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# Prevention of corticosteroid-induced osteoporosis in young women

by

Joanne Elizabeth Homik 

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Master of Science

in

Medical Sciences - Pulbic Health Sciences

Edmonton, Alberta
Spring 1998

**University of Alberta**

## Faculty of Graduate Studies and Research

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## DEDICATION

I dedicate this thesis to my husband, Allan, for his unwavering confidence in my ability to succeed, to my children, Alexandra and Cameron, who make it all worthwhile, and to my parents, Alexander and Mary, for the love and attention which nurtured my dreams.

# ABSTRACT

After completing a systematic review of the literature, a meta-analysis on the efficacy of bisphosphonates in the prevention and treatment of corticosteroid-induced osteoporosis (CIOP) was performed using the guidelines of the Cochrane Collaboration. We also examined the cost-effectiveness of two strategies to prevent corticosteroid-induced osteoporosis in young women.

The meta-analysis results showed an effect size of 4.5% difference in bone mineral density (BMD)between the treatment and placebo groups.

A strategy of prophylaxis with etidronate, conditional on low bone mass, was shown to be more cost-effective than offering prophylaxis to all patients who start corticosteroids. Compared to no prophylaxis, the preferred strategy prevented 40 vertebral and 0.5 hip fractures per 1,000 women treated.

The strategy identified by this analysis is based on the best available medical evidence to date, and its systematic approach to the problem of CIOP in young women, if adopted, would lessen the morbidity of this condition.

# ACKNOWLEDGEMENTS

I would like to thank Dr. Maria Suarez-Almazor for her guidance and encouragement throughout my work on this thesis. She has been an exemplary mentor, and continues to act as a source of inspiration for me.

I would also like to acknowledge the assistance of Ms. Marlene Dorgan in the systematic review and Mrs. Brenda Topliss in preparation of the thesis.

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| | |
|---|---|
| **BMD** | **Bone mineral density** |
| **CIOP** | **corticosteroid-induced osteoporosis** |

# CHAPTER 1 - REVIEW OF THE LITERATURE

# I BACKGROUND

## A. Bone Biology and Osteoporosis

Bone is a dynamic tissue that is constantly undergoing remodeling. It is composed of collagen fibres and hydroxyapatite crystals. Bone also contains cellular constituents, namely osteoblasts, osteocytes and osteoclasts. Osteoblasts are bone marrow derived cells that produce the collagen that is subsequently mineralized into bone. They contain receptors for parathyroid hormone, estrogen, and vitamin D. Osteoblasts eventually lose their secretory function and become osteocytes. Osteoclasts are multinucleated cells that are responsible for the resorption of bone. These cells contain receptors for calcitonin and estrogen (1). They are indirectly stimulated by parathyroid hormone (2) and vitamin D (3), and inhibited by calcitonin (4).

Bone deposition and bone resorption are tightly coupled to maintain homeostasis. After the age of forty, net bone loss at a rate of 0.5% per year begins to occur.(5-7) Both bone resorption and deposition decrease, but resorption decreases less. This is felt to be due to decreased physical activity, decreased calcium absorption, decreased vitamin D levels, and lower levels of gonadal hormones.(5) This bone loss is usually referred to as involutional, and affects both cortical and trabecular bone. It results in a condition known as senile osteoporosis.

With the onset of menopause, women experience an accelerated rate of bone loss (2-3% per year) for 5-8 years after the loss of ovarian function.(8) This is mostly due to more active bone resorption, which is physiologically suppressed by estrogen. This type

of bone loss involves mostly trabecular bone, and results in vertebral and wrist fractures early in the post-menopausal period.

Individual rates of bone loss may vary significantly. As well, individuals enter their middle years with a wide range of bone densities (peak bone mass). The main determinants of peak bone mass are adequate calcium intake, exercise and genetic predisposition.

Bone loss is chiefly measured as the change in bone mineral density over time. The technology used to measure bone density has expanded over time, with the current gold standard being dual energy xray absorptiometry or DEXA. Bone mass or density is measured in grams per cubic centimeter, however in order to report a more meaningful result a standardized measurement is reported. This also allows comparison between different machines, different centers, and even different techniques. Bone mineral density can be compared to two different standards: one being the age and sex matched mean value for a reference population; the other being the sex matched peak bone mass of the reference population. Comparing to the former gives one a Z score, while comparing to the latter gives the T score. Both scores refer to the number of standard deviations the patient's value differs from the reference mean. Current WHO criteria for osteoporosis define that clinical state as a T score of =-2.5, with osteopenia being defined as a T score of =-1(9).

Bone strength is related to structural bone density in an exponential relationship.(10) Given this equation, even small amounts of bone loss can result in significant decreases in bone strength.

The other feature of bone that determines fracture risk is architectural deterioration. With bone loss comes local areas of trabecular thinning and disruption, as well as micro-fractures. These features contribute to bone fragility, which is an important risk factor for fracture. A marker of bone fragility is the positive history of non-traumatic fracture. It is important to note that while some therapies many prevent bone loss, there is no way to reverse loss of trabecular integrity (11).

## B. Risk factors for osteoporosis

There are many risk factors that have been associated with the development of osteoporosis. One category could be classified as nutritional: calcium intake; vitamin D level; alcohol consumption; and use of caffeine. Calcium and vitamin D are directly required for the maintenance of bone mass. There are no clearly defined mechanisms for the association between osteoporosis and alcohol and caffeine use. Endocrine factors such as gonadal hormone level and corticosteroid excess are another category of risk factor. Both of these hormone classes have a direct influence on osteoclasts and osteoblasts. Lifestyle factors are also been important, with exercise having a positive effect on bone mass, and cigarette smoking a negative one. Another category is classified as genetic factors and include race, sex, and familial prevalence. Familial prevalence includes mechanical factors, such as bone density and fragility as well as skeletal geometry (hip axis length, cortical thickness).

## C. Impact of osteoporosis

Osteoporosis itself is an asymptomatic condition, with problems arising when non-traumatic fractures occur. In conditions where rapid bone loss occurs, such as corticosteroid use and the post-menopausal period, trabecular bone is lost first. Thus,

there is a high incidence of vertebral crush fractures as well as fractures of the distal radius in these patients. Bone loss at the hip occurs at a slower pace and is manifest as hip fractures approximately ten years after the rise in vertebral fracture incidence. Hip fracture rates correlate with bone mineral density in older women, but not in very elderly women, suggesting the presence of other strong predictive factors in this age group.

Hip fractures carry substantial mortality and morbidity rates. In elderly women, mortality following hip fracture has been estimated at 12% to 30% (12). Institutionalization after the initial hospitalization is said to occur in 50% of patients acutely, and 25% of patients at one year (13,14). Vertebral and wrist fractures are also associated with an increase in mortality, although much less pronounced, as well as significant morbidity (15).

## D. Treatment of osteoporosis

There is controversy in the literature regarding the timing of osteoporosis therapy. The most conservative view is to wait until a fragility fracture (non-traumatic) has occurred, and low bone density is confirmed on bone density testing. Others would advocate identification of "at risk" individuals in order to initiate preventative measures.

Most attention is usually given to persons with rapid bone losing states, such as post-menopausal women. Evaluation of baseline bone density and presence of risk factors occurs at the onset of menopause. Interventions usually include lifestyle and nutritional modifications (calcium intake, vitamin D supplementation, smoking cessation and exercise) initially. Depending on the baseline bone density and underlying genetic factors, the physician may initiate hormone replacement therapy, or use a bone anti-resorptive agent such as calcitonin or bisphosphonates.

Hormone replacement therapy, specifically estrogen with or without progesterone has proved efficacious in halting bone loss in post-menopausal women (16,17,18). Rapid bone loss does resume, however when hormone replacement therapy is discontinued. Long term follow-up studies suggest that long term efficacy for bone loss prevention only occurs if hormone replacement therapy is continued for at least ten years.(16) It is interesting to note that estrogen also appears to be effective in elderly women who are >15 years beyond the menopause (18)

There is less data on the use of calcitonin to halt post-menopausal bone loss. It is felt that a higher dose of the drug is needed to prevent the rapid bone loss seen in this state, than the dose required to treat senile osteoporosis.(11) The main drawbacks to therapy include side effects (flushing and nausea), and the development of antibodies to the foreign-derived protein.

Bisphosphonates have been used both in the prevention and treatment of post-menopausal osteoporosis. They have proven efficacy in preventing bone loss, as well as preventing fractures (19,20)

## E. Corticosteroids and their effect on bone

The body produces a number of hormones, which regulate the function of various body systems. One such hormone is cortisol, which is the major glucocorticoid produced by the adrenal glands. The physiologic action of this hormone is to regulate protein, carbohydrate, and lipid metabolism. It has mainly catabolic effects, which results in increase energy stores (glucose) available for rapid use. This and other less well defined actions allow this hormone to protect the body during times of stress. The same features

of cortisol action which allow homeostasis during stressful events can be detrimental if allowed to continue unchecked. This is seen clearly in Cushing's syndrome, which is a clinical syndrome of cortisol excess usually due to excess stimulation of the adrenal glands. The features of Cushing's syndrome include hypertension, glucose intolerance, and osteoporosis.

Cortisol has other physiologic properties which make it appealing to use as a therapeutic agent. It has anti-inflammatory properties, mediated through microvascular and lysosomal membrane stabilization, as well as impairment of cellular-mediated immunity. For these reasons cortisol analogues (corticosteroids) are widely used in inflammatory conditions. Diseases treated with corticosteroids include connective tissue diseases, asthma, and organ transplantation.

The bone loss that occurs as a result of corticosteroid treatment has a multifactorial pathophysiology. This therapy interferes with calcium homeostasis, being associated with both decreased calcium absorption, and increased calcium excretion (21,22). Corticosteroids may also cause osteoporosis through inhibition of gonadal hormones(23) and direct inhibition of osteoblasts (24) as evidenced by decreased serum osteocalcin levels (23,25,26).

There is some evidence that lower doses of corticosteroids (less than 7 mg ) are not associated with increases rates of bone loss (27,28). Other studies have reported bone loss rates ranging from 0% to 13.9% per year in patients on ≥7.5 mg/day prednisone (29-32). It is uncertain whether bone loss occurs primarily in the initial stages of corticosteroid treatment or if there are continued losses with time.

## F. Prophylaxis and treatment of corticosteroid-induced osteoporosis.

Routine use of prophylactic therapy to prevent osteoporosis in corticosteroid treated patients does not occur. A recent Canadian study reported a 43% rate of osteoporosis therapy, with the highest prescription rates for post-menopausal women, lower for pre-menopausal women and men (33) This rate is higher than what was previously reported in the literature, others finding a 5.6% and 14% prevalence of co-prescription (34,35).

Much of the literature regarding treatment of corticosteroid-induced osteoporosis is in the form of case series and retrospective cohorts. There are some clinical trials evaluating the use of calcium, vitamin D, calcitonin, and bisphosphonates. The bisphosphonate literature shows the most promise. Studies report varied magnitudes of efficacy, however, making it difficult to draw conclusions from this literature.

# II OBJECTIVES

A. To conduct a meta-analysis on the efficacy of bisphosphonates in the prevention and treatment of corticosteroid-induced osteoporosis.

B. To perform decision analysis modeling to determine the cost effectiveness of three treatment options for young women (age 35) starting a course of corticosteroids.

# III RATIONALE

## A. Meta-analysis

Meta-analysis is a tool that can be used to combine data from different studies in order to achieve a more confident estimate of outcome. The quality of the meta-analysis depends on the methodologic quality of the studies used. For that reason cohort studies (when looking at etiologic outcomes), and randomized controlled trials (when looking at efficacy outcomes) provide the strongest "raw" data. In some cases only one study exists that fulfills your requirements, and this must be used instead.

The initial task in performing a meta-analysis is to identify all relevant literature. This requires a systematic review which includes searching of bibliographic databases, as well as hand searching of reference lists and scientific proceedings. Selection of appropriate studies is the next task, and is best done in a systematic manner.

The three steps involved in meta-analysis itself include calculating a summary measure of effect size, determining its confidence interval or statistical significance, and testing for heterogeneity between trials.

There are two basic models used for calculating summary effect size, the fixed effects and random effects models. The major difference between the two is that the fixed effects model addresses the question of whether or not the treatment is efficacious in the set of studies analyzed. The random effects model, on the other hand, assumes that the studies analyzed are a random sample of the 'population' of studies on this subject. Because of this assumption, it includes in its calculation of effect size and confidence interval, a measure of the between-study variance (36,37). Because of this added variance component the results of a random effects analysis are generally more

conservative, with a wider confidence interval. When studies are homogeneous the fixed and random effects models yield identical results (38). In the presence of significant heterogeneity, the between-study variance dominates the equation, and causes all studies to be weighted equally, regardless of sample size. In the fixed effects model (and random effects model with homogeneity), studies are weighted by sample size and within-study variance. The result is that analyses found to have a statistically significant conclusion using fixed effects models may not be statistically significant if re-analyzed using a random effects model (39).

Each analysis must deal individually with the presence of heterogeneity, and try to account for it. The analysis should use both models and conclusions drawn accordingly.

Another consideration that needs to be made when choosing a method of combining studies is the type of variable involved in the analysis. In studies where the outcome is a dichotomous variable (number of new fractures, dropouts due to side effects) the effect of treatment is often expressed as an odds ratio. There are three methods commonly used to calculate summary odds ratios in a fixed effects model, the Mantel-Haenszel, Peto, and general variance based methods. The Mantel-Haenszel and Peto methods are similar in computational simplicity and both may be used when analyzing data from experimental studies (38). The general variance based method is used when rate difference is the summary measure required (39). Where a random effects model is required the method used is the DerSimonian-Laird method which also provides an odds ratio (40).

In studies where the outcome measure is a continuous variable, there are two methods, based on the analysis of variance model to summarize treatment effect. These were initially described by Cochran in 1954 (41). One is used for fixed effects models and the

other for random effects models. They both provide, as a measure of effect size, a weighted mean difference between treatment and control groups. To clarify, if our outcome is the change in bone mineral density from start to finish of the trial, the mean difference is equal to the mean change in the control group minus the mean change in the treatment group. Each study is weighted (by sample size and variance), and all studies combined, resulting in a weighted mean difference. This can be regarded as the change in bone density that is attributable to therapy.

