JOURNAL OF BONE AND MINERAL RESEARCH
Volume 21, Number 1, 2006
Published online on September 6, 2005; doi: 10.1359/JBMR.050903

Review

Anti-Hip Fracture Efficacy of Bisphosphonates: A Bayesian Analysis of Clinical Trials

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ABSTRACT: In postmenopausal women, the efficacy of bisphosphonates on hip fracture risk is not clear. This Bayesian meta-analysis quantitatively reviewed data from 12 randomized clinical trials with 18,667 patients and found that bisphosphonate treatment was associated with a reduced risk for hip fracture by 42%.

Introduction: The efficacy of antiresorptive bisphosphonates therapy on reducing hip fracture is not clear, because evidence from randomized clinical trials (RCTs) is inconclusive. This study was undertaken to quantitatively assess the effect of bisphosphonates on hip fracture using literature review and meta-analysis.
Materials and Methods: Bayesian methods of meta-analysis were applied to synthesize data from 12 RCTs available between 1990 and 2004. The trials involved 18,667 postmenopausal women with low BMD or osteoporosis who have been followed or treated for between 1 and 4 years. The medications used were etidronate (two trials) alendronate (six trials), risedronate (three trials), and clodronate (one trial). The primary endpoint was the incidence of hip fracture.
Results: When data from all 12 studies were pooled, treatment with bisphosphonates was associated with a reduced risk for hip fracture by 42% (relative risk [RR], 0.58; 95% credible interval [CrI], 0.42–0.80). The absolute rate reduction was 52 hip fractures per 10,000 women (95% CrI, 4–110) for a period of 3-year treatment. The probability that bisphosphonates are better than placebo (in reducing hip fracture risk by at least 30%) was 0.90.
Conclusions: In postmenopausal women with osteoporosis or low BMD, bisphosphonate treatment is associated with reduced risk of hip fracture.
J Bone Miner Res 2006;21:340–349. Published online on September 6, 2005; doi: 10.1359/JBMR.050903

Key words: meta-analysis, hip fracture, Bayesian approach, bisphosphonates, osteoporosis, postmenopause, etidronate, alendronate, risedronate, clodronate

INTRODUCTION

HIP FRACTURE IS the most serious consequence of osteoporosis, because it is associated with increased mortality risk, reduced quality of life, and incurs significant health care cost.[1,2] Strategies for preventing or reducing the burden of hip fracture in the general population have included both pharmacologic and nonpharmacologic interventions. In women, hormone replacement therapy (HRT) has been shown to reduce hip fracture risk by ~34–38%.[3,4] However, because of concerns about the possible deleterious effects of HRT on breast cancer risk and cardiovascular outcomes, the treatment is not considered an optimal choice. In recent years, bisphosphonates (i.e., alendronate, risedronate, and clodronate) have emerged as an alternative treatment of osteoporosis because these agents have been shown in randomized clinical trials to be beneficial in the reduction of vertebral fracture risk and increased BMD,[5] while having few concerns about deleterious effects.

Because virtually all previous randomized clinical trials (RCTs) were designed to test the efficacy of bisphosphonates on vertebral fracture risk, hip fracture risk was largely considered a secondary outcome. As a result, the effect of bisphosphonates on hip fracture risk is uncertain, because results from different studies have been conflicting, ranging from statistically nonsignificant to highly significant effects.[6–9] Nevertheless, a recent review of six clinical trials found that alendronate treatment of postmenopausal women with low BMD or established osteoporosis reduced the risk hip fracture risk by 45%.[10]

In the presence of uncertain evidence, a systematic re-

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view by compiling all available data and synthesizing them into a coherent summary may provide a better and more reliable conclusion about treatment efficacy than a single trial does. This can be done by meta-analysis in which a common effect size of all studies is estimated. This study was undertaken to assess the efficacy of bisphosphonates on hip fracture risk by using the meta-analysis approach.

MATERIALS AND METHODS

Search strategy and study inclusion

A systematic search the literature was carried out by using electronic resource including Pubmed, Ovid (from 1966 to March 2004), and the Cochrane Controlled Trials Registered from 1960 to March 2004. The keywords used for searching included randomized placebo-and/or controlled trial(s) or controlled-clinical trial, postmenopause, etidronate, alendronate, risedronate, clodronate, pamidronate, zoledronate, ibandronate, diphosphonates, bisphosphonates, fracture, nonvertebral/or hip fracture. Two reviewers (NN and TN) identified eligible articles for which the abstracts were recorded. If the abstract was consistent with the inclusion criteria, the full article text was obtained.

