change in lumbar BMD 12 months - secondary prevention - all trials | 7 | 410 | Mean Difference (IV, Fixed, 95% CI) | 3.45 [2.95, 3.95] |
| 10 % change in lumbar BMD 12 months - primary prevention- homogeneous | 5 | 283 | Mean Difference (IV, Fixed, 95% CI) | 4.46 [3.63, 5.29] |
| 11 % change in lumbar BMD 12 months - secondary prevention- homogeneous | 5 | 336 | Mean Difference (IV, Fixed, 95% CI) | 3.23 [2.71, 3.74] |
| 12 % change in lumbar BMD-DEXA | 5 | 214 | Mean Difference (IV, Fixed, 95% CI) | 4.88 [4.06, 5.70] |
| 13 % change in lumbar BMD 12 months - randomized - all trials | 9 | 554 | Mean Difference (IV, Fixed, 95% CI) | 3.74 [3.06, 4.41] |
| 14 % change in lumbar BMD 12 months - nonrandomized - all trials | 4 | 180 | Mean Difference (IV, Fixed, 95% CI) | 3.54 [2.99, 4.09] |
| 15 % change in lumbar BMD 12 months - randomized - homogeneous | 8 | 519 | Mean Difference (IV, Fixed, 95% CI) | 3.70 [3.03, 4.38] |
| 16 % change in lumbar BMD 12 months - nonrandomized - homogeneous | 2 | 100 | Mean Difference (IV, Fixed, 95% CI) | 3.47 [2.90, 4.04] |
| 17 % change in lumbar BMD at 6 months - all trials | 5 | 161 | Mean Difference (IV, Fixed, 95% CI) | 4.12 [3.40, 4.85] |

| | | | | |
|---|---|---|---|---|
| 18 % change lumbar BMD 6 months - homogeneous | 3 | 81 | Mean Difference (IV, Fixed, 95% CI) | 4.55 [3.71, 5.39] |
| 19 % change in lumbar BMD within 2 years - all trials | 12 | 722 | Mean Difference (IV, Fixed, 95% CI) | 3.63 [3.19, 4.06] |
| 20 % change in lumbar BMD within 2 years - homogeneous trials | 7 | 472 | Mean Difference (IV, Fixed, 95% CI) | 3.57 [3.10, 4.03] |
| 21 % change lumbar BMD within 2 years - quality high | 4 | 305 | Mean Difference (IV, Fixed, 95% CI) | 3.16 [2.59, 3.73] |
| 22 risk of new vertebral fractures | 4 | 298 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.76 [0.37, 1.53] |
| 23 dropouts due to side effects | 6 | 289 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 6.01 [1.58, 22.93] |

**Analysis 1.1. Comparison 1 bisphosphonates vs placebo, Outcome 1 % change in femoral BMD at 6 months - all trials.**

Review: Bisphosphonates for steroid induced osteoporosis

Comparison: 1 bisphosphonates vs placebo

Outcome: 1 % change in femoral BMD at 6 months - all trials

| Study or subgroup | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Struys 95 | 19 | 4.6 (4.4) | 20 | -1.5 (2.7) | | 80.9 % | 6.10 [ 3.79, 8.41 ] |
| VanCleemput 96 | 19 | -8.5 (8) | 22 | -3.3 (7.4) | | 19.1 % | -5.20 [ -9.94, -0.46 ] |
| **Total (95% CI)** | **38** | | **42** | | | **100.0 %** | **3.94 [ 1.87, 6.01 ]** |

Heterogeneity: Chi² = 17.63, df = 1 (P = 0.00003); I² =94%

Test for overall effect: Z = 3.73 (P = 0.00020)

Test for subgroup differences: Not applicable

### Analysis 1.2. Comparison 1 bisphosphonates vs placebo, Outcome 2 % change in femoral BMD at 12 months - all trials.

Review: Bisphosphonates for steroid induced osteoporosis

Comparison: 1 bisphosphonates vs placebo

Outcome: 2 % change in femoral BMD at 12 months - all trials

| Study or subgroup | | | Control | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Adachi 97 | 53 | 0.19 (4.95) | 63 | -1.67 (5.3) | | 7.8 % | 1.86 [ -0.01, 3.73 ] |
| Roux 97 | 51 | -1.28 (4.14) | 56 | -2.59 (5.01) | | 9.0 % | 1.31 [ -0.43, 3.05 ] |
| Saag 97 | 69 | 0.22 (4.57) | 67 | -1.71 (4.58) | | 11.4 % | 1.93 [ 0.39, 3.47 ] |
| Skingle 94 | 20 | -1 (1) | 18 | -1 (1) | | 66.7 % | 0.0 [ -0.64, 0.64 ] |
| Struys 95 | 19 | 6.8 (6.1) | 20 | -4.1 (3.1) | | 2.9 % | 10.90 [ 7.84, 13.96 ] |
| VanCleemput 96 | 19 | -8.9 (8.9) | 22 | -5.9 (6.3) | | 1.2 % | -3.00 [ -7.79, 1.79 ] |
| Wolfhagen 97 | 6 | -0.1 (3.7) | 6 | -1.5 (5.1) | | 1.1 % | 1.40 [ -3.64, 6.44 ] |
| **Total (95% CI)** | **237** | | **252** | | | **100.0 %** | **0.78 [ 0.26, 1.30 ]** |

Heterogeneity: $Chi^2$ = 54.00, df = 6 (P<0.00001); $I^2$ =89%

Test for overall effect: Z = 2.93 (P = 0.0034)