## B. Decision analysis

Decision analysis involves the synthesis of data from multiple sources to better estimate the usefulness of a treatment or procedure. A tree is assembled outlining the various treatment options (treatment node) and all the possible outcomes for each option (decision node). Treatment nodes are defined arbitrarily by the researcher (e.g. how many patients will receive drug A and how many drug B). The distribution of outcomes for each treatment are determined for each decision node such that the sum of the probabilities pertaining to one treatment option is 1.

In the past, researchers have used expert opinion or consensus panels to determine probabilities for various outcomes. In today's drive towards evidenced based medicine, more objective data should be sought to provide these probabilities. Effect sizes from large randomized controlled trials, or from a meta-analysis of all the available clinical trials should be used if possible (38).

Costs are also incorporated into the model. The costs of various interventions and outcomes are determined. Most analyses use direct costs (i.e. resources) and not indirect costs (negative productivity). Direct costs usually include hospitalization costs,

outpatient costs, drug costs, and physician fees. There are many valid methods for calculating costs, such as direct assessment, charges, disease related group costs, and sample surveys (38). One must ensure that costs can be generalized to the population of interest, and are not center specific. It is generally felt that costs should be discounted (42). This relates to the concept of time preference for money, which means that people value money in the present more than the same money in the future. It is because of this that discounting is done.

Cost effectiveness is one of the outcomes of a decision analysis. It informs us how much money must be spent to achieve a particular outcome. Since cost effectiveness is by definition a comparison, the cost effectiveness ratio expresses how much excess cost is required to achieve a certain measure of increased effectiveness. This is usually accomplished by comparing a new intervention to "standard therapy".

Because there is always uncertainty surrounding any scientific result, sensitivity analyses are performed to take all variations into account. This includes uncertainty around the chance nodes, as well as uncertainty regarding the costing estimates. Where uncertainty exists at many chance nodes, the sensitivity analysis can be simplified to define the best and worst case scenarios. Sensitivity analysis for cost variations should be calculated separately.

The decision analysis is usually run with a well defined, hypothetical cohort of individuals. Interventions and outcomes are tailored to this population, and appropriate probabilities determined. Although this limits generalizability of the analysis, it is necessary to maintain the validity of the assumptions made.

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# CHAPTER 2 - A META-ANALYSIS ON THE USE OF BISPHOSPHONATES IN CORTICOSTEROID-INDUCED OSTEOPOROSIS

# I BACKGROUND

Corticosteroids are widely used in inflammatory conditions as an immunosuppressive agent. Conditions 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 (1,2). 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 (3-6). Bone loss is likely mediated through a variety of mechanisms. Studies have provided evidence for decreased calcium absorption and increased calcium excretion (7,8), decreased serum concentration of sex hormones (9), and direct inhibition of bone formation (10) as evidenced by decreased serum osteocalcin levels (9,11,12).

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 (13,14). One study showed a 5.6% prevalence of co-prescription, and another showed a 14.0% 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 (15-34). 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. For this reason a meta-analysis was performed using the methods recommended by the Cochrane Collaboration (35).

# II METHODS

## A. Systematic Review of the Literature

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 (36) with the addition of the clinical keywords listed in appendix 1, 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 2

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.

## B. Eligibility Criteria

Initially all controlled clinical trials were selected for further assessment. Subsequently, trials were assessed for the presence of random allocation and blinding. We chose studies where participants were men and/or women over the age of 18, with underlying inflammatory disorders, currently being treated with systemic corticosteroids, and who had not received bisphosphonates in the six months prior to the start of the study. 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. 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.

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

## C. Data Extraction

Data was extracted for the outcomes of interest by two independent and blinded observers (JH, AC). The observers were blinded as to the identity of the authors, institutions, and journal for each trial.

## D. Quality Assessment

Methodological quality of the trials was assessed by two reviewers (JH, MSA), using the criteria of Jadad et al (37). The criteria included assessment of random allocation, blinding techniques, and completeness of follow-up with the possible range of scores

being 0 to 5 (5 indicating the best quality). Calculation of a weighted kappa statistic was performed to assess agreement between the two assessors.

## E. Statistical Analysis

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 (38). Results at 6 and 12 months were analyzed separately. The outcome measurement of interest was the mean difference in change of BMD. That is, the percent change in BMD (treatment group) minus the percent change in BMD (placebo group). Each trial was weighted taking into account sample size and variance in the outcome variable (39). The overall treatment effect of the combined trials was calculated as a weighted mean difference between the two treatment groups.

A fixed effects model was used initially, and heterogeneity of the trials was assessed using a chi square test. Where significant heterogeneity was present a random effects model was included, in order to provide a more conservative estimate of effect size (39). Where standard error of the mean was reported, standard deviation was calculated as SD=SEM$\sqrt{n}$. 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. The weighted mean differences were calculated using Revman 3.0 (35)

Sensitivity analysis was performed for a) quality, using the median quality score of 2 as a cut off value, defining higher and lower quality trials; b) primary vs. Secondary

prevention trials; and c) heterogeneity, excluding those trials with methodological differences.

# III. RESULTS

## A. Systematic Review of the Literature

After review of the abstracts in the search, a total of 20 controlled studies were found (13 found in the electronic databases and 7 by hand searching), assessing the treatment of corticosteroid induced osteoporosis with a bisphosphonate (15-34). There were 9 abstracts from scientific meetings, 1 letter and 10 full length journal articles. Fourteen were controlled clinical trials. Of these 1 was excluded for only reporting biochemical data (23). One study reported a mean corticosteroid dose of 6 mg/day (28), and was excluded. The 12 remaining trials reported data on 598 participants. Two of the included trials, presented in abstract form, did not report the mean dose of prednisone in the study groups (17,27). Another two only reported two year data (26,32), and these studies were included in a sensitivity analysis with the one year studies, along with a study reporting only 6 month data (17). One trial reported two treatment groups (same drug, different dose), as well as the control group, and the data was entered as two studies (32).

The characteristics of the included studies are presented in Table 1. Most trials used etidronate, administered in a cyclic fashion. There was one trial that used daily etidronate, one using oral risedronate and one using daily oral pamidronate. Eight out of 12 studies used dual energy xray absorptiometry (DXA), 1 used dual photon absorptiometry (felt to be comparable to DXA), and 2 did not specify the method used to

measure BMD. One study used quantitative computed tomography (QCT) (22). Six studies involved primary prevention of osteoporosis (16,21,25,27,29,34) and six dealt with secondary prevention (17,18,19,22,26,32).

A summary of trial results is reported in Table 2. All 12 trials reported data on bone loss at the lumbar spine, while only 7 reported changes at the femoral neck. Eleven 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 (21), even over the control group. Three studies reported a significant improvement over controls in femoral neck BMD (18,25,32), while the other 4 reported no significant difference between the two groups (19,21,29,34).

Four studies reported fracture data. One study found an increased number of fractures in the treatment group (21), and 3 found a decreased number (17,25,29).

## B. Quality Assessment

The agreement between the two investigators regarding the methodological quality of the trials was substantial, as indicated by a kappa statistic of 0.73 (40). Where scores differed, the average was used. Scores ranged from 1 to 4 with 6 trials scoring higher than the median rating of 2, and 5 scoring equal to or lower than average. Six of the trials were double blinded studies, 3 of the studies used alternate allocation, and one abstract did not specify the method of allocation.

## C. Pooled Analysis for Lumbar and Femoral Neck BMD

Results for lumbar spine and femoral neck at 6 and 12 months were analyzed separately. 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 4.5%(95% CI 2.6, 6.4). That is, on average the treatment and placebo groups had a percent change in bone density that differed by 4.5 percentage points.

Analysis of trials reporting lumbar BMD at 6 months resulted in a weighted mean difference of 3.5%(95% CI 1.1, 5.9).

Results at the femoral neck for all trials reporting data at twelve months were not statistically significant. The weighted mean difference was 2.2%(95% CI -0.5, 4.9). The data for change in BMD at 6 months also reveals a nonsignificant result [weighted mean difference 0.6 (95% CI-10.4, 11.7)].

## D. Pooled Analysis for Fractures and Adverse Effects

Four studies reported the number of participants with new lumbar fractures (17,21,25,29). 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: 0.8%(95%CI 0.4, 1.5).

Six studies reported withdrawals due to adverse effects. Three found an increased number of withdrawals in the treatment group, and the other three 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. In total 8/136

patients in the treatment groups were withdrawn for adverse effects, compared to 1/153 patients in the control groups (pooled across trials).

## E. Sensitivity Analysis for Heterogeneity

Sensitivity analyses were performed excluding those trials that were felt to contribute to the majority of the heterogeneity in the analysis. These included the trial involving cardiac transplant patients (21), the trial where QCT measurements were used (22), and the trial where extremely osteoporotic patients were enrolled (18). For the twelve month analysis at the lumbar spine, this resulted in a weighted mean difference of 4.5% (95%CI 3.4, 5.6). The Q test for heterogeneity in this analysis was significantly reduced (10.47 df5). For the six month analysis, the resulting weighted mean difference was 4.8% (95%CI 2.6, 6.9).

The twelve month femoral neck data was re-analyzed, resulting in a weighted mean difference of 0.8% (95%CI -0.3, 1.8). In the six month analysis, there were only two studies (18,21), both of which were excluded in the sensitivity analysis.

## F. Sensitivity Analysis for Primary vs. Secondary Prevention:

Sensitivity analysis was also used to compare primary vs. secondary prevention trials. Excluding the heterogeneous trials as before, the primary prevention trials (lumbar 12 months) showed a weighted mean difference of 4.4% (95%CI 3.0, 5.8). The secondary prevention trials, on the other hand had a weighted mean difference of 3.4% (95%CI 1.9, 4.9).

## G. Sensitivity Analysis for Methodologic Quality and Study Duration

A sensitivity analysis comparing those trials with higher than average vs. lower than average methodologic quality was performed for change in lumbar BMD at 12 months. There were only 2 trials in the high quality subgroup, which resulted in a skewed estimate.

Inclusion of the two studies reporting two year data, and the one study reporting 6 month data with all of the one year trials, resulted in a weighted mean difference of 2.7%(95%CI 2.3, 3.0), using a random effects model. Excluding the 3 heterogeneous trials as above yielded a weighted mean difference of 2.6%(95%CI 2.2, 2.9).

# IV. 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 (41,42), but the mechanisms of bone loss are sufficiently different in corticosteroid-induced osteoporosis to require independent review of their efficacy.

We analyzed the results of only controlled clinical trials. We included studies that were single or double blinded because BMD is an objective measure, measured and calculated by machine, and we felt it unlikely that there would be bias in the reporting of this measurement on the basis of inadequate blinding. In all cases outcome assessor was blinded. We also included studies that used alternate allocation instead of random allocation. Other investigators have found that nonrandomized clinical trials can overestimate the magnitude of effect by up to 40% (43). A sensitivity analysis comparing

randomized vs. nonrandomized studies resulted in point estimates of 4.4%(95%CI 3.1, 5.7) and 3.5%(95%CI 1.5, 5.6) respectively. Excluding the three heterogeneous trials, the point estimates were 4.1% and 3.5%. As the nonrandomized studies underestimated the effect size in this analysis, we felt it unnecessary to exclude them.

The results 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 5%. 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 this value constitutes a fall by one standard deviation (Hologic Inc., Waltham, Massachusetts, USA). Interventions that bring about a 5% change in bone density would likely have a significant impact on the T score. In studies of fracture prognosis, a BMD decrease one standard deviation has been shown to carry a statistically significant increased risk of fracture (44). The response to therapy appears to be greater in the primary prevention vs. 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 (tables 1 and 2). 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 (21,22,18). The study which showed continued rapid bone loss in the treatment group (21), used a unique study population, (cardiac transplant recipients) in whom other factors may contribute to bone loss. Several cohort studies have reported high rates of bone loss in the first year after organ transplantation (45-48). Bone loss was related to length of hospital stay in one study, prompting the authors to conclude that immobility may be a contributing factor (48). Cyclosporin A, which is routinely used in all transplant recipients, has been shown to increase bone resorption in animal models (49), and likely contributes to the excessive bone loss seen in this population. Another trial included in the meta-analysis reported a large percentage of bone accrual in the treatment group compared to other trials (22). 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 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, explaining 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 no statistically significant difference in femoral neck BMD between the treatment and placebo groups. 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 (Table 2). There were only 6 studies reporting femoral BMD, and heterogeneity in this series was prominent, with essentially three different results (Table 2). Even after excluding the two heterogeneous trials (18, 21), the effect size was small (<1%) and did not reach statistical significance. It is generally believed that corticosteroid-induced bone loss is not as prominent in cortical bone (38), and it may be that a small change between groups is hard to document with the small sample sizes involved. Although the difference did not reach statistical significance, the magnitude of the effect comparing the treatment and control groups appeared to be small.

In the two year analysis, we included a study which had two active treatment groups (same intervention, different dosage). The results 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.

Throughout the analyses, we used 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. The results are reported for 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. However, a recent meta-analysis of fracture risk for various levels of BMD shows an increased risk (odds ratio 1.5) for fractures at all sites with a BMD that is only 1 standard deviation below peak bone mass (44). In the absence of fracture outcome data in most clinical trials of osteoporosis, the proxy outcome of BMD gives good information regarding fracture risk. Studies of bone resorbing agents that are able to achieve the results presented here would be expected to have an impact on fracture prevention.

In all trials examined, the mean age of patients was greater than 50. There is a theoretical concern that the changes in bone density reflect post-menopausal losses and efficacy of bisphosphonates in preventing this loss. One trial, however, contained a sub-group analysis (25), and bone loss and response to therapy was evident for males, as well as, pre-menopausal women. This implies that bisphosphonates are efficacious in preventing and treating this special type of bone loss.