The inclusion criteria were randomized placebo-control trials comparing postmenopausal women receiving any bisphosphonates (e.g., etidronate, alendronate, risedronate, or clodronate) to those not receiving bisphosphonates with the duration of follow-up of at least 12 months and the incidence of hip fracture recorded. Only original studies and papers/abstracts written in English and published in peer-reviewed journals were selected for analysis.

Data extraction

The full texts of all potentially relevant papers were obtained, and two reviewers (NN and TN) independently checked for data consistency. If more than one paper with the same data were identified, only that which contained the definitive data were included. For each study, relevant data including details of study design, study duration, agent used in the treatment, medication dose, inclusion and exclusion criteria, and incidence of hip fractures were extracted. The primary outcome in this meta-analysis was incidence of newly occurred hip fracture during the study period (Table 1).

Statistical methods

Data synthesis: In each study, the outcome data were summarized by a two-by-two table format with four cells, where a and b were the number of hip fractures in the treatment and placebo group, respectively, and c and d were the number of individuals without fractures in the treatment and placebo group, respectively. The effect size for each study was estimated by the relative risk (RR_i), which is defined as $[a/(a + c)]/[b/(b + d)]$, where i indexes a study ($i = 1, 2, 3 \ldots 12$). The primary aim of the meta-analysis was to make use of these RR_i to estimate an overall RR and its uncertainty. This can be done by both a so-called fixed-effects and random-effects model, which have widely been described elsewhere.[5] Briefly, each logarithm of RR_i was assumed to be normally distributed with a "true" but unknown effect size θ_i and a within-study variance σ_i^2. The collection of the logarithms of the RR_i across the different studies is assumed to follow a normal distribution with mean θ and variance τ^2. Here, θ is the overall logarithmic relative risk across studies and τ^2 is the between-study variance. The synthesis of data were performed both with the classical random-effects[11] and Bayesian random-effects models.[12,13] In the classical random-effects model, the parameters θ, σ^2, and τ^2 are assumed to be fixed; however, in Bayesian random-effects model, σ_i^2 and τ^2 are assumed to be random variables. In the Bayesian analysis, the prior distribution for θ and τ^2 must be specified. In this analysis, θ was given a vague prior normal distribution of mean 0 and variance of 10, whereas τ^2 was assumed to be uniformly distributed with parameters (0, 10). These prior distributions were specified on the basis of the high homogeneity in the population studies and the possible wide range of treatment effects. Estimates of the Bayesian random-effects parameters were obtained by the method of Markov Chain Monte Carlo (MCMC) as implemented within the WinBUGS program.[14] A similar Bayesian analysis based on absolute difference, rather than logit of relative risk, was also performed by using the MCMC technique.[13] In the analysis of absolute risk difference, only 3-year period trials were included.

Heterogeneity: The heterogeneity of effects across studies was assessed by computing the Cochran's Q statistic[15] and the coefficient of inconsistency (I^2) as described by Higgins and Thompson.[16] I^2 is an estimate of the proportion of total variation in study estimates that is caused by heterogeneity. To illustrate the heterogeneity between the treatment effects in different trials, a funnel plot of sample size against estimated treatment effect and funnel plot regression were provided as described by Macaskill et al.[17] Finally, recursive cumulative meta analysis[18] was also performed to examine whether the magnitude of effects has been changing markedly over time, as new studies have been published on this topic. In this analysis, each calendar year was considered as an informative step, in which evidence was updated by studies published in the interim.

RESULTS

Characteristics of studies

Between 1990 and 2004, there were 12 eligible RCTs involving 18,667 individuals (range per study, 66–5445),[6–9,19–26] among whom 263 hip fractures were observed. Three RCTs related to etidronate treatment[27–29] were excluded from the analysis because no hip fractures were ascertained during the trial period. Furthermore, another trial was excluded because of duplicated data.[30] Among the 12 trials identified, 2 trials were on etidronate,[23,24] 6 were on alendronate,[6,7,19,20,25,26] 3 were on risedronate,[6–9,19–26] and 1 was on clodronate.[22] In the etidronate trials, patients received intermittent oral etidronate therapy: 400-mg daily dose for 2 weeks, followed by a 10- or 13-week period in which no drugs was given. In the alendronate trials, the majority of patients initially received