Test for subgroup differences: Not applicable

### Analysis 1.3. Comparison 1 bisphosphonates vs placebo, Outcome 3 % change in femoral BMD at 12 months - homogeneous.

Review: Bisphosphonates for steroid induced osteoporosis

Comparison: 1 bisphosphonates vs placebo

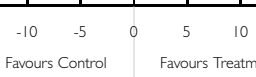
Outcome: 3 % change in femoral BMD at 12 months - homogeneous

| Study or subgroup | | | Control | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Adachi 97 | 53 | 0.19 (4.95) | 62 | -1.67 (5.3) | | 8.0 % | 1.86 [ -0.02, 3.74 ] |
| Roux 97 | 51 | -1.28 (4.14) | 56 | -2.59 (5.01) | | 9.4 % | 1.31 [ -0.43, 3.05 ] |
| Saag 97 | 69 | 0.22 (4.57) | 67 | -1.71 (4.58) | | 11.9 % | 1.93 [ 0.39, 3.47 ] |
| Skingle 94 | 20 | -1 (1) | 18 | -1 (1) | | 69.6 % | 0.0 [ -0.64, 0.64 ] |
| Wolfhagen 97 | 6 | -0.1 (3.7) | 6 | -1.5 (5.1) | | 1.1 % | 1.40 [ -3.64, 6.44 ] |
| **Total (95% CI)** | **199** | | **209** | | | **100.0 %** | **0.52 [ -0.01, 1.05 ]** |

Heterogeneity: Chi² = 8.66, df = 4 (P = 0.07); I² =54%

Test for overall effect: Z = 1.91 (P = 0.056)

Test for subgroup differences: Not applicable



### Analysis 1.4. Comparison 1 bisphosphonates vs placebo, Outcome 4 % change in lumbar BMD at 12 months - all trials.

Review: Bisphosphonates for steroid induced osteoporosis

Comparison: 1 bisphosphonates vs placebo

Outcome: 4 % change in lumbar BMD at 12 months - all trials

| Study or subgroup | | | Control | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Adachi 97 | 54 | 0.61 (3.97) | 62 | -3.23 (4.72) | | 14.6 % | 3.84 [ 2.26, 5.42 ] |
| Jenkins 97 | 15 | 1.8 (1.57) | 13 | -3.7 (5.81) | | 3.4 % | 5.50 [ 2.24, 8.76 ] |
| Mulder 94 | 10 | 1.42 (1.42) | 10 | -4.95 (2.02) | | 15.6 % | 6.37 [ 4.84, 7.90 ] |
| Reid 88 | 16 | 19.5 (24) | 19 | -8.7 (30.5) | | 0.1 % | 28.20 [ 10.13, 46.27 ] |
| Roux 97 | 51 | 0.3 (4.35) | 56 | -2.79 (4.71) | | 12.4 % | 3.09 [ 1.37, 4.81 ] |
| Saag 97 | 69 | 2.78 (3.9) | 67 | -0.04 (3.27) | | 25.0 % | 2.82 [ 1.61, 4.03 ] |
| Skingle 94 | 20 | 4.1 (3.6) | 18 | -0.8 (0.79) | | 13.9 % | 4.90 [ 3.28, 6.52 ] |
| Struys 95 | 19 | 5.7 (5.2) | 20 | -3.4 (3.1) | | 5.0 % | 9.10 [ 6.40, 11.80 ] |
| VanCleemput 96 | 19 | -10.3 (7.2) | 22 | -7 (3.5) | | 2.9 % | -3.30 [ -6.85, 0.25 ] |
| Wolfhagen 97 | 6 | 0.4 (2.2) | 6 | -3 (1.8) | | 7.1 % | 3.40 [ 1.13, 5.67 ] |
| **Total (95% CI)** | **279** | | **293** | | | **100.0 %** | **4.14 [ 3.54, 4.75 ]** |

Heterogeneity: $Chi^2$ = 52.83, df = 9 (P<0.00001); $I^2$ =83%

Test for overall effect: Z = 13.44 (P < 0.00001)

Test for subgroup differences: Not applicable

## Analysis 1.5. Comparison 1 bisphosphonates vs placebo, Outcome 5 % change in lumbar BMD at 12 months - homogeneous trials.

Review: Bisphosphonates for steroid induced osteoporosis

Comparison: 1 bisphosphonates vs placebo

Outcome: 5 % change in lumbar BMD at 12 months - homogeneous trials

| Study or subgroup | | | Control | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Adachi 97 | 54 | 0.61 (3.97) | 62 | -3.23 (4.72) | | 15.9 % | 3.84 [ 2.26, 5.42 ] |
| Jenkins 97 | 15 | 1.8 (1.57) | 13 | -3.7 (5.81) | | 3.7 % | 5.50 [ 2.24, 8.76 ] |
| Mulder 94 | 10 | 1.42 (1.42) | 10 | -4.95 (2.02) | | 16.9 % | 6.37 [ 4.84, 7.90 ] |
| Roux 97 | 51 | 0.3 (4.35) | 56 | -2.79 (4.71) | | 13.5 % | 3.09 [ 1.37, 4.81 ] |
| Saag 97 | 69 | 2.78 (3.9) | 67 | -0.04 (3.27) | | 27.2 % | 2.82 [ 1.61, 4.03 ] |
| Skingle 94 | 20 | 4.1 (3.6) | 18 | -0.8 (0.79) | | 15.1 % | 4.90 [ 3.28, 6.52 ] |
| Wolfhagen 97 | 6 | 0.4 (2.2) | 6 | -3 (1.8) | | 7.7 % | 3.40 [ 1.13, 5.67 ] |
| **Total (95% CI)** | **225** | | **232** | | | **100.0 %** | **4.08 [ 3.45, 4.71 ]** |