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 (50). A randomized controlled trial of adjunct prednisone therapy in 40 rheumatoid arthritis patients showed that after discontinuation of prednisone at 6 months, there was bone accrual at a rate of 5.3% in the following 6 months (51). A case series of 6 corticosteroid treated sarcoid patients reported that bone loss reversed after exogenous steroids were discontinued (52). One must

consider, however, that patients experience significant bone loss and increased risk of fractures while on corticosteroid therapy. However, the above studies (50-52), suggest that anti-resorptive therapy does not need to be continued beyond the duration of corticosteroid therapy.

## V. CONCLUSION

Bisphosphonates appear to be efficacious at preventing and treating corticosteroid-induced bone mineral loss at the lumbar spine. There does not appear to be a significant treatment effect of bisphosphonates on femoral BMD. 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.

# TABLE 1 - CHARACTERISTICS OF INCLUDED TRIALS

| AUTHOR | INTERVENTION AND DOSE | CONTROL | TIME POINTS (months) | PATIENT POPULATION | TYPE OF PREVENTION | QUALITY SCORE | MEAN AGE (years) |
|---|---|---|---|---|---|---|---|
| Adachi (25) | cyclic etidronate 400 mg/day | placebo + calcium | 12 | rheumatoid arthritis, PMR | primary | 2 | 61 |
| Jenkins (27) | cyclic etidronate 400 mg/day | placebo + calcium | 6, 12 | rheumatoid arthritis, PMR | primary | 2 | NS |
| Mulder (16) | cyclic etidronate 400 mg/day | no intervention | 6, 12 | temporal arteritis | primary | 1 | 73 |
| Reid (22) | pamidronate 150 mg/day | placebo | 12 | asthma, collagen vasc. | secondary | 4 | 50 |
| Roux (29) | cyclic etidronate 400 mg/day | placebo + calcium | 12 | rheumatoid arthritis, PMR | primary | 2 | NS |
| Skingle (19) | cyclic etidronate 400 mg/day | calcium | 12 | PMR, temporal arteritis, COPD | secondary | 1 | 64.5 |
| Struys (18) | cyclic etidronate 400 mg/day | calcium | 6,12 | asthma, COPD, temporal arteritis | secondary | 1 | 63.4 |
| Vancleemput (21) | cyclic etidronate 400 mg/day | calcium vitamin D | 6, 12 | cardiac transplant recipients | primary | 1 | 53 |

## TABLE 1 - CHARACTERISTICS OF INCLUDED TRIALS (continued)

| AUTHOR | INTERVENTION AND DOSE | CONTROL | TIME POINTS (months) | PATIENT POPULATION | TYPE OF PREVENTION | QUALITY SCORE | MEAN AGE (years) |
|---|---|---|---|---|---|---|---|
| Pitt (26) | cyclic etidronate 400 mg/day | placebo | 24 | asthma, lupus, PMR | secondary | 2 | NS |
| Eastell #1 (32)* | risedronate 2.5 mg/day | placebo | 24 | rheumatoid arthritis | secondary | 2 | 46-79 |
| Eastell #2 (32)* | cyclic risedronate 15 mg/day | placebo | 24 | rheumatoid arthritis | secondary | 2 | 46-79 |
| Wolfhagen (34) | cyclic etidronate 400 mg/day | calcium | 12 | primary biliary cirrhosis | primary | 2 | 53 |
| Worth (17) | etidronate 7.5 mg/day | calcium | 6 | asthma | secondary | 2 | 56.5 |

PMR = polymyalgia rheumatica COPD = chronic obstructive pulmonary disease
NS = not specified
* 2 treatment groups are listed as 2 trials resulting in 12 trials from 11 papers.

# TABLE 2 - SUMMARY OF RESULTS

| AUTHOR | INTERVENTION AND DOSE | PATIENTS PER GROUP | | % CHANGE BMD IN LUMBAR SPINE | | % CHANGE BMD IN FEMORAL NECK | |
|---|---|---|---|---|---|---|---|
| | | T | P | T | P | T | P |
| Adachi (25) | cyclic etidronate 400 mg/day | 54 | 62 | +0.6 | -3.2 | +0.2 | -1.7 |
| Jenkins (27) | cyclic etidronate 400 mg/day | 15 | 13 | +1.8 | -3.7 | — | — |
| Mulder (10) | cyclic etidronate 400 mg/day | 10 | 10 | +1.4 | -5.0 | — | — |
| Reid (22) | pamidronate 150 mg/day | 16 | 19 | +20.0 | -8.8 | — | — |
| Roux(29) | cyclic etidronate 400 mg/day | 51 | 56 | +0.3 | -2.8 | -1.3 | -2.6 |
| Skingle (19) | cyclic etidronate 400 mg/day | 18 | 20 | +4.1 | -0.8 | -1.0 | -1.0 |
| Struys (18) | cyclic etidronate 400 mg/day | 19 | 20 | +5.7 | -3.4 | +6,8 | -4.1 |
| Vancleemput (21) | cyclic etidronate 400 mg/day | 19 | 22 | -10.3 | -7.0 | -8.9 | -5.6 |
| Pitt (26) | cyclic etidronate 400 mg/day | 26 | 23 | +5.1 | +1.0 | — | — |
| Eastell #1 (32)* | risedronate 2.5 mg/day | 40 | 40 | +1.4 | -1.6 | -1.0 | -3.6 |
| Eastell #2 (32)* | cyclic risedronate 15 mg/day | 40 | 40 | -0.1 | -1.6 | +0.9 | -3.6 |
| Wolfhagen (34) | cyclic etidronate 400mg/day | 6 | 6 | +0.4 | -3.0 | -0.1 | -1.5 |
| Worth (17) | etidronate 7.5 mg/day | 14 | 19 | +5.5 | -4.6 | — | — |

T = treatment group P = placebo group

* 2 treatment groups are listed as 2 trials resulting in 12 trials from 11 papers.

## TABLE 3 - CHANGE IN BONE MINERAL DENSITY AT THE LUMBAR SPINE AT 12 MONTHS

| AUTHOR | INTERVENTION | PATIENT POPULATION | MEAN DIFFERENCE | 95% CONFIDENCE INTERVAL |
|---|---|---|---|---|
| Adachi | etidronate | rheumatoid arthritis, PMR | 3.8 | 2.3, 5.4 |
| Jenkins | etidronate | rheumatoid arthritis, PMR | 5.5 | 2.2, 8.8 |
| Mulder | etidronate | temporal arteritis | 6.4 | 4.8, 7.9 |
| Reid | pamidronate | asthma, CVD | 28.2 | 23.9, 32.5 |
| Roux | etidronate | rheumatoid arthritis, PMR | 3.1 | 1.4, 4.8 |
| Skingle | etidronate | PMR, temporal arteritis, asthma | 4.9 | 3.3, 6.5 |
| Struys | etidronate | asthma, COPD | 9.1 | 6.4, 11.8 |
| Vancleemput | etidronate | cardiac transplant recipients | -3.3 | -6.8, 0.25 |
| Wolfhagen | etidronate | Primary biliary Cirrhosis | 3.4 | 1.1, 5.7 |
| | | | Weighted mean difference | 95% confidence interval |
| Pooled estimate (random effects; n = 436) | | | 4.7 | 2.6, 6.8 |

## TABLE 4 - CHANGE IN BONE MINERAL DENSITY AT THE LUMBAR SPINE AT 6 MONTHS

| AUTHOR | INTERVENTION | PATIENT POPULATION | MEAN DIFFERENCE | 95% CONFIDENCE INTERVAL |
|---|---|---|---|---|
| Jenkins | etidronate | rheumatoid arthritis, PMR | 3.2 | 1.8, 4.6 |
| Mulder | etidronate | temporal arteritis | 5.2 | 4.1, 6.3 |
| Struys | etidronate | asthma, COPD | 4.7 | 3.0, 6.4 |
| Worth | EHDP | asthma | 10.1 | 3.7, 16.5 |
| Vancleemput | etidronate | cardiac transplant recipients | -3.1 | -6.1, -0.1 |
| | | | Weighted mean difference | 95% confidence interval |
| Pooled estimate (random effects; n = 161) | | | 3.5 | 1.1, 5.9 |

## TABLE 5 - CHANGE IN BONE MINERAL DENSITY AT THE FEMORAL NECK

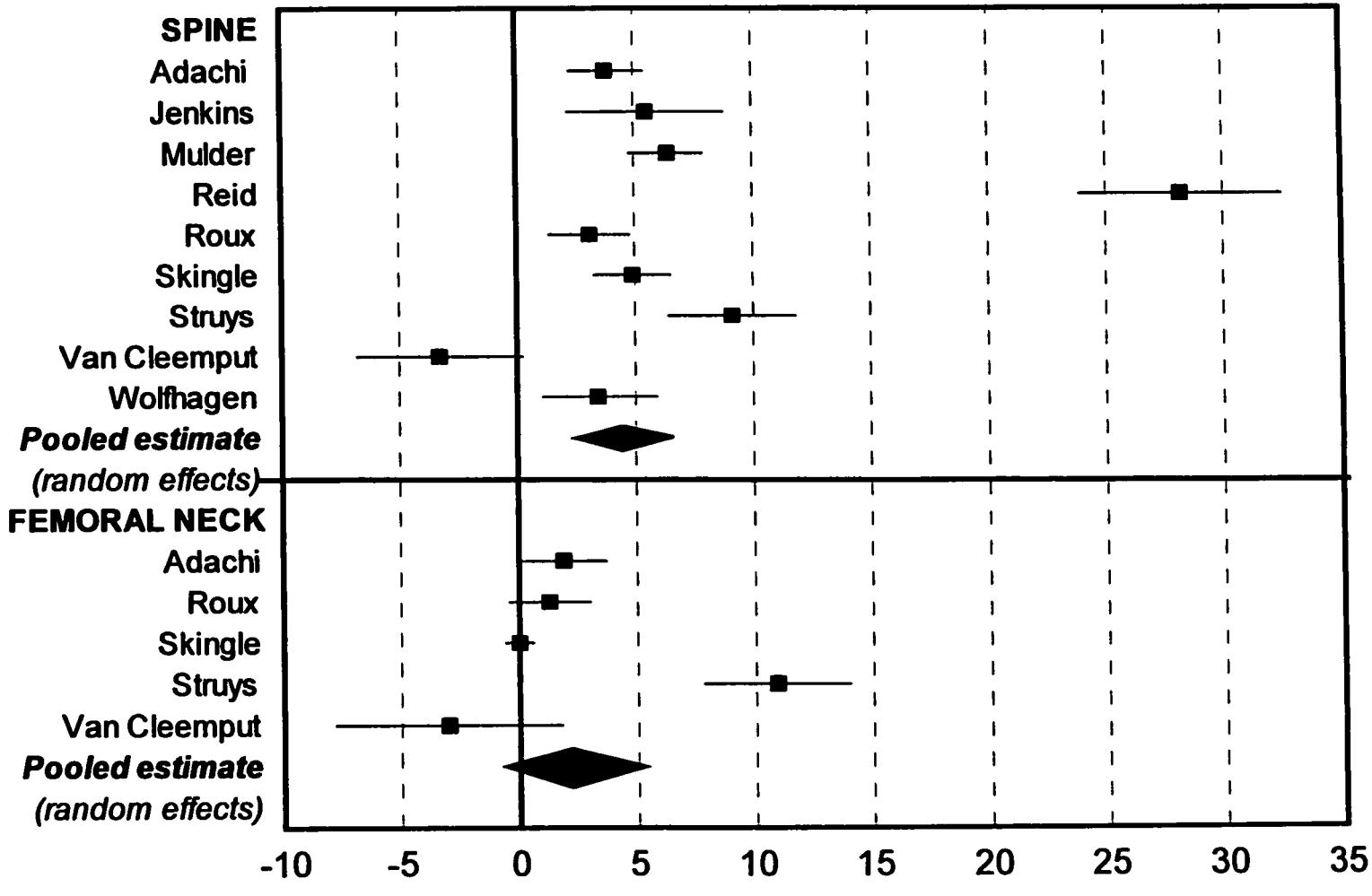
| Author | Intervention | Patient population | Mean difference | 95% confidence interval |
|---|---|---|---|---|
| ***Results at twelve months*** | | | | |
| Adachi | etidronate | rheumatoid arthritis, PMR | 1.9 | -0.0, 3.7 |
| Roux | etidronate | rheumatoid arthritis, PMR | 1.3 | -0.4, 3.0 |
| Skingle | etidronate | PMR, temporal arteritis, COPD | 0.0 | -0.6, 0.6 |
| Struys | etidronate | asthma, COPD | 10.9 | 7.8, 14.0 |
| Vancleemput | etidronate | cardiac transplant recipients | -3.0 | -7.8, 1.8 |
| Wolfhagen | Etidronate | Primary biliary Cirrhosis | 1.4 | -3.6, 6.4 |
| | | | Weighted mean difference | 95% confidence interval |
| Pooled estimate (random effects; n = 353) | | | 2.2 | -0.5, 4.9 |
| ***Results at six months*** | | | | |
| Struys | etidronate | asthma, COPD | 6.1 | 3.8, 8.4 |
| Vancleemput | etidronate | cardiac transplant recipients | -5.2 | -9.9, -0.5 |
| | | | Weighted mean difference | 95% confidence interval |
| Pooled estimate (random effects; n = 80) | | | 0.6 | -10.4, 11.7 |

## TABLE 6 - SENSITIVITY ANALYSES FOR HETEROGENEITY AND PRIMARY PREVENTION

| ANALYSIS | | WEIGHTED MEAN DIFFERENCE | 95% CONFIDENCE INTERVAL |
|---|---|---|---|
| Lumbar spine 12 months (n = 321) | | 4.5 | 3.4, 5.6 |
| Lumbar spine 6 months (n = 81) | | 4.8 | 2.6, 6.9 |
| Femoral neck 12 months (n = 272) | | 0.8 | -0.3, 1.8 |
| Primary prevention | Lumbar spine 12 months* (n = 283) | 4.4 | 3.0, 5.8 |
| Secondary prevention | Lumbar spine 12 months** (n = 280) | 3.4 | 1.9, 4.9 |

*trials 25, 27,10, 29, 34
**trials 32, 26, 19, 17
All analyses performed using a random effects model