TABLE 1. SUMMARY OF CONTROL TRIALS OF BISPHOSPHONATES MATCHING INCLUSION CRITERIA FOR ANALYSIS

Reference	*Design*	*Inclusion criteria*	*Agent and dose used (daily)*	*Duration (years)*	*Variables analysed/results*
23	RCT, DB	Menopausal women from 56 to 75. Presence at least one but not more than four atraumatic vertebral fractures. Excluded secondary cause of osteoporosis, such as hyperparathyroidism, Paget's disease of bone, renal osteodystrophy; impairment of renal, cardiac or thyroid function; or a history of therapy with corticosteroids, estrogen, calcitonin, calcium or vitamin D for ≥3 months. Also excluded if using fluoride or diphosphonate therapy.	50% received placebo; 400 mg of oral etidronate for 2 weeks followed by a 13-week period in which no drugs were given. Throughout the 15-week study cycle all patients received 500 mg calcium and 400 UI vitamin D. All patients were to receive 10 cycles of treatment lasting 15 weeks.	3	BMD change, incidence of fracture
24	RCT, MC, DB	Postmenopausal (at least 12 months) white and Asian women with presence at least one but not more than four atraumatic vertebral fractures. Excluded subjects taking estrogen, glucocorticoids, androgens, anabolic steroids, phosphate, or pharmacologic dose of calcium (>1 g daily) or vitamin D (>1000 IU daily); age > 75 years, weight < 40 or > 80 kg, secondary osteoporosis, and medical conditions that might confound study participation.	Four blocks: each patient received 1 g of phosphate or placebo, or twice daily for 3 days and 400 mg of etidronate or placebo daily for the next 14 days followed by 500 mg of calcium daily for the next 74 days	3*	BMD change, incidence of fracture, biochemical parameters
7	RCT, MC, DB in third year	Women from 45 to 80 (≥5 years postmenopause); LSBMD ≤ 2.5 SD; no other causes of osteoporosis or disorders of bone and mineral metabolism.	40% received placebo; 5, 10, or 20 mg of alendronate (20% in each dose group) in the first 2 years then group 20 mg switched to 5 mg.	3	BMD change, incidence of fracture
6	RCT, MC, DB	Women from 55 to 81 years (≥2 years postmenopause), FNBMD ≤ 2.1 SD. Excluded gastric related diseases, who was on HRT, calcitonin or bisphosphonates treatment.	50% received placebo; 5 mg of alendronate for the first 24 months then switched to 10 mg	3	BMD change, incidence of fracture
19	RCT, MC, B	Women from 55 to 82 years (≥2 years postmenopause), FNBMD ≤ 2.0 SD. Excluded gastric related diseases, who was on HRT, calcitonin or bisphosphonates treatment.	50% received placebo; 5 mg of alendronate for the first 24 months then switched to 10 mg	4.2	BMD change, incidence of fracture
26	RCT, MC, DB	Postmenopausal women with osteoporosis	Patients received either alendronate or alendronate + Ca or Ca only	2	BMD change, incidence of fracture
20	RCT, MC, DB	Postmenopausal women (at least 2 years) <85 years old, LSBMD ≤ 2.0 SD. Excluded other metabolic bone disorder, disturbed parathyroid or thyroid function, major gastrointestinal disease, hypertension, myocardial infarction, and who was on HRT, calcitonin, fluoride or bisphosphonates treatment	50% received placebo; 10 mg of alendronate for treatment group 1	1	BMD change, incidence of fracture

Table 1. Summary of Control Trials of Bisphosphonates Matching Inclusion Criteria for Analysis (continued)

Reference	*Design*	*Inclusion criteria*	*Agent and dose used (daily)*	*Duration (years)*	*Variables analysed/results*
25	RCT, MC, DB	Women 65 years old and above with BMD lower than a T score of –2.0 at lumbar spine of total hip. Excluded subjects disorder of bone mineralization, 25(OH) calciferol < 25 nM undertreated hyperthyroidism, recent major upper gastrointestinal mucosal erosive disease or use of bone active agents.	50% received placebo; 10 mg/day alendronate. All patients received vitamin D, 400 IU/day; Calcium carbonate was given to patients whose daily dietary calcium intake was <1500 mg.	2	BMD change, incidence of fracture
21	RCT, MC, DB	Postmenopausal women (at least 5 years) <85 years old, LSBMD ≤ 2.0 SD. Excluded who was on HRT, calcitonin, fluoride or bisphosphonates treatment	30% received placebo. 30% received 5 mg risedronate, 30% received 2.5 mg risedronate for the first year and then switched to 5 mg	3	BMD change, incidence of fracture
9	RCT, MC, DB	Postmenopausal women (at least 5 years) <85 years old, and if had at least two symptomatic vertebral fractures. Excluded who was on HRT, calcitriol, calcitonin, fluoride or bisphosphonates treatment	30% received placebo. 30% received 5 mg risedronate, 30% received 2.5 mg risedronate for the first 2 years and then switched to 5 mg	3	BMD change, incidence of fracture
8	RCT, MC	One group of women between 70 and 79 years with FNBMD < 4 SD or FNBMD < 3 SD plus at least one risk factor for hip fracture. The other group of 80+ years who had at least non-skeleton risk factor for hip fracture with FNBMD < 4 SD or FNBMD < 3 SD plus a hip axis length ≥ 11.1 cm. Exclusion any major medical illness, cancer, bone mineral metabolic disorder.	30% received placebo. 30% received 5 mg risedronate, 30% received 2.5 mg.	3	BMD change, incidence of fracture
22	RCT, MC, DB	Women with postmenopausal or secondary osteoporosis: all women had spine T score ≤ –2.5 and/or had at least one prevalent vertebral fracture at entry. Exclusion those receiving treatment for a malignancy; those currently taking medication likely to influence skeletal metabolism or the interpretation of results (i.e. > 500 mg daily calcium supplements, HRT, calcitonin, anabolic steroids and bisphosphonates).	51% received placebo. 49% received 800 mg daily clodronate.	3	BMD change, incidence of fracture