Heterogeneity: Chi² = 16.20, df = 6 (P = 0.01); I² =63%

Test for overall effect: Z = 12.69 (P < 0.00001)

Test for subgroup differences: Not applicable

### Analysis 1.6. Comparison 1 bisphosphonates vs placebo, Outcome 6 % change lumbar BMD 12 months - quality high.

Review: Bisphosphonates for steroid induced osteoporosis

Comparison: 1 bisphosphonates vs placebo

Outcome: 6 % change lumbar BMD 12 months - quality high

| Study or subgroup | N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Adachi 97 | 54 | 0.61 (3.97) | 62 | -3.23 (4.72) | | 99.2 % | 3.84 [ 2.26, 5.42 ] |
| Reid 88 | 16 | 19.5 (24) | 19 | -8.7 (30.5) | | 0.8 % | 28.20 [ 10.13, 46.27 ] |
| **Total (95% CI)** | **70** | | **81** | | | **100.0 %** | **4.03 [ 2.45, 5.60 ]** |

Heterogeneity: Chi² = 6.93, df = 1 (P = 0.01); I² =86%

Test for overall effect: Z = 5.01 (P < 0.00001)

Test for subgroup differences: Not applicable


### Analysis 1.7. Comparison 1 bisphosphonates vs placebo, Outcome 7 % change lumbar BMD 12 months - quality low.

Review: Bisphosphonates for steroid induced osteoporosis

Comparison: 1 bisphosphonates vs placebo

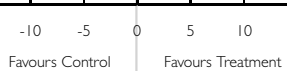
Outcome: 7 % change lumbar BMD 12 months - quality low

| Study or subgroup | N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Mulder 94 | 10 | 1.42 (1.42) | 10 | -4.95 (2.02) | | 25.0 % | 6.37 [ 4.84, 7.90 ] |
| Saag 97 | 69 | 2.78 (3.9) | 67 | -0.04 (3.27) | | 40.1 % | 2.82 [ 1.61, 4.03 ] |
| Skingle 94 | 20 | 4.1 (3.6) | 18 | -0.8 (0.79) | | 22.3 % | 4.90 [ 3.28, 6.52 ] |
| Struys 95 | 19 | 5.7 (5.2) | 20 | -3.4 (3.1) | | 8.0 % | 9.10 [ 6.40, 11.80 ] |
| VanCleemput 96 | 19 | -10.3 (7.2) | 22 | -7 (3.5) | | 4.6 % | -3.30 [ -6.85, 0.25 ] |
| **Total (95% CI)** | **137** | | **137** | | | **100.0 %** | **4.39 [ 3.62, 5.15 ]** |

Heterogeneity: Chi² = 42.95, df = 4 (P<0.00001); I² =91%

Test for overall effect: Z = 11.25 (P < 0.00001)

Test for subgroup differences: Not applicable



### Analysis 1.8. Comparison 1 bisphosphonates vs placebo, Outcome 8 % change in lumbar BMD 12 months - primary prevention - all trials.

Review: Bisphosphonates for steroid induced osteoporosis

Comparison: 1 bisphosphonates vs placebo

Outcome: 8 % change in lumbar BMD 12 months - primary prevention - all trials

| Study or subgroup | | | Control | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Adachi 97 | 54 | 0.61 (3.97) | 62 | -3.23 (4.72) | | 26.1 % | 3.84 [ 2.26, 5.42 ] |
| Jenkins 97 | 15 | 1.8 (1.57) | 13 | -3.7 (5.81) | | 6.2 % | 5.50 [ 2.24, 8.76 ] |
| Mulder 94 | 10 | 1.42 (1.42) | 10 | -4.95 (2.02) | | 27.9 % | 6.37 [ 4.84, 7.90 ] |
| Roux 97 | 51 | 0.3 (4.35) | 56 | -2.79 (4.71) | | 22.1 % | 3.09 [ 1.37, 4.81 ] |
| VanCleemput 96 | 19 | -10.3 (7.2) | 22 | -7 (3.5) | | 5.2 % | -3.30 [ -6.85, 0.25 ] |
| Wolfhagen 97 | 6 | 0.4 (2.2) | 6 | -3 (1.8) | | 12.6 % | 3.40 [ 1.13, 5.67 ] |
| **Total (95% CI)** | **155** | | **169** | | | **100.0 %** | **4.06 [ 3.25, 4.86 ]** |

Heterogeneity: Chi² = 27.62, df = 5 (P = 0.00004); I² =82%

Test for overall effect: Z = 9.84 (P < 0.00001)

Test for subgroup differences: Not applicable

## Analysis 1.9. Comparison 1 bisphosphonates vs placebo, Outcome 9 % change in lumbar BMD 12 months - secondary prevention - all trials.