**Figure 1- WMD and 95% CI for change in BMD at the lumbar spine and femoral neck**

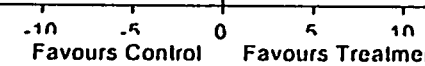


# FIGURE 2-2 - MEAN DIFFERENCE IN BMD AT THE LUMBAR SPINE AT 12 MONTHS

**Review: PREVENTION OF STEROID INDUCED OSTEOPOROSIS**
**Comparison: bisphosphonates vs placebo**
**Outcome: percent change in lumbar bmd at 12 months R**

| Study | Expt n | Expt mean(sd) | Ctrl n | Ctrl mean(sd) | WMD (95%CI Random) | Weight % | WMD (95%CI Random) |
|---|---|---|---|---|---|---|---|
| Adachi#41 | 54 | 0.61 (3.97) | 62 | -3.23 (4.72) | | 13.8 | 3.840 [2.258,5.422] |
| Jenkins#44 | 15 | 1.80 (1.57) | 13 | -3.70 (5.81) | | 10.4 | 5.500 [2.243,8.757] |
| Mulder #9 | 10 | 1.42 (1.42) | 10 | -4.95 (2.02) | | 13.9 | 6.370 [4.840,7.900] |
| Reid #6 | 16 | 19.50 (24.00) | 19 | -8.70 (30.50) | | 1.0 | 28.200 [10.134,46.266] |
| Roux#43 | 51 | 0.30 (4.35) | 56 | -2.79 (4.71) | | 13.5 | 3.090 [1.373,4.807] |
| Skingle #37 | 20 | 4.10 (3.60) | 18 | -0.80 (0.79) | | 13.7 | 4.900 [3.281,6.519] |
| Struys #29 | 19 | 5.70 (5.20) | 20 | -3.40 (3.10) | | 11.5 | 9.100 [6.396,11.804] |
| VanCleemput #30 | 19 | -10.30 (7.20) | 22 | -7.00 (3.50) | | 9.8 | -3.300 [-6.853,0.253] |
| Wolfhagen#45 | 6 | 0.40 (2.20) | 6 | -3.00 (1.80) | | 12.4 | 3.400 [1.125,5.675] |
| Total (95%CI) | 210 | | 226 | | | 100.0 | 4.500 [2.647,6.352] |

Chi-square 46.68 (df=8) Z=4.76

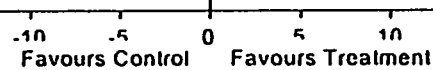


# FIGURE 2-3 - MEAN DIFFERENCE IN BMD AT THE LUMBAR SPINE AT 6 MONTHS

**Review: PREVENTION OF STEROID INDUCED OSTEOPOROSIS**
**Comparison: bisphosphonates vs placebo**
**Outcome: percent change in lumbar bmd at 6 months 1**

| Study | Expt n | Expt mean(sd) | Ctrl n | Ctrl mean(sd) | WMD (95%CI Random) | Weight % | WMD (95%CI Random) |
|---|---|---|---|---|---|---|---|
| Jenkins#44 | 15 | 1.90 (1.65) | 13 | -1.30 (2.04) | | 24.1 | 3.200 [1.812,4.588] |
| Mulder #9 | 10 | 1.10 (0.98) | 10 | -4.09 (1.42) | | 24.9 | 5.190 [4.121,6.259] |
| Struys #29 | 19 | 2.70 (2.60) | 20 | -2.00 (2.70) | | 23.3 | 4.700 [3.037,6.363] |
| VanCleemput #30 | 19 | -7.70 (5.90) | 22 | -4.60 (3.30) | | 18.6 | -3.100 [-6.090,-0.110] |
| Worth #40 | 14 | 5.50 (8.90) | 19 | -4.60 (9.80) | | 9.1 | 10.100 [3.685,16.515] |
| Total (95%CI) | 77 | | 84 | | | 100.0 | 3.500 [1.105,5.895] |

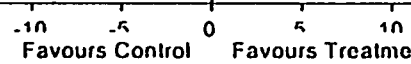
Chi-square 31.74 (df=4) Z=2.86



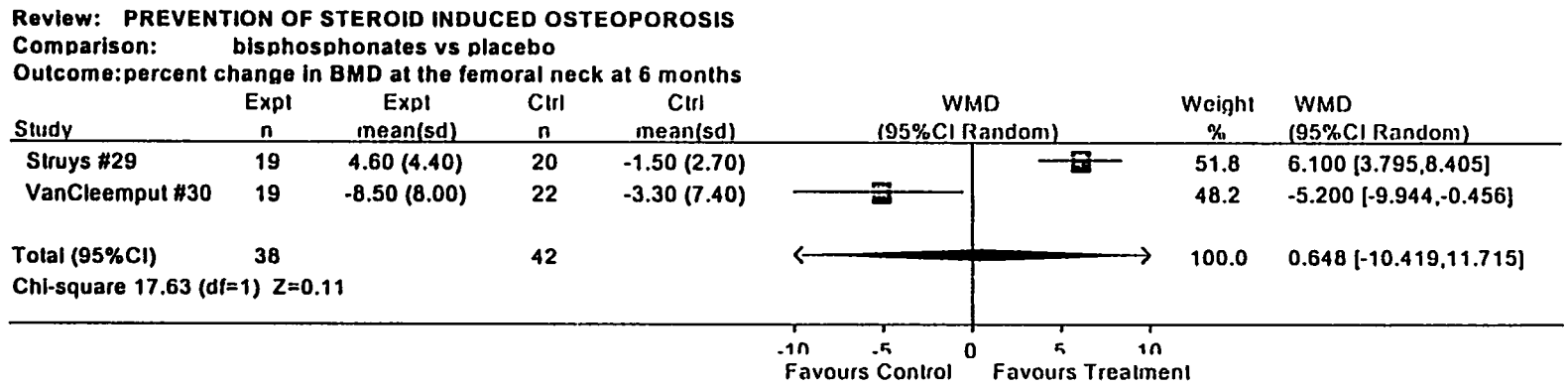
# FIGURE 2-4 - MEAN DIFFERENCE IN BMD AT THE FEMORAL NECK AT 12 MONTHS

**Review: PREVENTION OF STEROID INDUCED OSTEOPOROSIS**
**Comparison: bisphosphonates vs placebo**
**Outcome:percent change in BMD at the femoral neck at 12 months**

| Study | Expt n | Expt mean(sd) | Ctrl n | Ctrl mean(sd) | WMD (95%CI Random) | Weight % | WMD (95%CI Random) |
|---|---|---|---|---|---|---|---|
| Adachi#41 | 53 | 0.19 (4.95) | 63 | -1.67 (5.30) | | 19.0 | 1.860 [-0.008,3.728] |
| Roux#43 | 51 | -1.28 (4.14) | 56 | -2.59 (5.01) | | 19.2 | 1.310 [-0.426,3.046] |
| Skingle #37 | 20 | -1.00 (1.00) | 18 | -1.00 (1.00) | | 20.7 | 0.000 [-0.637,0.637] |
| Struys #29 | 19 | 6.80 (6.10) | 20 | -4.10 (3.10) | → | 16.5 | 10.900 [7.839,13.961] |
| VanCleemput #30 | 19 | -8.90 (8.90) | 22 | -5.90 (6.30) | | 12.6 | -3.000 [-7.790,1.790] |
| Wolfhagen#45 | 6 | -0.10 (3.70) | 6 | -1.50 (5.10) | | 12.0 | 1.400 [-3.642,6.442] |
| Total (95%CI) | 168 | | 185 | | | 100.0 | 2.191 [-0.492,4.874] |
| Chi-square 51.56 (df=5) Z=1.60 | | | | | | | |



# FIGURE 2-5 - MEAN DIFFERENCE IN BMD AT THE FEMORAL NECK AT 6 MONTHS

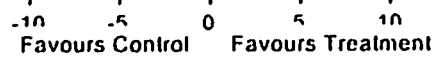


# FIGURE 2-6 - MEAN DIFFERENCE IN BMD AT THE LUMBAR SPINE AT 12 MONTHS - SENSITIVITY ANALYSIS FOR HOMOGENEOUS TRIALS

**Review: PREVENTION OF STEROID INDUCED OSTEOPOROSIS**
**Comparison: bisphosphonates vs placebo**
**Outcome: percent change in lumbar bmd at 12 months F3**

| Study | Expt n | Expt mean(sd) | Ctrl n | Ctrl mean(sd) | WMD (95%CI Random) | Weight % | WMD (95%CI Random) |
|---|---|---|---|---|---|---|---|
| Adachi#41 | 54 | 0.61 (3.97) | 62 | -3.23 (4.72) | | 19.7 | 3.840 [2.258,5.422] |
| Jenkins#44 | 15 | 1.80 (1.57) | 13 | -3.70 (5.81) | | 8.5 | 5.500 [2.243,8.757] |
| Mulder #9 | 10 | 1.42 (1.42) | 10 | -4.95 (2.02) | | 20.2 | 6.370 [4.840,7.900] |
| Roux#43 | 51 | 0.30 (4.35) | 56 | -2.79 (4.71) | | 18.4 | 3.090 [1.373,4.807] |
| Skingle #37 | 20 | 4.10 (3.60) | 18 | -0.80 (0.79) | | 19.3 | 4.900 [3.281,6.519] |
| Wolfhagen#45 | 6 | 0.40 (2.20) | 6 | -3.00 (1.80) | | 13.8 | 3.400 [1.125,5.675] |
| Total (95%CI) | 156 | | 165 | | | 100.0 | 4.500 [3.395,5.606] |

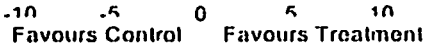
Chi-square 10.47 (df=5) Z=7.98



# FIGURE 2-7 - MEAN DIFFERENCE IN BMD AT THE LUMBAR SPINE AT 6 MONTHS - SENSITIVITY ANALYSIS FOR HOMOGENEOUS TRIALS

**Review: PREVENTION OF STEROID INDUCED OSTEOPOROSIS**
**Comparison: bisphosphonates vs placebo**
**Outcome: percent change lumbar bmd 6 months 2**

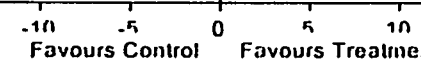
| Study | Expt n | Expt mean(sd) | Ctrl n | Ctrl mean(sd) | WMD (95%CI Random) | Weight % | WMD (95%CI Random) |
|---|---|---|---|---|---|---|---|
| Jenkins#44 | 15 | 1.90 (1.65) | 13 | -1.30 (2.04) | | 43.6 | 3.200 [1.812,4.588] |
| Mulder #9 | 10 | 1.10 (0.98) | 10 | -4.09 (1.42) | | 47.2 | 5.190 [4.121,6.259] |
| Worth #40 | 14 | 5.50 (8.90) | 19 | -4.60 (9.80) | | 9.2 | 10.100 [3.685,16.515] |
| Total (95%CI) | 39 | | 42 | | | 100.0 | 4.773 [2.635,6.912] |
| Chi-square 7.88 (df=2) Z=4.37 | | | | | | | |



## FIGURE 2-8 - MEAN DIFFERENCE IN BMD AT THE FEMORAL NECK AT 12 MONTHS - SENSITIVITY ANALYSIS FOR HOMOGENEOUS TRIALS

**Review: PREVENTION OF STEROID INDUCED OSTEOPOROSIS**
**Comparison: bisphosphonates vs placebo**
**Outcome: percent change in femoral bmd at 12 months - 2**

| Study | Expt n | Expt mean(sd) | Ctrl n | Ctrl mean(sd) | WMD (95%CI Random) | Weight % | WMD (95%CI Random) |
|---|---|---|---|---|---|---|---|
| Adachi#41 | 53 | 0.19 (4.95) | 62 | -1.67 (5.30) | | 21.2 | 1.860 [-0.015,3.735] |
| Roux#43 | 51 | -1.28 (4.14) | 56 | -2.59 (5.01) | | 23.4 | 1.310 [-0.426,3.046] |
| Skingle #37 | 20 | -1.00 (1.00) | 18 | -1.00 (1.00) | | 51.3 | 0.000 [-0.637,0.637] |
| Wolfhagen#45 | 6 | -0.10 (3.70) | 6 | -1.50 (5.10) | | 4.1 | 1.400 [-3.642,6.442] |
| Total (95%CI) | 130 | | 142 | | | 100.0 | 0.759 [-0.301,1.819] |
| Chi-square 4.99 (df=3) Z=1.40 | | | | | | | |

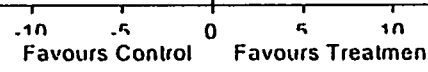


# FIGURE 2-9 - MEAN DIFFERENCE IN BMD AT THE LUMBAR SPINE AT 12 MONTHS - SENSITIVITY ANALYSIS FOR PRIMARY PREVENTION

**Review: PREVENTION OF STEROID INDUCED OSTEOPOROSIS**
**Comparison: bisphosphonates vs placebo**
**Outcome:percent change in lumbar bmd-primary prevention-2**

| Study | Expt n | Expt mean(sd) | Ctrl n | Ctrl mean(sd) | WMD (95%CI Random) | Weight % | WMD (95%CI Random) |
|---|---|---|---|---|---|---|---|
| Adachi#41 | 54 | 0.61 (3.97) | 62 | -3.23 (4.72) | | 23.7 | 3.840 [2.258,5.422] |
| Jenkins#44 | 15 | 1.80 (1.57) | 13 | -3.70 (5.81) | | 11.9 | 5.500 [2.243,8.757] |
| Mulder #9 | 10 | 1.42 (1.42) | 10 | -4.95 (2.02) | | 24.2 | 6.370 [4.840,7.900] |
| Roux#43 | 51 | 0.30 (4.35) | 56 | -2.79 (4.71) | | 22.5 | 3.090 [1.373,4.807] |
| Wolfhagen#45 | 6 | 0.40 (2.20) | 6 | -3.00 (1.80) | | 17.8 | 3.400 [1.125,5.675] |
| Total (95%CI) | 136 | | 147 | | | 100.0 | 4.401 [3.013,5.790] |