* Blinded in several ways: participants, collection, and review data.

RCT, randomized control trial; MC, multicenters; DB, double-blind; B, blind; LS, lumbar spine; FN, femoral neck.

TABLE 2. BASIS CHARACTERISTICS OF RCTS

Authors	Agent	Duration (years)	Age of subjects		Subjects in study (n)		Hip fracture (n)		FNBMD change (%)*
			Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	
Storm et al. 1990[23]	Etidronate	3	69 ± 1	69 ± 1	33	33	2	1	—
Harris et al. 1993[24]	Etidronate	3	65 ± 1	65 ± 1	211	212	2	1	1.3
Liberman et al. 1995[7]	Alendronate	3	64	64	397	597	3	1	5.9
Black et al. 1996[6]	Alendronate	3	71 ± 6	71 ± 6	1005	1022	22	11	4.1
Cummings et al. 1998[19]	Alendronate	4.2	68 ± 6	68 ± 6	2218	2214	24	19	4.6
Bonnick et al. 1998[26]	Alendronate	2	66	66	138	563	3	5	2.9†
Pols et al. 1999[20]	Alendronate	1	63 ± 7	63 ± 8	958	950	3	2	2.5
Greenspan et al. 2002[25]	Alendronate	2	79	79	162	165	4	2	3.4
Harris et al. 1999[21]	Risedronate	3	68 ± 7	69 ± 8	450	489	15	12	1.6
Reginster et al. 2000[9]	Risedronate	3	71 ± 7	71 ± 7	406	406	11	9	3.1
McClung et al. 2001[8]	Risedronate	3	74 ± 3	74 ± 3	1821	3624	49	55	3.4
McCloskey et al. 2004[22]	Clodronate	3	68 ± 8	68 ± 8	301	292	6	1	3.7

* FNBMD, femoral neck BMD, changes were the percentage changes of FNBMD between the treatment and control groups based on the total subjects in each arm at the end of study.

† Obtained from subjects at dose of 5 mg.

a 5-mg daily dose for the first 12 or 24 months and then switched to the 10-mg dose. In one alendronate trial,[7] patients were treated with a 20/5- and 10-mg daily dose. In the risedronate trials, the 5-mg daily dose was mainly used; in a trial,[8] a third of subjects received the 2.5-mg dose for 3 years. In the clodronate trial, patients were on a 800-mg daily dose. The average length of follow-up was 2.9 years (range, 1–4.2 years). The average age of participants in each study ranged from 64 to 79 years (Table 2).

Homogeneity of studies

In each study, the incidence of hip fracture in the bisphosphonate-treated group was lower than that in control group (Fig. 1). Although the magnitudes of the effect varied among studies, there was no statistically significant heterogeneity ($p = 0.998$). The coefficient of inconsistency (I^2) was estimated at 0.88% (95% uncertainty interval: 0.82–0.92%).

A funnel plot of relative risk and sample size is shown in Fig. 2, where smaller trials tended to produce more pronounced effect than large trials did. However, a regression analysis of the standardized effect size (defined as log RR divided by SE) and sample size revealed no significant gradient ($p = 0.116$), suggesting that there was no significant selection bias in the analysis.

Pooled treatment efficacy

Figure 3 presents estimates of RR for individual studies as well as the pooled estimate of RR based on the Bayesian random-effects model. All studies showed a RR of <1, indicating that bisphosphonate treatment reduced the risk of hip fracture. However, based on the traditional criteria of $p < 0.05$, only two trials[6,8] showed a significant treatment effect; the remaining trials were unable to show a significant treatment effect because the 95% CIs were >1. Nevertheless, when results of all studies were pooled, the effect was statistically significant, with the RR being 0.58 (95% credible interval [CrI], 0.42–0.80).