Review: Bisphosphonates for steroid induced osteoporosis

Comparison: 1 bisphosphonates vs placebo

Outcome: 9 % change in lumbar BMD 12 months - secondary prevention - all trials

| Study or subgroup | | | Control | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Eastell 96 | 40 | 1.4 (1.22) | 40 | -1.6 (1.57) | | 66.8 % | 3.00 [ 2.38, 3.62 ] |
| Pitt 97 | 26 | 5.1 (5.1) | 23 | 1 (7.19) | | 2.0 % | 4.10 [ 0.57, 7.63 ] |
| Reid 88 | 16 | 19.5 (24) | 19 | -8.7 (30.5) | | 0.1 % | 28.20 [ 10.13, 46.27 ] |
| Saag 97 | 69 | 2.78 (3.9) | 67 | -0.04 (3.27) | | 17.4 % | 2.82 [ 1.61, 4.03 ] |
| Skingle 94 | 20 | 4.1 (3.6) | 18 | -0.8 (0.79) | | 9.7 % | 4.90 [ 3.28, 6.52 ] |
| Struys 95 | 19 | 5.7 (5.2) | 20 | -3.4 (3.1) | | 3.5 % | 9.10 [ 6.40, 11.80 ] |
| Worth 94 | 14 | 5.5 (8.9) | 19 | -4.6 (9.8) | | 0.6 % | 10.10 [ 3.69, 16.51 ] |
| **Total (95% CI)** | **204** | | **206** | | | **100.0 %** | **3.45 [ 2.95, 3.95 ]** |

Heterogeneity: $Chi^2$ = 34.41, df = 6 (P<0.00001); $I^2$ =83%

Test for overall effect: Z = 13.43 (P < 0.00001)

Test for subgroup differences: Not applicable

### Analysis 1.10. Comparison 1 bisphosphonates vs placebo, Outcome 10 % change in lumbar BMD 12 months - primary prevention- homogeneous.

Review: Bisphosphonates for steroid induced osteoporosis

Comparison: 1 bisphosphonates vs placebo

Outcome: 10 % change in lumbar BMD 12 months - primary prevention- homogeneous

| Study or subgroup | | | Control | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Adachi 97 | 54 | 0.61 (3.97) | 62 | -3.23 (4.72) | | 27.5 % | 3.84 [ 2.26, 5.42 ] |
| Jenkins 97 | 15 | 1.8 (1.57) | 13 | -3.7 (5.81) | | 6.5 % | 5.50 [ 2.24, 8.76 ] |
| Mulder 94 | 10 | 1.42 (1.42) | 10 | -4.95 (2.02) | | 29.4 % | 6.37 [ 4.84, 7.90 ] |
| Roux 97 | 51 | 0.3 (4.35) | 56 | -2.79 (4.71) | | 23.3 % | 3.09 [ 1.37, 4.81 ] |
| Wolfhagen 97 | 6 | 0.4 (2.2) | 6 | -3 (1.8) | | 13.3 % | 3.40 [ 1.13, 5.67 ] |
| **Total (95% CI)** | **136** | | **147** | | | **100.0 %** | **4.46 [ 3.63, 5.29 ]** |

Heterogeneity: $Chi^2$ = 10.25, df = 4 (P = 0.04); $I^2$ =61%

Test for overall effect: Z = 10.53 (P < 0.00001)

Test for subgroup differences: Not applicable

### Analysis 1.11. Comparison 1 bisphosphonates vs placebo, Outcome 11 % change in lumbar BMD 12 months - secondary prevention- homogeneous.

Review: Bisphosphonates for steroid induced osteoporosis

Comparison: 1 bisphosphonates vs placebo

Outcome: 11 % change in lumbar BMD 12 months - secondary prevention- homogeneous

| Study or subgroup | N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Eastell 96 | 40 | 1.4 (1.22) | 40 | -1.6 (1.57) | | 69.2 % | 3.00 [ 2.38, 3.62 ] |
| Pitt 97 | 26 | 5.1 (5.1) | 23 | 1 (7.19) | | 2.1 % | 4.10 [ 0.57, 7.63 ] |
| Saag 97 | 69 | 2.78 (3.9) | 67 | -0.04 (3.27) | | 18.0 % | 2.82 [ 1.61, 4.03 ] |
| Skingle 94 | 20 | 4.1 (3.6) | 18 | -0.8 (0.79) | | 10.0 % | 4.90 [ 3.28, 6.52 ] |
| Worth 94 | 14 | 5.5 (8.9) | 19 | -4.6 (9.8) | | 0.6 % | 10.10 [ 3.69, 16.51 ] |
| **Total (95% CI)** | **169** | | **167** | | | **100.0 %** | **3.23 [ 2.71, 3.74 ]** |

Heterogeneity: $Chi^2 = 9.70$, df = 4 (P = 0.05); $I^2 = 59\%$

Test for overall effect: Z = 12.34 (P < 0.00001)

Test for subgroup differences: Not applicable

### Analysis 1.12. Comparison 1 bisphosphonates vs placebo, Outcome 12 % change in lumbar BMD-DEXA.

Review: Bisphosphonates for steroid induced osteoporosis

Comparison: 1 bisphosphonates vs placebo

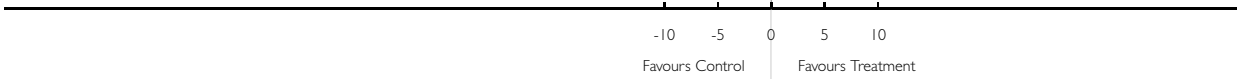
Outcome: 12 % change in lumbar BMD-DEXA

| Study or subgroup | N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Adachi 97 | 54 | 0.61 (3.97) | 62 | -3.23 (4.72) | | 26.7 % | 3.84 [ 2.26, 5.42 ] |
| Jenkins 97 | 15 | 1.8 (1.57) | 13 | -3.7 (5.81) | | 6.3 % | 5.50 [ 2.24, 8.76 ] |
| Mulder 94 | 10 | 1.42 (1.42) | 10 | -4.95 (2.02) | | 28.5 % | 6.37 [ 4.84, 7.90 ] |
| Skingle 94 | 20 | 4.1 (3.6) | 18 | -0.8 (0.79) | | 25.5 % | 4.90 [ 3.28, 6.52 ] |
| Wolfhagen 97 | 6 | 0.4 (2.2) | 6 | -3 (1.8) | | 12.9 % | 3.40 [ 1.13, 5.67 ] |
| **Total (95% CI)** | **105** | | **109** | | | **100.0 %** | **4.88 [ 4.06, 5.70 ]** |