Chi-square 10.25 (df=4) Z=6.21

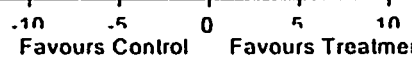


# FIGURE 2-10 - MEAN DIFFERENCE IN BMD AT THE LUMBAR SPINE AT 12 MONTHS - SENSITIVITY ANALYSIS FOR SECONDARY PREVENTION

**Review: PREVENTION OF STEROID INDUCED OSTEOPOROSIS**
**Comparison: bisphosphonates vs placebo**
**Outcome: percent change in lumbar bmd -secondary prevention-2**

| Study | Expt n | Expt mean(sd) | Ctrl n | Ctrl mean(sd) | WMD (95%CI Random) | Weight % | WMD (95%CI Random) |
|---|---|---|---|---|---|---|---|
| Eastell#39 | 40 | 1.40 (1.22) | 40 | -1.60 (1.57) | | 30.1 | 3.000 [2.384,3.616] |
| Eastell#39-2 | 40 | -0.10 (0.09) | 40 | -1.60 (1.57) | | 30.7 | 1.500 [1.013,1.987] |
| Pitt#42 | 26 | 5.10 (5.10) | 23 | 1.00 (7.19) | | 11.5 | 4.100 [0.568,7.632] |
| Skingle #37 | 20 | 4.10 (3.60) | 18 | -0.80 (0.79) | | 23.1 | 4.900 [3.281,6.519] |
| Worth #40 | 14 | 5.50 (8.90) | 19 | -4.60 (9.80) | | 4.6 | 10.100 [3.685,16.515] |
| Total (95%CI) | 140 | | 140 | | | 100.0 | 3.435 [1.938,4.932] |

Chi-square 31.87 (df=4) Z=4.50

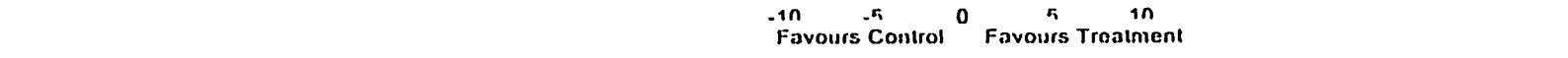


# FIGURE 2-11 - MEAN DIFFERENCE IN BMD AT THE LUMBAR SPINE AT 12 MONTHS - SENSITIVITY ANALYSIS FOR HOMOGENEOUS RANDOMIZED TRIALS

**Review: PREVENTION OF STEROID INDUCED OSTEOPOROSIS**
**Comparison: bisphosphonates vs placebo**
**Outcome: percent change in lumbar bmd -randomized 2**

| Study | Expt n | Expt mean(sd) | Ctrl n | Ctrl mean(sd) | WMD (95%CI Random) | Weight % | WMD (95%CI Random) |
|---|---|---|---|---|---|---|---|
| Adachi#41 | 54 | 0.61 (3.97) | 62 | -3.23 (4.72) | | 25.1 | 3.840 [2.258,5.422] |
| Jenkins#44 | 15 | 1.80 (1.57) | 13 | -3.70 (5.81) | | 7.1 | 5.500 [2.243,8.757] |
| Pitt#42 | 26 | 5.10 (5.10) | 23 | 1.00 (7.19) | | 6.1 | 4.100 [0.568,7.632] |
| Roux#43 | 51 | 0.30 (4.35) | 56 | -2.79 (4.71) | | 22.0 | 3.090 [1.373,4.807] |
| Skingle #37 | 20 | 4.10 (3.60) | 18 | -0.80 (0.79) | | 24.2 | 4.900 [3.281,6.519] |
| Wolfhagen#45 | 6 | 0.40 (2.20) | 6 | -3.00 (1.80) | | 13.6 | 3.400 [1.125,5.675] |
| Worth #40 | 14 | 5.50 (8.90) | 19 | -4.60 (9.80) | | 1.9 | 10.100 [3.685,16.515] |
| Total (95%CI) | 186 | | 197 | | | 100.0 | 4.124 [3.231,5.016] |

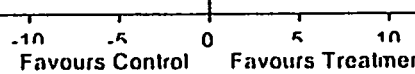
Chi-square 6.81 (df=6) Z=9.05



# FIGURE 2-12 - MEAN DIFFERENCE IN BMD AT THE LUMBAR SPINE AT 12 MONTHS - SENSITIVITY ANALYSIS FOR HOMOGENEOUS NON-RANDOMIZED TRIALS

**Review: PREVENTION OF STEROID INDUCED OSTEOPOROSIS**
**Comparison: bisphosphonates vs placebo**
**Outcome:percent change in lumbar bmd -nonrandomized 2**

| Study | Expt n | Expt mean(sd) | Ctrl n | Ctrl mean(sd) | WMD (95%CI Random) | Weight % | WMD (95%CI Random) |
|---|---|---|---|---|---|---|---|
| Eastell#39 | 40 | 1.40 (1.22) | 40 | -1.60 (1.57) | | 35.0 | 3.000 [2.384,3.616] |
| Eastell#39-2 | 40 | -0.10 (0.09) | 40 | -1.60 (1.57) | | 35.4 | 1.500 [1.013,1.987] |
| Mulder #9 | 10 | 1.42 (1.42) | 10 | -4.95 (2.02) | | 29.6 | 6.370 [4.840,7.900] |
| Total (95%CI) | 90 | | 90 | | | 100.0 | 3.467 [1.517,5.417] |
| Chi-square 42.46 (df=2) Z=3.48 | | | | | | | |

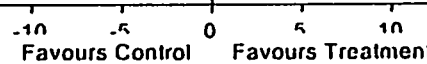


# FIGURE 2-13 - MEAN DIFFERENCE IN BMD AT THE LUMBAR SPINE WITHIN 2 YEARS

**Review: PREVENTION OF STEROID INDUCED OSTEOPOROSIS**
**Comparison: bisphosphonates vs placebo**
**Outcome: percent change in lumbar bmd within 2 years**

| Study | Expt n | Expt mean(sd) | Ctrl n | Ctrl mean(sd) | WMD (95%CI Random) | Weight % | WMD (95%CI Random) |
|---|---|---|---|---|---|---|---|
| Adachi#41 | 54 | 0.61 (3.97) | 62 | -3.23 (4.72) | | 10.6 | 3.840 [2.258,5.422] |
| Eastell#39 | 40 | 1.40 (1.22) | 40 | -1.60 (1.57) | | 12.0 | 3.000 [2.384,3.616] |
| Eastell#39-2 | 40 | -0.10 (0.09) | 40 | -1.60 (1.57) | | 12.2 | 1.500 [1.013,1.987] |
| Jenkins#44 | 15 | 1.80 (1.57) | 13 | -3.70 (5.81) | | 7.4 | 5.500 [2.243,8.757] |
| Mulder #9 | 10 | 1.42 (1.42) | 10 | -4.95 (2.02) | | 10.7 | 6.370 [4.840,7.900] |
| Pitt#42 | 26 | 5.10 (5.10) | 23 | 1.00 (7.19) | | 6.9 | 4.100 [0.568,7.632] |
| Reid #6 | 16 | 19.50 (24.00) | 19 | -8.70 (30.50) | | 0.6 | 28.200 [10.134,46.266] |
| Roux#43 | 51 | 0.30 (4.35) | 56 | -2.79 (4.71) | | 10.4 | 3.090 [1.373,4.807] |
| Skingle #37 | 20 | 4.10 (3.60) | 18 | -0.80 (0.79) | | 10.6 | 4.900 [3.281,6.519] |
| Struys #29 | 19 | 5.70 (5.20) | 20 | -3.40 (3.10) | | 8.4 | 9.100 [6.396,11.804] |
| VanCleemput #30 | 19 | -10.30 (7.20) | 22 | -7.00 (3.50) | | 6.8 | -3.300 [-6.853,0.253] |
| Worth #40 | 14 | 5.50 (8.90) | 19 | -4.60 (9.80) | | 3.4 | 10.100 [3.685,16.515] |
| Total (95%CI) | 324 | | 342 | | | 100.0 | 4.206 [2.814,5.598] |

Chi-square 104.24 (df=11) Z=5.92

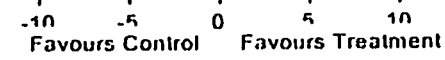


# FIGURE 2-14 - MEAN DIFFERENCE IN BMD AT THE LUMBAR SPINE WITHIN 2 YEARS - SENSITIVITY ANALYSIS FOR HOMOGENEOUS TRIALS

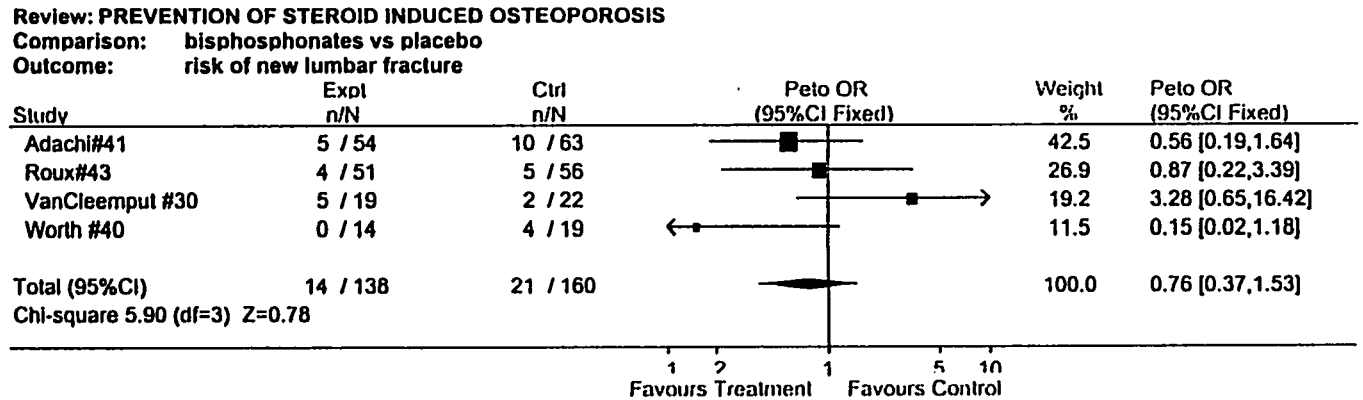
**Review: PREVENTION OF STEROID INDUCED OSTEOPOROSIS**
**Comparison: bisphosphonates vs placebo**
**Outcome:percent change in lumbar bmd within 2 years-3**

| Study | Expt n | Expt mean(sd) | Ctrl n | Ctrl mean(sd) | WMD (95%CI Random) | Weight % | WMD (95%CI Random) |
|---|---|---|---|---|---|---|---|
| Adachi#41 | 54 | 0.61 (3.97) | 62 | -3.23 (4.72) | | 16.1 | 3.840 [2.258,5.422] |
| Eastell#39 | 40 | 1.40 (1.22) | 40 | -1.60 (1.57) | | 19.1 | 3.000 [2.384,3.616] |
| Eastell#39-2 | 40 | -0.10 (0.09) | 40 | -1.60 (1.57) | | 19.4 | 1.500 [1.013,1.987] |
| Mulder #9 | 10 | 1.42 (1.42) | 10 | -4.95 (2.02) | | 16.3 | 6.370 [4.840,7.900] |
| Pitt#42 | 26 | 5.10 (5.10) | 23 | 1.00 (7.19) | | 9.2 | 4.100 [0.568,7.632] |
| Skingle #37 | 20 | 4.10 (3.60) | 18 | -0.80 (0.79) | | 15.9 | 4.900 [3.281,6.519] |
| Worth #40 | 14 | 5.50 (8.90) | 19 | -4.60 (9.80) | | 4.1 | 10.100 [3.685,16.515] |
| Total (95%CI) | 204 | | 212 | | | 100.0 | 4.087 [2.628,5.545] |

Chi-square 60.52 (df=6) Z=5.49



# FIGURE 2-15 - ODDS RATIO FOR RISK OF NEW LUMBAR FRACTURE



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# CHAPTER 3 - COST-EFFECTIVENESS OF TWO STRATEGIES FOR PREVENTING CORTICOSTEROID-INDUCED OSTEOPOROSIS IN YOUNG WOMEN

# I. INTRODUCTION

Osteoporosis and the resulting increase in incidence of nontraumatic fractures is a major health concern. This is usually a problem for post-menopausal women, and the elderly of both sexes. There are situations however, in which osteoporosis occurs in younger individuals. Such is the case with corticosteroid-induced osteoporosis. There are a number of conditions that require treatment with this medication, despite its known risks. Young and old patients with asthma, systemic lupus erythematosus, and rheumatoid arthritis are frequently treated with low to moderate doses of corticosteroid (5-15 mg/day), for prolonged periods of time. (1-4) Often the goal of therapy is to use a short course of corticosteroid as bridging therapy while slower acting immunosuppressive agents are initiated. In reality, many patients end up on corticosteroid therapy longer than expected, or require frequent short courses of the medication. Side-effects such as bone loss and fractures then occur (4,5).

In young adult patients the issue of bone loss is often ignored. These patients are usually starting therapy with a normal bone mineral density, and it may take several years before they become osteoporotic. There is also a belief among some investigators that bone loss can reverse to some extent after the discontinuation of steroids (6,7). Despite this, fractures do occur. In studies of young women with lupus and asthma, fracture rates of 11 to 42% have been found (5).

The American College of Rheumatology has recommended that patients with normal bone mass who initiate corticosteroid therapy should be started on calcium and vitamin D (8). A recent meta-analysis has shown modest difference in bone change in patients on calcium and vitamin D as compared to placebo (9), but given an average bone loss of 5% per year while on corticosteroids, this therapy only slows bone loss. The ACR

guidelines also recommend that post-menopausal women treated with steroids should receive hormone replacement therapy. There are no clinical trials evaluating hormone replacement therapy in this population, although this therapy might be expected to be beneficial. Bisphosphonates have proven efficacy in treating post-menopausal osteoporosis (10,11), as well as in the prevention and treatment of corticosteroid-induced osteoporosis (12-21) and some believe that they should be the first line agent for patients receiving this therapy (22). Most studies in corticosteroid-induced osteoporosis have evaluated etidronate, as opposed to the newer bisphosphonates.