When the analysis was conducted on individual drugs with at least two trials (Fig. 4), it was noted that none of the individual drugs provided conclusive evidence for treatment efficacy, because none of the pooled RRs (Fig. 4, right) for any individual drug were statistically significant. The distribution of effects was widespread and the upper 95% CI of RR was >1. Nevertheless, among the drugs, alendronate (six trials) appeared to show an RR (RR = 0.55; 95% CrI, 0.27–1.12) that was similar to the overall estimate of RR. The overall absolute risk reduction estimated from all 3-year trials (Fig. 4, left) was 0.0052 (95%

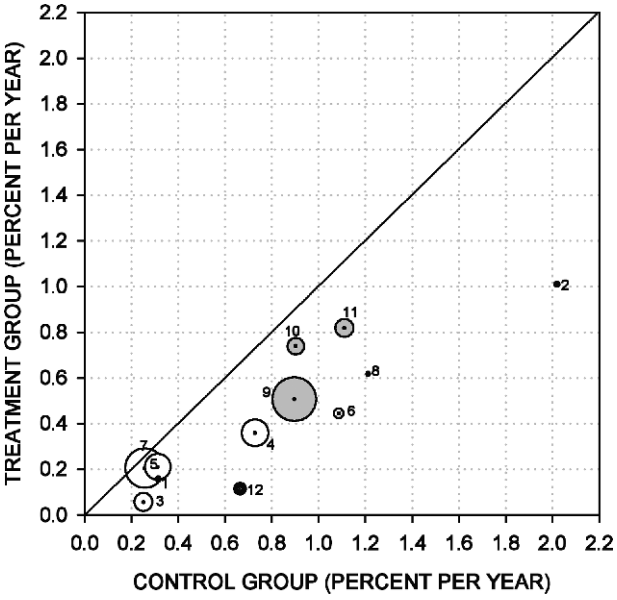

FIG. 1. The incidence of hip fracture (percent/year) in the treatment and control groups. The size of the symbol is proportional to the total sample size. 1, Storm et al. 1990[23]; 2, Harris et al. 1993[24]; 3, Liberman et al. 1995[7]; 4, Black et al. 1996[6]; 5, Cummings et al. 1998[19]; 6, Bonnick et al. 1998[26]; 7, Pols et al. 1999[20]; 8, Greenspan et al. 2002[25]; 9, Harris et al. 1999[21]; 10, Reginster et al. 2000[9]; 11, McClung et al. 2001[8]; 12, McCloskey et al. 2004.[22]

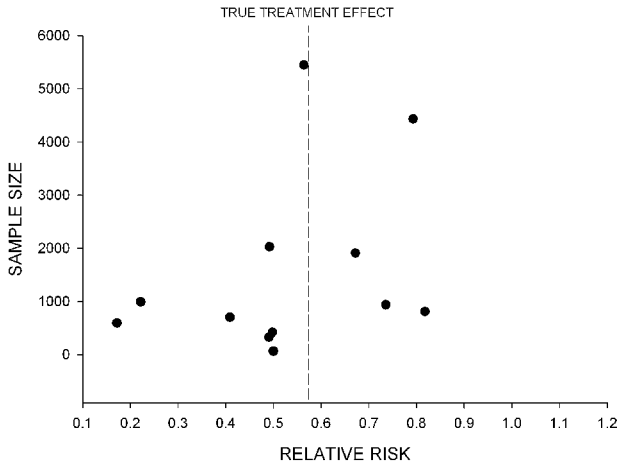

FIG. 2. Funnel plot of sample size vs. RR. Studies with higher effect size tended to have small sample size.

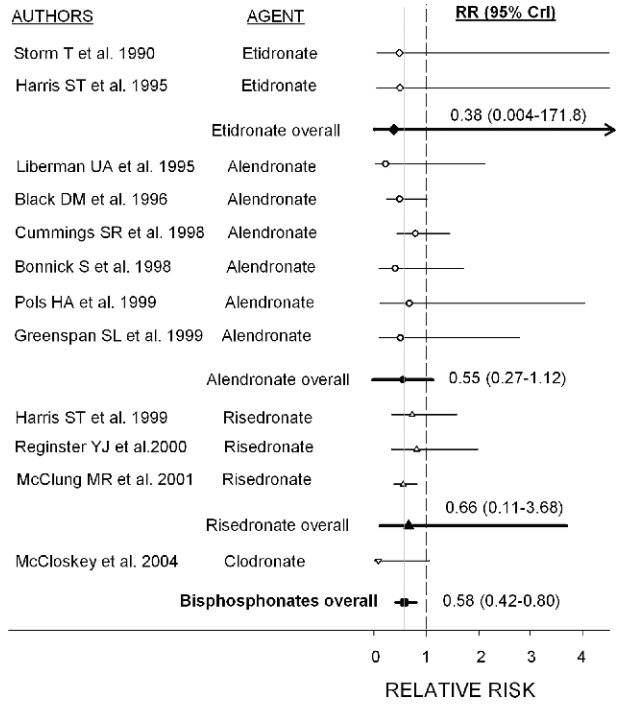

FIG. 3. RR of hip fracture for each clinical trial and combined trials (etidronate, alendronate, risedronate, and clodronate). The black (diamond, triangle, circle, and square) plots with bold solid lines are pooled RRs obtained from the Bayesian random-effects analysis.