Heterogeneity: $Chi^2$ = 7.07, df = 4 (P = 0.13); $I^2$ =43%

Test for overall effect: Z = 11.70 (P < 0.00001)

Test for subgroup differences: Not applicable



### Analysis 1.13. Comparison 1 bisphosphonates vs placebo, Outcome 13 % change in lumbar BMD 12 months - randomized - all trials.

Review: Bisphosphonates for steroid induced osteoporosis

Comparison: 1 bisphosphonates vs placebo

Outcome: 13 % change in lumbar BMD 12 months - randomized - all trials

| Study or subgroup | | | Control | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Adachi 97 | 54 | 0.61 (3.97) | 62 | -3.23 (4.72) | | 18.2 % | 3.84 [ 2.26, 5.42 ] |
| Jenkins 97 | 15 | 1.8 (1.57) | 13 | -3.7 (5.81) | | 4.3 % | 5.50 [ 2.24, 8.76 ] |
| Pitt 97 | 26 | 5.1 (5.1) | 23 | 1 (7.19) | | 3.6 % | 4.10 [ 0.57, 7.63 ] |
| Reid 88 | 16 | 19.5 (24) | 19 | -8.7 (30.5) | | 0.1 % | 28.20 [ 10.13, 46.27 ] |
| Roux 97 | 51 | 0.3 (4.35) | 56 | -2.79 (4.71) | | 15.4 % | 3.09 [ 1.37, 4.81 ] |
| Saag 97 | 69 | 2.78 (3.9) | 67 | -0.04 (3.27) | | 31.1 % | 2.82 [ 1.61, 4.03 ] |
| Skingle 94 | 20 | 4.1 (3.6) | 18 | -0.8 (0.79) | | 17.3 % | 4.90 [ 3.28, 6.52 ] |
| Wolfhagen 97 | 6 | 0.4 (2.2) | 6 | -3 (1.8) | | 8.8 % | 3.40 [ 1.13, 5.67 ] |
| Worth 94 | 14 | 5.5 (8.9) | 19 | -4.6 (9.8) | | 1.1 % | 10.10 [ 3.69, 16.51 ] |
| **Total (95% CI)** | **271** | | **283** | | | **100.0 %** | **3.74 [ 3.06, 4.41 ]** |

Heterogeneity: $Chi^2$ = 16.83, df = 8 (P = 0.03); $I^2$ =52%

Test for overall effect: Z = 10.86 (P < 0.00001)

Test for subgroup differences: Not applicable

### Analysis 1.14. Comparison 1 bisphosphonates vs placebo, Outcome 14 % change in lumbar BMD 12 months - nonrandomized - all trials.

Review: Bisphosphonates for steroid induced osteoporosis

Comparison: 1 bisphosphonates vs placebo

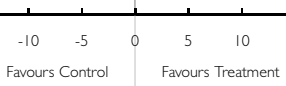
Outcome: 14 % change in lumbar BMD 12 months - nonrandomized - all trials

| Study or subgroup | N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Eastell 96 | 40 | 1.4 (1.22) | 40 | -1.6 (1.57) | | 80.4 % | 3.00 [ 2.38, 3.62 ] |
| Mulder 94 | 10 | 1.42 (1.42) | 10 | -4.95 (2.02) | | 13.0 % | 6.37 [ 4.84, 7.90 ] |
| Struys 95 | 19 | 5.7 (5.2) | 20 | -3.4 (3.1) | | 4.2 % | 9.10 [ 6.40, 11.80 ] |
| VanCleemput 96 | 19 | -10.3 (7.2) | 22 | -7 (3.5) | | 2.4 % | -3.30 [ -6.85, 0.25 ] |
| **Total (95% CI)** | **88** | | **92** | | | **100.0 %** | **3.54 [ 2.99, 4.09 ]** |

Heterogeneity: $Chi^2$ = 46.57, df = 3 (P<0.00001); $I^2$ =94%

Test for overall effect: Z = 12.56 (P < 0.00001)

Test for subgroup differences: Not applicable



### Analysis 1.15. Comparison 1 bisphosphonates vs placebo, Outcome 15 % change in lumbar BMD 12 months - randomized - homogeneous.