Despite the proven efficacy of etidronate in corticosteroid-induced osteoporosis, and the ACR recommendations, patients are not routinely started on a prophylactic agent when corticosteroids are initiated (23). Perhaps the various treatment strategies need to be formally evaluated with regards to costs and outcomes, before they are embraced by the medical community.

We have conducted a systematic review of the use of etidronate in patients treated with steroids, and developed a decision analysis model based on data available in the literature. This has allowed us to evaluate the cost-effectiveness of universal, conditional prophylaxis and no prophylaxis with etidronate. We chose this patient population because it represents the greatest challenge to the physician. Older individuals with polymyalgia rheumatica or rheumatoid arthritis are likely have osteopenia to begin with, and treatment strategies are justified by scientific evidence on the treatment of post-menopausal and senile osteoporosis.

# II. METHODS

## A. Target Population

A hypothetical cohort of 35 year old women with asthma or systemic lupus erythematosus (SLE), about to initiate corticosteroid therapy was used. The women were assumed to be pre-menopausal and healthy but for their underlying diagnosis of asthma or systemic lupus erythematosus. All had normal bone mineral density, defined by a T score of 0.

## B. Probability Model

We evaluated three arms in a probability-based decision model:

- one that involved no prophylactic therapy
- one that involved universal prophylaxis with etidronate
- a conditional prophylaxis arm that involved the yearly measurement of bone mineral density, and the initiation of bisphosphonate therapy if the T score fell to -1.

All patients were treated for a period of five years. We chose this length of treatment to reflect the data in published cross-sectional studies regarding mean duration of steroid therapy in this population (1-4). Reporting of fractures in these studies was variable, so we extended the fracture risk period for another 10 years after the five years of therapy (15 years total) and used the higher risk estimates published. For the no prophylaxis and universal prophylaxis arms, outcomes were measured at the end of the five year period for BMD and after 15 years for fractures. For all arms, the cohort moved through a series of bone density states that had both fracture and cost implications. Transition

through the states was determined by pre-defined probabilities. Outcomes were determined on a yearly basis.

## C. Outcomes

The main outcome of interest was the mean change in bone density at the end of the five year treatment period. This was expressed as both the percent change from baseline, as well as the mean change in the T score. From the T score we were able to calculate the future probability of femoral neck and vertebral fractures for each arm of the model. We did not include fractures at other sites in this analysis. There were no data on forearm fractures in this patient population. The limited data on rib fractures from the asthma literature, were not felt to be generalizable to the SLE population.

We did not include other outcomes such as hypertension, glucose intolerance, or atherosclerosis in the model as these side effects of corticosteroid therapy would be expected to occur equally in all three groups. This is because therapy with bisphosphonates has no effect on these diseases.

## D. Costs

Costs included the cost of bisphosphonate therapy as well as cost of a hip and lumbar fracture. The analysis was performed from a health services perspective, and all direct medical costs were included. For each arm of the model, the expected costs incurred by that group of women was calculated.

## E. Economic Analysis

The cost-effectiveness ratios compared both the universal and conditional prophylaxis arms with the no prophylaxis arm. As well, the incremental cost-effectiveness of

universal prophylaxis compared to conditional prophylaxis was calculated. Thus there were three cost-effectiveness ratios generated for each outcome. For each arm of the model, results were expressed as the cost to prevent a loss of one T score, and the costs to prevent a hip or vertebral fracture.

## F. Data and Assumptions

It was assumed that after five years of corticosteroid treatment, women would discontinue corticosteroids, and etidronate prophylaxis if they were taking it. Bone density outcomes were assessed at this point. It was further assumed that bone density would remain stable until the onset of menopause. The fracture outcomes were calculated based on the end of treatment BMD, and reflect risk over the five year treatment period, as well as the following ten years (fifteen years total).

***a) Efficacy of etidronate:***

Efficacy of etidronate in this disease was determined from the results of the treatment arm of a clinical trial (16). We used the results reported for the pre-menopausal sub-group for the universal prophylaxis group, because the starting BMD was normal. Since the conditional prophylaxis arm did not start treatment until they had achieved low BMD, we used the results from the total treatment arm to estimate efficacy. This was done because the total group had a baseline BMD T score of -1. The pooled results from the treatment arm of the meta-analysis reported in Chapter 2 was used in a sensitivity analysis (21). It was assumed that response to therapy followed a normal distribution. This has been observed by other investigators (24). Rates of bone loss or accrual were converted to probability of maintaining bone mass or losing bone over a one year period. For the purposes of this analysis, patients had to lose or gain 10% of their bone

mass before their T score changed. We were unable to identify any serious adverse effects of bisphosphonate therapy. Nausea was a fairly common complaint, but drop-outs due to this side-effect were not consistently more frequent than that seen in the placebo group (21). For this reason, adverse effects were not included in the model. It should be noted that this model assumes treatment with etidronate, and that the newer bisphosphonates may have a higher incidence of gastro-intestinal adverse effects.

***b) Probability of developing osteoporosis:***

*i. No prophylaxis:*

Cross-sectional studies of younger women with asthma or lupus were examined to determine the incidence of osteopenia and osteoporosis after a mean of five years of steroid therapy without prophylaxis (1-4).

Results were expressed as the probability of having a certain T score at the end of five years. We were also able to calculate the expected or mean percent change in bone mass for each arm from these data.

*ii. Conditional arm*

The range of probabilities was determined in two ways for this arm. First we used data from the placebo arm in clinical trials to determine the yearly rate of bone loss experienced by patients initiating treatment with corticosteroids, in the absence of etidronate prophylaxis (16,21). Using the mean percent change plus standard deviation in the placebo arms, a probability curve was derived resulting in the annual probability for maintaining normal bone mass. For this analysis, we have assumed a linear rate of bone loss, that is the probability of bone loss is the same for all five years. As a comparison, we used the probabilities derived from the cross-sectional

studies, as outlined for the no prophylaxis arm. We chose point estimates for probability of osteopenia such that the probability of normal bone mass was the same for the no prophylaxis and conditional prophylaxis arm; as would be true in life.

*iii. Universal prophylaxis*

As all patients in this arm were treated with etidronate, the probability of osteoporosis was derived from the efficacy of etidronate estimate. That is, if there was 99% efficacy, then there was a 1% probability of osteoporosis.

***c) Fracture risk***

For both vertebral and hip fracture locations relative risks for a one standard deviation loss of lumbar bone density were identified from a recent meta-analysis (25).

*i. Vertebral fractures*

For the calculation of vertebral fracture incidence we used a baseline rate of vertebral fractures, which was reported as occurring in a group of normal women (not on corticosteroids) with the highest quartile of lumbar BMD over an eight year period (26). Another paper reported the risk of vertebral fracture over a 5 year period, in a group of post-menopausal women with the highest tertile of bone mass (27). The values reported for vertebral fractures in the Melton paper (26) were determined from a group of women who were over age 50 at baseline. The vertebral fracture results were tempered by the results reported by Ross (27) which were half the magnitude. Multiplying the baseline risk by the relative risk gave us the cumulative incidence for vertebral fractures that corresponded to the three different levels of lumbar BMD. These results were compared with those reported for young

women on steroids for five years (4), to validate the fracture rate used in the no prophylaxis arm.

*ii. Hip fracture*

Previously published data (28) on annual risk of hip fracture for women age 45-54, with normal bone density were used to calculate baseline risk of hip fracture. In order to accurately calculate cummulative hip fracture rates from an annual propability, we assumed that fractures were independant events. We therefore calculated the cumulative risk of hip fracture over the next ten years, as ten times the annual probability.

***d) Costs***

Direct medical costs only were included due to the lack of information regarding indirect costs for these clinical problems. All costs are expressed in 1997 Canadian dollars, except where indicated. An exchange rate of 1.46 was used to convert the hip fracture costs from US dollars. As inflation was felt to be minimal in the last three years, it was not taken into account. For this same reason an adjustment was not made to the hip fracture costs reported in 1994 dollars.

*i. Treatment*

Costs of cyclic etidronate therapy were determined through the University of Alberta Hospital formulary. Our estimate for the treatment cost was $147.00/year. There were no extra costs from physician visits for monitoring therapy, as patients were being seen on a regular basis for their underlying condition.

*ii. Lumbar fracture*

Costs of lumbar fracture were calculated for provincial sources, and included a visit to the emergency room, a spinal radiograph (PA and lateral), and ten days therapy with calcitonin. We estimated that only 33% of vertebral fractures would be symptomatic, and therefore the expected cost of a lumbar fracture was one third the calculated cost, or $100/fracture.

*iii. Hip fracture:*

Costs of a hip fracture were determined from a recent study that calculated the excess health costs in the year following a primary hip fracture (29). This method takes into account the background level of health care utilization. Costs reflect both hospital, long term care facility, and homecare costs incurred in the first year after hip fracture. All hip fracture sequelae were included in the costing, such as death and institutionalization. Estimates for excess health care costs in the year following hip fracture ranged from $9,255 to $31,175, with a mean value of 22,273 (1994 US dollars). We used the figure of 11,690 $US or 17,067 $CDN, which represents the costs incurred by women in the 50 - 64 year age range.

*iv. Densitometry*

Densitometry costs were not considered. It was felt that patients on steroids would have their BMD measured on a regular basis, regardless of whether or not they were receiving prophylactic therapy.

*v. Discounting:*

Discounting of the cost of fracture over the ten year period was done by using the five year discounted rate as an average value ($13,375/hip fracture and

$78/vertebral fracture). Costs were discounted at a rate of 5% per year. Cost of treatment was not discounted.

***e) Sensitivity analysis***

One way sensitivity analyses only were done. We don not do a sensitivity analysis on costs.

*i. Bone loss*

We varied the estimates for osteopenia and osteoporosis in the conditional and no prophylaxis arms, expressed as a best and worse case scenario. Again, we had to keep the probability of abnormal bone mass consistent for the 2 arms.

*ii. Efficacy of bisphosphonates*

We conducted a sensitivity analysis varying the estimate for efficacy. The pooled effect estimate from the meta-analysis was used.

*iii. Reversal of bone loss*

As a sensitivity analysis, we examined the possibility of bone density recovery after discontinuation of corticosteroid therapy. This was assumed to occur over a period of five years after discontinuation of therapy. The fracture risk was halved, to reflect the shorter period of risk (ten years vs. fifteen).

# III. RESULTS

## A. Efficacy of Etidronate

For those women with normal bone mass starting etidronate, 99% would maintain their normal bone mass, and 1% would lose enough bone to lower their T score. In those starting treatment with low bone mass (conditional arm), 99% would maintain a low bone mass and 1% would gain bone mass. The difference in efficacy is due to larger standard deviation in the low bone mass group. We calculated response to therapy two ways, assuming either a linear response to therapy, or a plateau response after the first year. The bone accrual in the treated patients was small enough that assuming either response to therapy, the women were unable to increase their bone mass enough to raise their T score.

## B. Probabilities of Bone Loss

For the group who did not take prophylactic therapy with bisphosphonates, the probability of becoming osteopenic (-1>T>-2.5) over the five years was 45%, and the rate of osteoporosis (T<-2.5) was 15%. The five year cumulative probability of becoming osteopenic for the conditional prophylaxis arm was 59%, with 0% developing osteoporosis. In the women taking prophylactic therapy from the start, the probability of osteopenia was 1%. The probabilites used in the model, ranges reported in the literature, as well as sources used are summarized in Table 1.

## C. Expected Rates of Bone Loss

Bone loss in each group or arm was expressed as the expected T score in each arm, as well as the expected percent change in bone mass for each arm, after 5 years of

treatment with steroids. For the no prophylaxis arm, the average women would end up with a T score of -1, which relates to a 10% loss of bone over three years. For the conditional prophylaxis arm the results are a T score of -0.59 and a 5.9% loss of bone density. In the universal prophylaxis arm the expected T score was -0.01, and the expected change in bone density was 0.1%. These results are reported in Table 2.

## D. Expected Rates of Lumbar and Hip Fracture

The fifteen year cumulative lumbar fracture rates were 10%, 6%, and 2% for the no, conditional, and universal prophylaxis arms of the model respectively. For the conditional and no prophylaxis arms, we chose to use the higher estimates of fracture, which were derived from the cross-sectional study (4). We felt the data were more realistic, as the lower estimates were derived from cohorts of normal post-menopausal women. The fifteen year cummulative probabilities of hip fractures are 0.47%, 0.42%, and 0.30% for the no, conditional, and universal prophylaxis arms of the model. The point estimates used, ranges, and sources are summarized in Table 3.

## E. Expected Costs

Given the above probabilities, the average cost per patient was $75 for the no prophylaxis arm, $167 for the conditional prophylaxis arm, and $777 for the universal prophylaxis group over the five year period.

## F. Incremental analysis

Comparing the conditional prophylaxis strategy with no treatment resulted in cost-effectiveness ratios of $2,300 for vertebral fractures, and $184,000 for hip fractures. That is, it would cost $2,300 to prevent one vertebral fracture, and $184,000 to prevent

one hip fracture. Universal prophylaxis vs no treatment costs $8,775 for vertebral fractures, and $351,000 for hip fractures. The incremental cost-effectiveness ratios comparing universal prophylaxis with conditional prophylaxis were $15,250 per vertebral fracture prevented, and $610,000 per hip fracture prevented. These results are summarized in Table 4.

## G. Aggregate Outcomes

Assuming 1,000 women to be treated in each arm, the no prophylaxis arm would cost $75,000 and result in 100 lumbar and 4.7 hip fractures. The conditional prophylaxis arm would cost $167,000 and result in 60 lumbar and 4.2 fractures. For universal prophylaxis, the cost would be $777,000 and result in 20 lumbar and 3 hip fractures.