CrI, 0.0004–0.011), equivalent to a reduction of 52 hip fractures per 10,000 women (95% CrI, 4–110).

The area under the curve between any two points on the distribution shown in Fig. 4 is an estimate of the probability of efficacy. The probabilities of efficacy defined by various criteria are shown in Table 3. For example, if efficacy is defined as a risk reduction of at least 20% (i.e., RR $\leq$ 0.80), the probability that bisphosphonates are better than placebo (in reducing hip fracture risk) was estimated at ~98%. However, if efficacy is defined as RR $\leq$ 0.50 (i.e., reduction of fracture risk by at least 50%), the overall efficacy probability was 20%, with alendronate showing a higher probability (38%) compared with risedronate (11%). In fact, for any given magnitude of efficacy, the probability of efficacy was higher in alendronate than in risedronate.

Sensitivity

Because the estimate of overall RR could be dependent on the prior distribution of the between-study variance, three further analyses were conducted with three parameter specifications: uniform distribution with parameters (0, 2) and γ distribution with parameters (0.1, 0.1) and (3.0, 0.1). The uniform distributions were chosen to reflect the uninformative (vague) knowledge of the between-study variance to cover all possible variability. The γ parameters were chosen to reflect the narrow range of between-study variance and to give the most diffuse finite variance distribution. Regardless of the type of prior distributions, the results were highly significant, with estimated overall RR being between 0.51 (95% CrI, 0.29–0.75) and 0.56 (95% CrI, 0.43–0.57).

Further sensitivity analysis combined the estimate of the RR after each increment of study one at a time (Fig. 5) and showed that the estimates of pooled RR ranged from 0.21 to 0.58. After the first three studies, other studies did not unduly influence the combined estimate.

DISCUSSION

Hip fracture has long been recognized as the most serious consequence of osteoporosis. Whereas the efficacy of bisphosphonates in the reduction of vertebral fractures has been well established, their role in hip fracture reduction has been uncertain because of lack of conclusive evidence of treatment efficacy. Although the beneficial effect of bisphosphonate treatment was observed in all specific drugs, most (10 of 12) trials were inconclusive primarily because of lack of statistical power and design issues (e.g., most studies were designed to assess the effect of bisphosphonates on vertebral fractures, not hip fracture). In this scenario, meta-analysis can increase the statistical power and reduce the uncertainty around the estimate of treatment effect by pooling the effects observed across trials. This meta-analysis indicates that bisphosphonates could reduce the incidence of hip fracture by as much as 58% in women with high risk of osteoporotic fracture, or established osteoporosis, or in women with low BMD. Using the Bayesian approach, it can also be stated that the probability was 0.90 that bisphosphonates, as a group, reduced hip fracture risk by at least 30%; however, the probability for alendronate and risedronate was 0.79 and 0.62, respectively.

The magnitude of effect observed in this analysis was somewhat comparable with the effect of bisphosphonates on vertebral fracture risk, where the average RRs were between 0.52 and 0.64.[5] It is, however, interesting to note that, whereas the effects of bisphosphonates on nonvertebral fractures varied according to drugs, their effects on hip fracture risk was fairly homogenous. Indeed, all studies considered in this analysis showed a positive trend of reduction in hip fracture risk associated with bisphosphonate treat-