Review: Bisphosphonates for steroid induced osteoporosis

Comparison: 1 bisphosphonates vs placebo

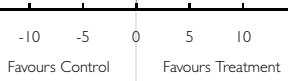
Outcome: 15 % change in lumbar BMD 12 months - randomized - homogeneous

| Study or subgroup | | | Control | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Adachi 97 | 54 | 0.61 (3.97) | 62 | -3.23 (4.72) | | 18.2 % | 3.84 [ 2.26, 5.42 ] |
| Jenkins 97 | 15 | 1.8 (1.57) | 13 | -3.7 (5.81) | | 4.3 % | 5.50 [ 2.24, 8.76 ] |
| Pitt 97 | 26 | 5.1 (5.1) | 23 | 1 (7.19) | | 3.6 % | 4.10 [ 0.57, 7.63 ] |
| Roux 97 | 51 | 0.3 (4.35) | 56 | -2.79 (4.71) | | 15.4 % | 3.09 [ 1.37, 4.81 ] |
| Saag 97 | 69 | 2.78 (3.9) | 67 | -0.04 (3.27) | | 31.2 % | 2.82 [ 1.61, 4.03 ] |
| Skingle 94 | 20 | 4.1 (3.6) | 18 | -0.8 (0.79) | | 17.4 % | 4.90 [ 3.28, 6.52 ] |
| Wolfhagen 97 | 6 | 0.4 (2.2) | 6 | -3 (1.8) | | 8.8 % | 3.40 [ 1.13, 5.67 ] |
| Worth 94 | 14 | 5.5 (8.9) | 19 | -4.6 (9.8) | | 1.1 % | 10.10 [ 3.69, 16.51 ] |
| **Total (95% CI)** | **255** | | **264** | | | **100.0 %** | **3.70 [ 3.03, 4.38 ]** |

Heterogeneity: $Chi^2$ = 9.78, df = 7 (P = 0.20); $I^2$ =28%

Test for overall effect: Z = 10.75 (P < 0.00001)

Test for subgroup differences: Not applicable



### Analysis 1.16. Comparison 1 bisphosphonates vs placebo, Outcome 16 % change in lumbar BMD 12 months - nonrandomized - homogeneous.

Review: Bisphosphonates for steroid induced osteoporosis

Comparison: 1 bisphosphonates vs placebo

Outcome: 16 % change in lumbar BMD 12 months - nonrandomized - homogeneous

| Study or subgroup | N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Eastell 96 | 40 | 1.4 (1.22) | 40 | -1.6 (1.57) | | 86.1 % | 3.00 [ 2.38, 3.62 ] |
| Mulder 94 | 10 | 1.42 (1.42) | 10 | -4.95 (2.02) | | 13.9 % | 6.37 [ 4.84, 7.90 ] |
| **Total (95% CI)** | **50** | | **50** | | | **100.0 %** | **3.47 [ 2.90, 4.04 ]** |

Heterogeneity: $Chi^2$ = 16.03, df = 1 (P = 0.00006); $I^2$ =94%

Test for overall effect: Z = 11.90 (P < 0.00001)

Test for subgroup differences: Not applicable


### Analysis 1.17. Comparison 1 bisphosphonates vs placebo, Outcome 17 % change in lumbar BMD at 6 months - all trials.

Review: Bisphosphonates for steroid induced osteoporosis

Comparison: 1 bisphosphonates vs placebo

Outcome: 17 % change in lumbar BMD at 6 months - all trials

| Study or subgroup | N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Jenkins 97 | 15 | 1.9 (1.65) | 13 | -1.3 (2.04) | | 27.4 % | 3.20 [ 1.81, 4.59 ] |
| Mulder 94 | 10 | 1.1 (0.98) | 10 | -4.09 (1.42) | | 46.2 % | 5.19 [ 4.12, 6.26 ] |
| Struys 95 | 19 | 2.7 (2.6) | 20 | -2 (2.7) | | 19.1 % | 4.70 [ 3.04, 6.36 ] |
| VanCleemput 96 | 19 | -7.7 (5.9) | 22 | -4.6 (3.3) | | 5.9 % | -3.10 [ -6.09, -0.11 ] |
| Worth 94 | 14 | 5.5 (8.9) | 19 | -4.6 (9.8) | | 1.3 % | 10.10 [ 3.69, 16.51 ] |
| **Total (95% CI)** | **77** | | **84** | | | **100.0 %** | **4.12 [ 3.40, 4.85 ]** |

Heterogeneity: $Chi^2$ = 31.74, df = 4 (P<0.00001); $I^2$ =87%

Test for overall effect: Z = 11.11 (P < 0.00001)

Test for subgroup differences: Not applicable

**Analysis 1.18. Comparison 1 bisphosphonates vs placebo, Outcome 18 % change lumbar BMD 6 months - homogeneous.**

Review: Bisphosphonates for steroid induced osteoporosis

Comparison: 1 bisphosphonates vs placebo

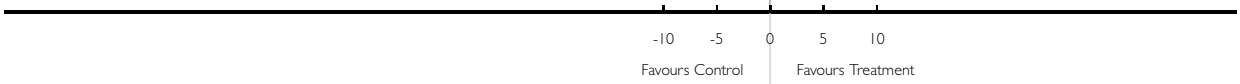
Outcome: 18 % change lumbar BMD 6 months - homogeneous

| Study or subgroup | N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Jenkins 97 | 15 | 1.9 (1.65) | 13 | -1.3 (2.04) | | 36.6 % | 3.20 [ 1.81, 4.59 ] |
| Mulder 94 | 10 | 1.1 (0.98) | 10 | -4.09 (1.42) | | 61.7 % | 5.19 [ 4.12, 6.26 ] |
| Worth 94 | 14 | 5.5 (8.9) | 19 | -4.6 (9.8) | | 1.7 % | 10.10 [ 3.69, 16.51 ] |
| **Total (95% CI)** | **39** | | **42** | | | **100.0 %** | **4.55 [ 3.71, 5.39 ]** |

Heterogeneity: $Chi^2$ = 7.88, df = 2 (P = 0.02); $I^2$ =75%

Test for overall effect: Z = 10.61 (P < 0.00001)

Test for subgroup differences: Not applicable



### Analysis 1.19. Comparison 1 bisphosphonates vs placebo, Outcome 19 % change in lumbar BMD within 2 years - all trials.