## H. Sensitivity analyses

***a) Bone loss***

Different rates of bone loss were used to assess the impact on the cost-effectiveness ratios. Changes in the probability of osteopenia had to be made for both the no and conditional prophylaxis arm at the same time for consistancy. When we used the best case scenario of 45% osteopenia in the conditional arm, 35% osteopenia in the no prophylaxis arm, and 12% osteoporosis in the no prophylaxis arm, the expected BMD change in the conditional and no prophylaxis arms changed to -4.5%, and -6.5% respectively. When we used the worst case scenario of 78% osteopenia in the conditional arm, 60% osteopenia, and 18% osteoporosis in the no prophylaxis arm, the expected change in BMD was -7.8% and -11% for the conditional and no prophylaxis arms respectively. Hip fracture rates did not vary significantly between the best and worst case scenarios: 0.44-0.51% for the no prophylaxis arm; and 0.4-0.47% for the

conditional prophylaxis arm. Lumbar fracture rates based on expected change in BMD would fluctuate between 6.5-11% for the no prophylaxis arm, and 4.5-8% for the conditional prophylaxis arm. The expected costs ranged from $165-$177 for the conditional prophylaxis strategy, and from $64-$77 for the no prophylaxis strategy. These results are summarized in Table 5. Cost-effectiveness ratios taking into account best and worst case scenarios are reported in Table 6.

***b) Efficacy of bisphosphonates***

We initially calculated the probability of maintaining normal bone mass for the subgroup of a clinical trial (16). Using the pooled effect estimate from the meta-analysis on bone density (21), changed the probability of maintaining bone mass while on prophylactic therapy from 99% to 100%, due to a smaller standard deviation. This did not change any of the fracture outcomes.

***c) Spontaneous reversal of osteopenia***

Given the suggestion by some authors (6,7) that bone density may improve after discontinuation of corticosteroids, we assumed a scenario where bone density would increase yearly, returning to pre-treatment values by five years. Patients were no longer at risk of fracture for the full ten years, and to reflect that the fracture rates were halved. The expected costs per arm were $37 for no prophylaxis, $138 for conditional prophylaxis, and $756 for universal prophylaxis. The cost-effectiveness ratios for the conditional arm were $5,050 for vertebral fractures and $202,000 for hip fractures. For the universal prophylaxis arm the ratios were $17,975 for vertebral fractures and $719,000 for hip fractures. All ratios were calculated by comparing the above treatment strategies to no prophylaxis (Table 7).

# IV. DISCUSSION

This study analyzed three strategies for dealing with the bone loss experienced by young women starting long term treatment with corticosteroids. We chose to compare the efficacy and costs of no prophylactic treatment with etidronate, universal prophylaxis, and conditional prophylaxis only if bone density decreased below a T score of -1.

It is difficult to estimate the proportion of patients currently being offered prophylactic therapy in this age groups. Some new data suggest that overall the prescription rate for all anti-resorptive therapy is increasing (23). This increase however is more evident in the post-menopausal age group, with the majority of young women receiving no prophylaxis. It is impossible to tell whether the variation in prescribing prophylaxis is due to practice patterns or selective screening of bone density. It would appear that a systematic process is not being used in decision making regarding osteoporosis prevention in corticosteroid treated patients.

The results of this analysis show a significant amount of osteopenia (T score -1) developing in the no prophylaxis arm. This would be associated with a large number of vertebral fractures. While it is true that the majority of these fractures are asymptomatic (30), there is increasing recognition of long term disability (31) and decreased quality of life associated with vertebral fractures.

Osteopenia carries a much smaller risk of hip fractures than osteoporosis (T score -2.5). The women in this simulation, however, are about to enter menopause, and will likely experience a second phase of rapid bone loss. Most women experience this rapid bone loss in the five to ten years after the onset of menopause (32). By entering the peri-

menopausal period with a lower than normal bone mass, these women might be expected to be more osteoporotic in their sixties than the average woman.

The cost-effectiveness ratios comparing the two treatment regimens with the no treatment option, reveal a more favorable result for the conditional arm ($2,300 and $184,000 for vertebral and hip fractures respectively) versus the universal arm ($8,775 and $351,000 for the same fractures). Even in the sensitivity analyses, which varied the probabilities of osteopenia and fracture, the conditional arm remained the more cost-effective of the two treatment options. Furthermore , the added cost of treating everyone over treating conditional on low BMD did not seem to justify the small increase in efficacy, as evidenced by the large cost-effectiveness ratios generated ($15,250 and $610,000 for vertebral and hip fractures respectively).

In determining prevalence rates for osteopenia and vertebral fractures for this analysis, we were limited by the paucity of data on this subject. There have been many more studies done on rheumatoid arthritis patients treated with corticosteroids (33-37). This population, however, is older and experiences a complex interaction between disease activity and corticosteroid adverse effects (33), which makes extrapolation of findings to other populations impossible. The data on young SLE and asthma patients was extracted from cross-sectional studies, with no prospective cohorts. Despite this limitation, the prevalence figures for osteopenia in this population were consistant among studies (1-5). The prevalence of vertebral fractures, however, was more variable.

Our estimates for hip fracture risk was likewise hampered by the limited availability of literature. We had to use estimates from post-menopausal women not taking steroids. For the purposes of this analysis, we assumed that the equivalent BMD levels in the two groups would result in equivalent hip fracture rates, regardless of the underlying

diagnosis. As a precaution, we used fracture risk over the subsequent ten years of follow-up and not lifetime risk of fractures in this analysis. Given the young age of this patient group, as well as the potential for increased mortality due to the underlying diseases, we did not feel we could use conventional methods for calculating lifetime risk of fracture.

The osteopenia and fracture data is therefore limited by the methodological short comings of cross-sectional study design, and use of extrapolated data from a normal population. True incidence and prevalence of osteopenia and fractures in this population can only be determined in prospective, inception cohort studies.

Data on efficacy of etidronate, on the other hand were plentiful, and of good quality. We feel confident that our estimates surrounding response to therapy are accurate. We chose to use the bisphosphonate, etidronate, rather than one of the second generation formulations because the efficacy literature is thus far dominated by etidronate data. Data on the use of alendronate in post-menopausal women has shown this drug to be at least as efficacious as etidronate in preventing bone loss and fractures (10,11). It seems likely that its use in corticosteroid-induced osteoporosis will be equally efficacious.

It was surprising to see that an analysis of prevention of corticosteroid-induced osteoporosis has not been previously reported in the literature. This is a heterogeneous problem, with subgroups of young individuals (SLE, asthma), post-menopausal women (rheumatoid arthritis), and even the elderly (polymyalgia rheumatica). We chose to examine the younger individuals, because the solution to the problem is not intuitive. If elderly or post-menopausal women with pre-existing osteoporosis are started on corticosteroids, there is abundant efficacy literature to support the use of etidronate (12-

21). It is not clear whether prophylaxis of individuals with normal bone density should be advocated. Our analysis aimed to clarify this issue, using the best available data.

## V. CONCLUSIONS

We would conclude that the routine use of etidronate prophylaxis in young women about to initiate long term corticosteroid therapy, is not supported by our findings. It seems prudent to screen for osteopenia in all patients in whom corticosteroids are initiated, and prescribe etidronate for those with a T score of -1, in order to prevent further bone loss and fractures.

# TABLE 1 - PROBABILITIES USED IN THE DECISION MODEL

| OUTCOME | BASELINE PROBABILITY | RANGE | SOURCE |
|---|---|---|---|
| Osteopenia in no prophylaxis | 45% | 35%-60% | Formiga, Pons, Packe, Adinoff |
| Osteoporosis in no prophylaxis | 15% | 12%-18% | Formiga, Pons |
| Osteopenia in conditional arm | 60% | 34%-78% | Adachi, Homik, Formiga, Pons, Packe, Adinoff |
| Osteoporosis in conditional arm | 0% | N/A | Adachi, Homik |
| Osteopenia in universal arm | 1% | N/A | Adachi, Homik |
| Osteoporosis in universal arm | 0% | N/A | Adachi, Homik |

## TABLE 2 - EXPECTED BMD FOR EACH ARM OF THE MODEL (AFTER 5 YEARS)

| OUTCOME | MODEL STRATEGY | | |
|---|---|---|---|
| | NO PROPHYLAXIS | CONDITIONAL PROPHYLAXIS | UNIVERSAL PROPHYLAXIS |
| BMD % change from baseline | 10 | 5.9 | 0.1 |
| change in T score | -1 | -0.59 | 0.01 |

## TABLE 3 - EXPECTED 15 YEAR CUMULATIVE PROBABILITY OF HIP AND LUMBAR FRACTURES FOR EACH ARM OF THE MODEL

| FRACTURE LOCATION | MODEL STRATEGY | | |
|---|---|---|---|
| | NO PROPHYLAXIS | CONDITIONAL PROPHYLAXIS | UNIVERSAL PROPHYLAXIS |
| Lumbar | 10%(5%-10%)<br>(Melton, Ross, Marshall*, Pons) | 6%(4%-6%)<br>(Melton, Ross, Marshall*, Pons) | 2%(2%-4%)<br>(Melton, Ross) |
| Hip | 0.47%<br>(Tosteson, Marshall**) | 0.42%<br>(Tosteson, Marshall**) | 0.30%<br>(Tosteson) |

*using a relative risk of 2.3

**using a relative risk of 1.6

## TABLE 4 - COST-EFFECTIVENESS RATIOS FOR PREVENTING VERTEBRAL AND HIP FRACTURES

| MODEL STRATEGY | VERTEBRAL FRACTURE | HIP FRACTURE |
|---|---|---|
| conditional prophylaxis* | $2,300 | $184,000 |
| universal prophylaxis* | $8,775 | $351,000 |
| universal prophylaxis** | $15,250 | $610,000 |

*compared to no prophylaxis

** compared to conditional prophylaxis

## TABLE 5 - SENSITIVITY ANALYSIS FOR BEST AND WORST CASE ESTIMATES OF BONE LOSS.

| OUTCOME | CONDITIONAL PROPHYLAXIS | | NO PROPHYLAXIS | |
|---|---|---|---|---|
| | **Best case** | **Worst case** | **Best case** | **Worst case** |
| Mean change BMD | -4.5% | -7.8% | -6.5% | -1.1% |
| Vertebral fractures | 4.5% | 8% | 6.5% | 11% |
| Hip fractures | 0.4% | 0.47% | 0.44% | 0.51% |
| Expected cost | $165 | $177 | $64 | $77 |

## TABLE 6 - COST-EFFECTIVENESS RATIOS FOR THE SENSITIVITY ANALYSIS ON BONE LOSS

| MODEL STRATEGY | VERTEBRAL FRACTURES | HIP FRACTURES |
|---|---|---|
| **Best case scenario** | | |
| Conditional prophylaxis* | $5,050 | $252,000 |
| Universal prophylaxis* | $15,844 | $509,285 |
| **Worst case scenario** | | |
| Conditional prophylaxis* | $3,333 | $250,000 |
| Universal prophylaxis* | $7,777 | $333,333 |

* as compared to no prophylaxis

## TABLE 7 - COST-EFFECTIVENESS RATIOS FOR THE SENSITIVITY ANALYSIS ON SPONTANEOUS REVERSAL OF OSTEOPENIA

| MODEL STRATEGY | VERTEBRAL FRACTURES | HIP FRACTURES |
|---|---|---|
| Conditional prophylaxis* | $5,050 | $202,000 |
| Universal prophylaxis* | $17,975 | $719,000 |

*as compared to no prophylaxis

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# CHAPTER 4 - CONCLUSIONS

This thesis aimed to examine the issue of bone loss in corticosteroid-treated individuals. Through systematic review of the literature, the populations at risk for this problem were identified. This included a selection of patients with asthma, systemic lupus erythematosus (SLE), rheumatoid arthritis, polymyalgia rheumatica, inflammatory bowel disease and primary biliary cirrhosis. This was a heterogeneous group of patients at risk, with many individual factors that contribute to bone loss. None the less, they share a similar exposure to moderate dose corticosteroids (7 - 15 mg/day), for a variable length of time (1-13). There are reports of significant osteopenia and osteoporosis in all patient populations, although prevalence differs between disease groups. In some, fractures occur while the patients are on therapy (4,5).

The scope of the problem is clearer if we separate the population at risk into categories. The first would be elderly individuals (age>70), with polymyalgia rheumatica or long standing rheumatoid arthritis. Many of these patients may already suffer from senile osteoporosis. With the initiation of corticosteroids, further bone loss occurs, and fractures are likely (11-13). In the second category we have post-menopausal women, predominantly suffering from rheumatoid arthritis. In rheumatoid arthritis we see disease-related bone loss, localized to the peri-articular area, as well as generalized bone loss. The patients have experienced menopause and the rapid phase of bone loss that accompanies that condition. In these patients initiation of corticosteroids may lessen disease activity and halt the disease-related loss of bone (6). On the other hand, it contributes to bone loss as well (6-10). The third category of patients who are treated with corticosteroids are young adults. Diseases such as asthma and SLE predominate. The SLE group is predominantly made up of women (mostly pre-menopausal). These individuals, for the most part, have normal bone mass. They lose bone when treated

with corticosteroids, but severe osteoporosis and fractures may not be evident until later in life (1-4).

Each of these patient categories represents a unique challenge to the physician aiming to prevent osteoporosis. One could argue that in the first two categories, the pre-existing risk factors for osteoporosis are enough of an indication for treatment with bone resorbing agents (14). In the third category, however, it is unclear how much of a lasting impact, therapy with corticosteroids will make on bone health.

Review of the literature also reveals that there is no systematic prescribing of prophylactic therapy in corticosteroid treated individuals (15), despite the presence of guidelines on this subject (16). There has been some concern that the guidelines are not based on the best scientific evidence available (17).

For this reason we decided to critically evaluate the evidence regarding efficacy of bone resorbing agents in preventing corticosteroid-induced osteoporosis. We then used that information to model several treatment strategies for the most challenging population, young women.

## I. SYSTEMATIC REVIEW OF THE LITERATURE

We conducted a systematic review of the English literature, in order to identify all experimental research on the subject of prevention or treatment of corticosteroid-induced osteoporosis. The systematic review was conducted in the context of a Cochrane Collaboration review. The Cochrane Collaboration was able to provide guidelines for the execution of a comprehensive systematic review of the literature(18).