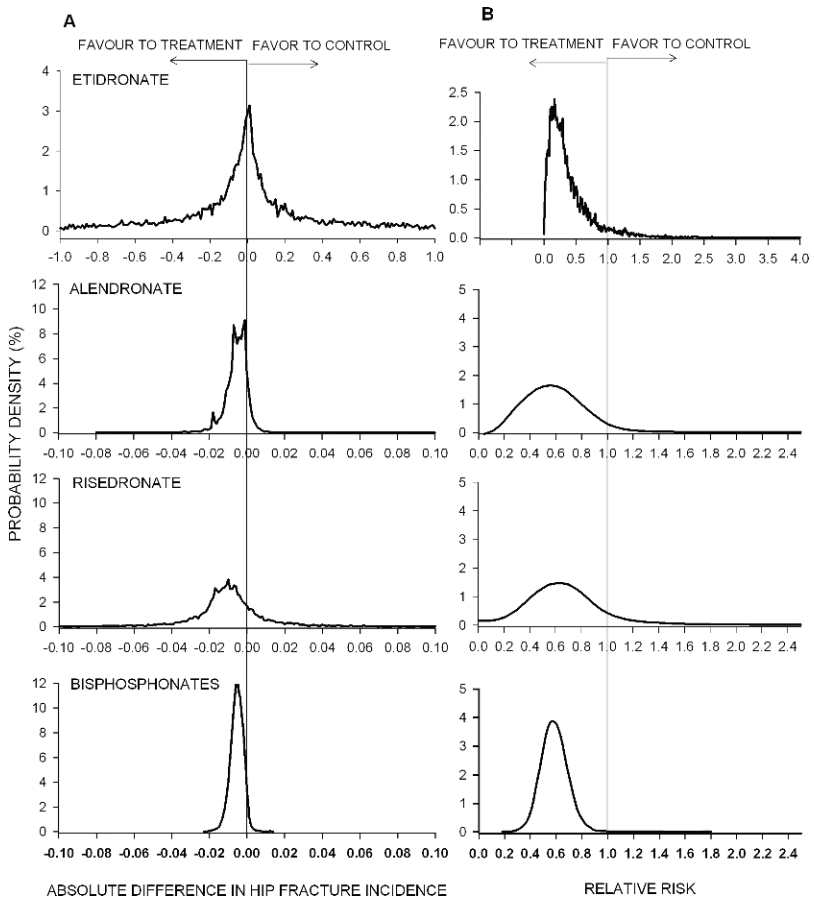

FIG. 4. Posterior distributions for (A) the absolute risk reduction (left) for 3-year trials (etidronate,[23,24] alendronate,[6,7,19] and risedronate[8,9,21]) and (B) RR reduction (right) for etidronate, alendronate, risedronate, and combined all bisphosphonates (including clodronate).

TABLE 3. PROBABILITY OF EFFICACY OF BISPHOSPHONATES TREATMENT BY VARIOUS RR CRITERIA

	Agent		
RR	*Bisphosphonates**	*Alendronate†*	*Risedronate‡*
≤0.8	0.982	0.895	0.746
≤0.7	0.902	0.787	0.602
≤0.6	0.605	0.598	0.422
≤0.5	0.197	0.380	0.111
≤0.4	0.025	0.166	0.108
≤0.3	0.002	0.056	0.061

For example, if efficacy is defined as risk reduction of at least 20% (i.e., RR ≤ 0.80), the probability that bisphosphonates are better than placebo (in reducing hip fracture risk) was estimated (by using random-effects model) at ~98%.

* Included 12 trials (6–9, 19–26).

† Included six trials (6,7,19,20,25,26).

‡ Included three trials (8,9,21).

ment. Although only two studies showed a "significant" effect[6,8] using the threshold of $p < 0.05$, the evidence of efficacy was stronger in alendronate and risedronate than in etidronate or clodronate. However, it should be noted that the number of studies and sample sizes of studies in etidronate or clodronate trials were modest.

In this analysis, alendronate emerged as the most efficacious agent in terms of reducing hip fracture risk, because there was a probability of 0.9 that alendronate reduced hip fracture risk by at least 20%, which is higher than any other drug considered here. The RR associated with alendronate treatment in this analysis was 0.55 (95% CrI, 0.27–1.12). This finding was comparable, but not numerically consistent, with a recent meta-analysis[10] in which Papapoulos et al. found that alendronate treatment reduced hip fracture risk by 45% (RR: 0.55; 95% CI, 0.36–0.84). There are important differences in data and methodology between the two analyses. For example, whereas this study estimated fracture risk as the number of fracture cases per 10,000 patients at risk, Papapoulos et al. estimated as number of fracture cases per 10,000 patient-years at risk. This study used the standard logit transformation within the random-effects model approach to synthesize the individual RRs, whereas Papapoulos et al. used the Poisson regression model to estimate the overall RR. More importantly, Papapoulos et al. considered a subgroup of patients (n = 3066) in the Fracture Intervention Trial (FIT) trial[19] whose BMD T scores ≤ –2.0 by the revised reference data, whereas this study considered the fully published data (n = 4432) of the study. Thus, the numerical discrepancy between the analysis of Papapoulos et al. and this analysis is caused by differences in data source and methodology used in the meta-analysis.