Review: Bisphosphonates for steroid induced osteoporosis

Comparison: 1 bisphosphonates vs placebo

Outcome: 19 % change in lumbar BMD within 2 years - all trials

| Study or subgroup | | | Control | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Adachi 97 | 54 | 0.61 (3.97) | 62 | -3.23 (4.72) | | 7.6 % | 3.84 [ 2.26, 5.42 ] |
| Eastell 96 | 40 | 1.4 (1.22) | 40 | -1.6 (1.57) | | 49.8 % | 3.00 [ 2.38, 3.62 ] |
| Jenkins 97 | 15 | 1.8 (1.57) | 13 | -3.7 (5.81) | | 1.8 % | 5.50 [ 2.24, 8.76 ] |
| Mulder 94 | 10 | 1.42 (1.42) | 10 | -4.95 (2.02) | | 8.1 % | 6.37 [ 4.84, 7.90 ] |
| Pitt 97 | 26 | 5.1 (5.1) | 23 | 1 (7.19) | | 1.5 % | 4.10 [ 0.57, 7.63 ] |
| Reid 88 | 16 | 19.5 (24) | 19 | -8.7 (30.5) | | 0.1 % | 28.20 [ 10.13, 46.27 ] |
| Roux 97 | 51 | 0.3 (4.35) | 56 | -2.79 (4.71) | | 6.4 % | 3.09 [ 1.37, 4.81 ] |
| Saag 97 | 69 | 2.78 (3.9) | 67 | -0.04 (3.27) | | 13.0 % | 2.82 [ 1.61, 4.03 ] |
| Skingle 94 | 20 | 4.1 (3.6) | 18 | -0.8 (0.79) | | 7.2 % | 4.90 [ 3.28, 6.52 ] |
| Struys 95 | 19 | 5.7 (5.2) | 20 | -3.4 (3.1) | | 2.6 % | 9.10 [ 6.40, 11.80 ] |
| VanCleemput 96 | 19 | -10.3 (7.2) | 22 | -7 (3.5) | | 1.5 % | -3.30 [ -6.85, 0.25 ] |
| Worth 94 | 14 | 5.5 (8.9) | 19 | -4.6 (9.8) | | 0.5 % | 10.10 [ 3.69, 16.51 ] |
| **Total (95% CI)** | **353** | | **369** | | | **100.0 %** | **3.63 [ 3.19, 4.06 ]** |

Heterogeneity: Chi² = 63.55, df = 11 (P<0.00001); I² =83%

Test for overall effect: Z = 16.34 (P < 0.00001)

Test for subgroup differences: Not applicable

### Analysis 1.20. Comparison 1 bisphosphonates vs placebo, Outcome 20 % change in lumbar BMD within 2 years - homogeneous trials.

Review: Bisphosphonates for steroid induced osteoporosis

Comparison: 1 bisphosphonates vs placebo

Outcome: 20 % change in lumbar BMD within 2 years - homogeneous trials

| Study or subgroup | | | Control | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Adachi 97 | 54 | 0.61 (3.97) | 62 | -3.23 (4.72) | | 8.6 % | 3.84 [ 2.26, 5.42 ] |
| Eastell 96 | 40 | 1.4 (1.22) | 40 | -1.6 (1.57) | | 56.9 % | 3.00 [ 2.38, 3.62 ] |
| Mulder 94 | 10 | 1.42 (1.42) | 10 | -4.95 (2.02) | | 9.2 % | 6.37 [ 4.84, 7.90 ] |
| Pitt 97 | 26 | 5.1 (5.1) | 23 | 1 (7.19) | | 1.7 % | 4.10 [ 0.57, 7.63 ] |
| Saag 97 | 69 | 2.78 (3.9) | 67 | -0.04 (3.27) | | 14.8 % | 2.82 [ 1.61, 4.03 ] |
| Skingle 94 | 20 | 4.1 (3.6) | 18 | -0.8 (0.79) | | 8.2 % | 4.90 [ 3.28, 6.52 ] |
| Worth 94 | 14 | 5.5 (8.9) | 19 | -4.6 (9.8) | | 0.5 % | 10.10 [ 3.69, 16.51 ] |
| **Total (95% CI)** | **233** | | **239** | | | **100.0 %** | **3.57 [ 3.10, 4.03 ]** |

Heterogeneity: $Chi^2$ = 24.40, df = 6 (P = 0.00044); $I^2$ =75%

Test for overall effect: Z = 15.06 (P < 0.00001)

Test for subgroup differences: Not applicable

### Analysis 1.21. Comparison 1 bisphosphonates vs placebo, Outcome 21 % change lumbar BMD within 2 years - quality high.