We identified a number of studies addressing the topic of prevention or treatment of corticosteroid-induced osteoporosis. About half were case series or retrospective cohort

studies. The rest were prospective clinical trials. Only calcium, vitamin D, calcitonin, bisphosphonates, and fluoride had clinical trials evidence with regards to their efficacy in this condition. Meta-analyses regarding the use of calcium, vitamin D and calcitonin showed only modest efficacy (19,20). The trials involving the use of bisphosphonates displayed the highest efficacy.

## II. EFFICACY OF BISPHOSPHONATES

We chose to conduct a meta-analysis of the clinical trials evaluating bisphosphonates, in order to provide a more accurate estimate of efficacy. While all but one of the trials showed a positive effect, the magnitude of that effect varied among the trials (21-24, 26-32).

Most of the studies evaluated etidronate, with one trial each evaluating two of the newer bisphosphonates (21,22). The study populations were heterogeneous, being comprised of a combination of disease and age groups. There was one study population of cardiac transplant recipients, and this group had quite a different response to therapy compared to the rest (23).

When we combined the trials there was significant statistical heterogeneity. Where we could account for this heterogeneity in study methodology, we excluded those trials in a sensitivity analysis. This was the case with three trials. One was the cardiac transplant trial (23), one used a different method of bone density measurement (felt to exaggerate changes in trabecular bone)(21), and one had extremely osteoporotic study subjects at baseline (24). The resulting efficacy estimates did not change dramatically after exclusion of these trials.

The results showed that patients treated with bisphosphonates, on average, gained 4.5% more bone mass than those patients on calcium alone, at the lumbar spine. The results for those trials involving primary prophylaxis of osteoporosis was 4.4%, while those trials using bisphosphonates for secondary prophylaxis reported a 3.4% difference between groups (25).

The results at the femoral neck were not as promising, with much more heterogeneity between trials. The summary difference between the treatment and placebo group was only 2.2%, and it did not reach statistical significance.

Vertebral fracture prevention could not be meaningfully assessed by this analysis, as only a small number of trials reported data, and results were heterogeneous.

Drop outs due to adverse effects were infrequent in the study subjects taking this drug. Because of the number of trials reporting no drop outs, the results were skewed by those trials where drop-outs were reported.

We conclude that bisphosphonates are efficacious in preventing and treating corticosteroid-induced osteoporosis. Furthermore, subgroup analysis in one of the trials seemed to indicate that efficacy was consistant across all age groups (28). We could not draw conclusions about fracture prevention, although the trend was towards less fractures in the treatment group.

## III. DECISION ANALYSIS

Our next task was to determine the optimum strategy for dealing with young women about to initiate corticosteroid therapy. It appeared that in the majority of cases, prophylactic therapy was not being prescribed (15). The possible strategies therefore

included: no prophylaxis, prophylaxis conditional on a low bone mass, and universal prophylaxis.

We determined from several cohort studies that young women with asthma and SLE were on corticosteroid therapy for 5-6 years (1-4) This is why we chose to run the model over a five year period. These papers also gave us an indication of the prevalence of osteopenia experienced by this group. This result was surprisingly consistent among studies, although reports of vertebral fracture prevalence were more variable.

We applied the efficacy estimates from the meta-analysis (as well as a single study reporting data on young women), and determined that once started on therapy a young woman would most likely maintain her initial bone mass. That is, The therapy appeared to halt further bone loss, more than actually causing significant bone accrual. This meant that the women in the universal prophylaxis group maintained a normal bone mass. On the other hand, a proportion of the women in the conditional arm developed osteopenia (T score = -1), and once treated, maintained that T score. The non treated individuals ended up with a whole range of bone states-that is, a portion were osteopenic, a portion osteoporotic, and a portion normal with respect to bone mass.

We then extrapolated the bone density results to fracture risk, again being guided by the cross-sectional data. Some risk estimates had to be obtained from post-menopausal women with normal bone density. Fractures of both the vertebra and femoral neck were predictably highest in the no prophylaxis group, and lowest in the universal prophylaxis group.

Costs for fractures were also estimated, and cost-effectiveness of the various treatment strategies calculated. The results showed that costs to prevent a vertebral fracture were

in the $2,000 - $15,000 range. The ratios for prevention of hip fractures were proportionately higher ($180,000 - $500,000), due to the low incidence of these fractures.

Because we examined two types of fracture, two sets of cost-effectiveness ratios were calculated. The only way to combine the results would be if there was a common outcome measure. This is usually presented in the form of quality adjusted life years or QALY's. This is one area where research is currently being done to assess the health impact of osteoporotic fractures (33-35). When this information is added to a cost-effectiveness analysis, the resulting cost-utility analysis may provide more clinically relevant conclusions. This is especially the case when we are dealing with low cost outcomes (vertebral fractures).

Taking into account the strengths and limitations of the analysis, we concluded that it was more cost-effective to treat selectively, based on the presence of low bone mass (conitional prophylaxis), than to provide either no treatment or universal prophylaxis.

## IV. RECOMMENDATIONS FOR FUTURE RESEARCH

This analysis was conducted using information currently published in the medical literature. While some aspects of this clinical problem have been fully addressed by the medical community other aspects have not.

The data on efficacy of bisphosphonates, particularly etidronate is strong, and consistently show a positive effect. There are a large number of randomized controlled trials, half of which deal with an inception cohort of patients about to initiate corticosteroids. This is important because of the premise that steroid-induced bone loss may be more prominent in the first year.

One area that requires further reseach is the efficacy of bisphosphonates in preventing organ transplant-related bone loss. The meta-analysis conducted identified a clinical trial whose study population included cardiac transplant recipiants. This was the only study which reported a lack of efficacy regarding bisphosphonates. Research has been done outlining factors in these patients which make their osteoporosis more difficult to treat. We now need clinical trials, evaluating different treatment regimens to identify an efficacious agent for the prophylaxis of bone loss.

Data on the incidence and prevalence of osteopenia and fractures in this population is lacking. Even in the other disease groups previously mentioned (elderly with polymyalgia rheumatica and post-menopausal women with rheumatoid arthritis), controversy exists regarding the magnitude of this problem. There are no inception cohorts to outline the natural history of bone loss in steroid treated individuals, and no long term follow-up studies to determine fracture incidence.

One of the problems with vertebral fracture diagnosis is the large percentage of asymptomatic fractures that require xray survey to be diagnosed. Criteria to diagnose these fractures are varied as are the corresponding sensitivities and specificities (36,37). For this reason, determining vertebral fracture incidence is difficult.

Hip fracture incidence and prevalence is much easier to document, as they almost always require hospitalization and surgery. This fracture, however, occurs much later in life than other osteoporotic fractures and would require extremely long follow-up studies to determine incidence and prevalence. In this situation, the problem may need to be addressed by case control studies.

Much study has gone into costing for hip fractures. As this problem involves hospitalization, large databases of resource utilization figures are available to calculate

costs. Vertebral fractures are more difficult to cost, due to the number of asymptomatic fractures, and the outpatient management of the remainder. There is recent evidence that vertebral fractures may be more costly than previously thought (38).

The deficits in costing are the lack of data on indirect costs. CCOHTA guidelines recommend that analyses conducted from a societal perspective, include indirect costs. At the same time only a minority of analyses include indirect costs. This is an area that requires further data to be gathered. Indirect costs would capture more of the impact of vertebral fractures.

Steroid-induced osteoporosis is a significant problem and has been insufficiently addressed by medical practitioners. Although many assumptions had to be made in order to complete this analysis, we believe that it has summarized the best of currently available knowledge on this subject.

Based on our findings, we would recommend that patients need to be screened in a more consistent manner, prior to receiving corticosteroids, and those with osteopenia receive bisphosphonate prophylaxis. Although not specifically addressed in this analysis, we believe that patients also need to be counseled regarding optimal nutritional and exercise strategies, that enhance maintenance of bone mass.

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# APPENDIX 1 - CLINICAL SEARCH TERMS USED IN MEDLINE

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 - CLINICAL SEARCH TERMS USED IN EMBASE

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

# APPENDIX 3 - FORMULAE FOR META-ANALYSIS:

### *1. Peto Odds Ratio (fixed effects)*

| | treatment | control |
|---|---|---|
| | a | b |
| | c | d |

$E_i$ = expected number of events in the treatment group.

$O_i$ = observed number of events in the treatment group

$V_i$ = variance of the odds ratio

$$E_i = \frac{(a+c)(a+b)}{ni}$$

$$O_i = a$$

$$V_i = \frac{E_i^*(b+d)(c+d)}{n_i(n_i - 1)}$$

### *2. Weighted mean difference using a fixed effects model:*

$Md_i$ = mean difference for each trial

$W_i$ = weight for each trial

c = control group

t = treatment group

$Md_i = mean_c - mean_t$

$$V_i = \frac{sd_c^2}{n_c} + \frac{sd_t^2}{n_t}$$

$$W_i = \frac{1}{V_i}$$

$V_i$ = variance of the mean difference for each trial

WMD = weighted mean difference

Q = statistical test for heterogeneity

$$WMD = \frac{s(W_i^*Md_i)}{sW_i}$$

$$Q = sW_i (Md_i - WMD)^2$$

### *3. Weighted mean difference for random effects model*

$Md_i$ = mean difference for each trial

$V_i$ = variance of the mean difference for each trial

$W_i$ = weight for each trial

WMD = weighted mean difference

c = control group

Q = statistical test for heterogeneity

t = treatment group

C = weighting correction for between study variation

$Md_i = mean_c - mean_t$

$T^2$ = between studies variation

df = degrees of freedom for the Q statistic

$$V_i = \frac{sd_c^2}{n_c} + \frac{sd_t^2}{n_t}$$

$$C = \sum Wi - \frac{\sum W_i^2}{\sum W_i}$$

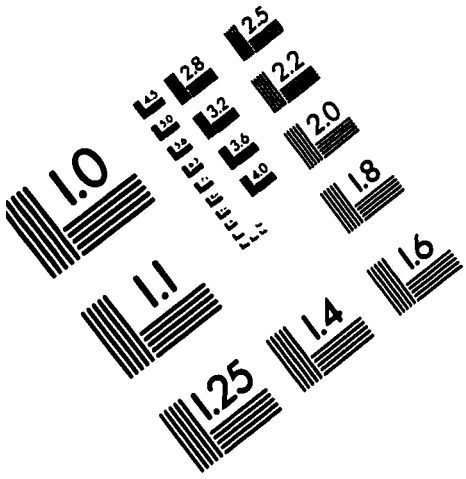
$$W_i = \frac{1}{V_i + T^2}$$

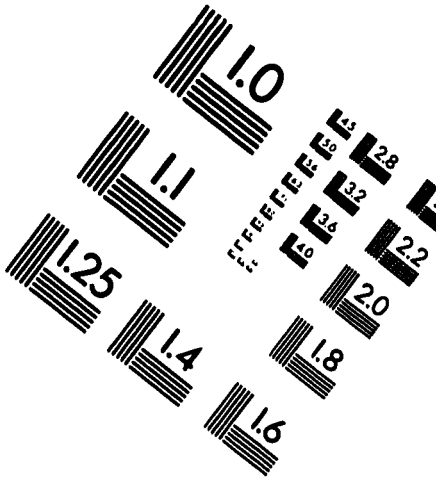
$$T^2 = \frac{Q - df}{C}$$

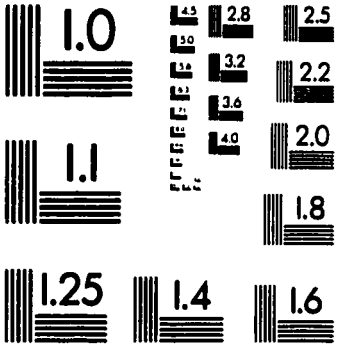
$$WMD = \frac{\sum(Wi * Md_i)}{\sum Wi}$$

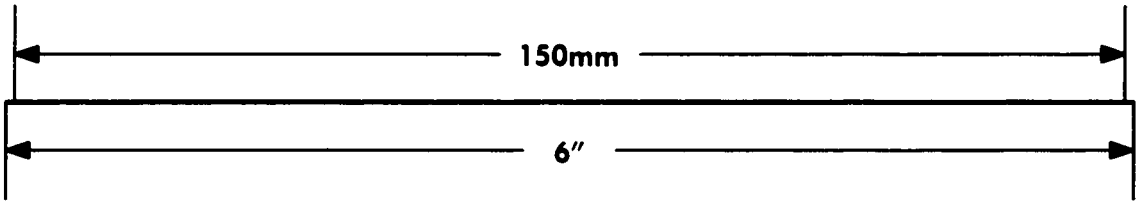
$$Q = \sum Wi\,(Md_i - WMD)^2$$

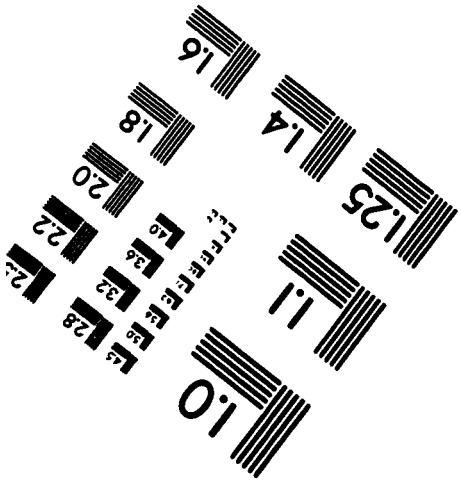
# IMAGE EVALUATION
# TEST TARGET (QA-3)

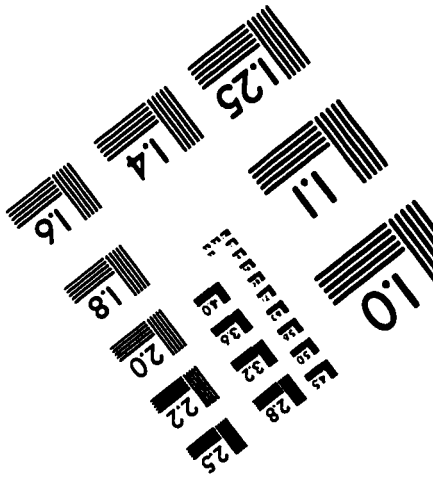
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