Review: Bisphosphonates for steroid induced osteoporosis

Comparison: 1 bisphosphonates vs placebo

Outcome: 21 % change lumbar BMD within 2 years - quality high

| Study or subgroup | | | Control | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Adachi 97 | 70 | 0.61 (4.52) | 71 | -3.23 (5.06) | | 12.8 % | 3.84 [ 2.26, 5.42 ] |
| Eastell 96 | 40 | 1.4 (1.22) | 40 | -1.6 (1.57) | | 84.5 % | 3.00 [ 2.38, 3.62 ] |
| Pitt 97 | 26 | 5.1 (5.1) | 23 | 1 (7.19) | | 2.6 % | 4.10 [ 0.57, 7.63 ] |
| Reid 88 | 16 | 19.5 (24) | 19 | -8.7 (30.5) | | 0.1 % | 28.20 [ 10.13, 46.27 ] |
| **Total (95% CI)** | **152** | | **153** | | | **100.0 %** | **3.16 [ 2.59, 3.73 ]** |

Heterogeneity: $Chi^2$ = 8.62, df = 3 (P = 0.03); $I^2$ =65%

Test for overall effect: Z = 10.94 (P < 0.00001)

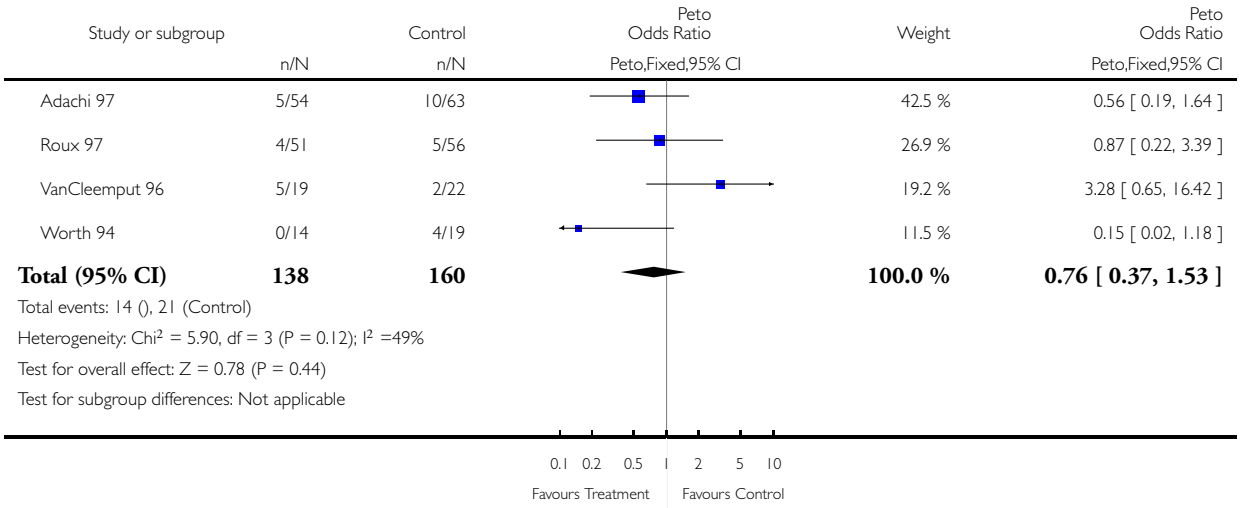
Test for subgroup differences: Not applicable

### Analysis 1.22. Comparison 1 bisphosphonates vs placebo, Outcome 22 risk of new vertebral fractures.

Review: Bisphosphonates for steroid induced osteoporosis

Comparison: 1 bisphosphonates vs placebo

Outcome: 22 risk of new vertebral fractures



### Analysis 1.23. Comparison 1 bisphosphonates vs placebo, Outcome 23 dropouts due to side effects.

Review: Bisphosphonates for steroid induced osteoporosis

Comparison: 1 bisphosphonates vs placebo

Outcome: 23 dropouts due to side effects

| Study or subgroup | | Control | Peto Odds Ratio | Peto Odds Ratio |
|---|---|---|---|---|
| | n/N | n/N | Peto,Fixed,95% CI | Peto,Fixed,95% CI |
| Adachi 97 | 4/58 | 1/63 | | 3.78 [ 0.63, 22.50 ] |
| Mulder 94 | 0/10 | 0/10 | | 0.0 [ 0.0, 0.0 ] |
| Reid 88 | 0/16 | 0/19 | | 0.0 [ 0.0, 0.0 ] |
| Struys 95 | 1/19 | 0/20 | | 7.79 [ 0.15, 393.02 ] |
| VanCleemput 96 | 0/19 | 0/22 | | 0.0 [ 0.0, 0.0 ] |
| Worth 94 | 3/14 | 0/19 | | 12.36 [ 1.16, 131.50 ] |
| **Total (95% CI)** | **136** | **153** | | **6.01 [ 1.58, 22.93 ]** |

Total events: 8 (), 1 (Control)

Heterogeneity: $Chi^2 = 0.63$, df = 2 (P = 0.73); $I^2 = 0.0\%$

Test for overall effect: Z = 2.63 (P = 0.0087)

Test for subgroup differences: Not applicable


## WHAT'S NEW

Last assessed as up-to-date: 16 November 1998.

| Date | Event | Description |
|---|---|---|
| 19 September 2008 | Amended | Converted to new review format. C012-R |

## HISTORY

Review first published: Issue 1, 1999

## DECLARATIONS OF INTEREST

None Known

## SOURCES OF SUPPORT


### Internal sources

- University of Alberta, Edmonton, Canada.
- University of Ottawa, Ontario, Canada.
- McMaster University, Hamilton, Canada.

### External sources

- No sources of support supplied


## INDEX TERMS

### Medical Subject Headings (MeSH)

Diphosphonates [*therapeutic use]; Glucocorticoids [*adverse effects]; Osteoporosis [*chemically induced; *prevention & control]

### MeSH check words

Humans