Recent evidence suggested that the antifracture efficacy brought about by antiresorptive therapies may be depen-

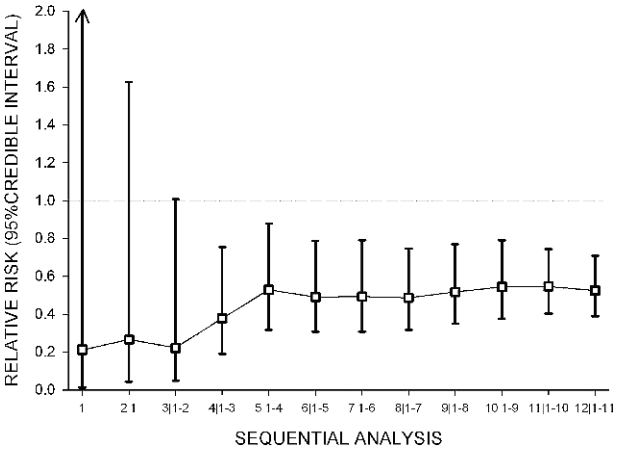

FIG. 5. Sequential conditional Bayesian analysis of effects of bisphosphonates on hip fracture risk in studies (1 through 12). The symbol "|" means "given" or "conditioned on." Thus, "2|1" means that the RR estimated in study 2 was conditioned on the result of study 1, and "3|1–2" means that the RR estimated in study 3 was conditioned on the results of studies 1 and 2, and so on. This analysis suggests that, after the fourth study, the accumulative data are adequate to conclude that bisphosphonates did significantly reduce hip fracture risk. The acronyms of and publication dates of the trials are as follows: 1, Storm et al. 1990[23]; 2, Harris et al. 1993[24]; 3, Liberman et al. 1995[7]; 4, Black et al. 1996[6]; 5, Cummings et al. 1998[19]; 6, Bonnick et al. 1998[26]; 7, Pols et al. 1999[20]; 8, Greenspan et al. 2002[25]; 9, Harris et al. 1999[21]; 10, Reginster et al. 2000[9]; 11, McClung et al. 2001[8]; 12, McCloskey et al. 2004.[22]

dent on the severity of osteoporosis. For example, when nonvertebral fracture was considered an outcome, the reduction in fracture risk was more pronounced in patients with low or very low BMD (i.e., T scores ≤ -2.5) than in patients with BMD T scores > -2.5.[19,20] In this analysis, although the interaction between BMD levels and treatment efficacy was not considered (because of methodological limitation), it should be noted that, in 5445 women with BMD T scores < -4.0, McClung et al.[8] was able to show a significant reduction in hip fracture risk. In the FIT study,[19] the effects of alendronate on hip fracture risk was only observed in those with BMD T scores < -2.[10] Because the incidence of fracture increases as BMD decreases, it is possible that trials with very low BMD patients could observe a higher incidence of hip fractures and thus increase the chance to detect a therapeutic effect.

It has been shown in this analysis that there was high degree of consistency (i.e., the coefficient of heterogeneity was <1%). Therefore, most of the variation in treatment effects was caused by within-study variation. The limitation of this meta-analysis is the inability to obtain the exact patient data from each individual trial, which would have permitted detailed analysis of treatment effect according to pertinent clinical and demographic subgroups. Such an analysis may be important, because characteristics of patients may differ among clinical trials and also from those seen in clinical practice. However, the results of posthoc analysis from this meta-analysis provide strong evidence of beneficial effect of the prevention of hip fracture in patients with established osteoporosis.

The results of this analysis have implications for future design and analysis of anti-hip fracture clinical trials. Based on the observed absolute difference in this analysis, it is clear that any future clinical trial with hip fracture being a primary endpoint requires a very large sample size. For example, if the 3-year incidence of hip fracture is 2% with an expected RR of 50%, such a study requires 5634 subjects per treatment group to achieve a power of 90%. Such a large sample size is not always achievable in the osteoporosis field. Therefore, the Bayesian approach of accumulating data from several small studies is a practical approach to estimating a reliable effect that can be applied to clinical management decisions.[31,32]

Clinical trial data represent an important source of medical knowledge, and knowledge should be accumulated or updated when new data become available. The issue of how to formally update knowledge has regrettably received little attention from clinical researchers, because research results are often considered in isolation from previous results. The Bayesian method of updating knowledge is considered to be the only one formal coherent calculus of statistical inference.[33]

In this study, we have shown by Bayesian analysis that, after only four clinical trials, accumulative evidence was strong enough to conclude that bisphosphonates, as a group, would confer beneficial effect on reducing hip fracture risk. Given the fact that all trials included in the analysis were methodologically sound, the evidence is strong enough that it seems there is little justification for pursuing further anti-hip fracture trials of bisphosphonates versus placebo in similar patients.

These results should be interpreted within the context of the Bayesian approach used in this analysis. In contrast to a classical meta-analysis that considers the probability (e.g., *p* value) of observed data given the hypothesis of no treatment effect, the Bayesian analysis considers the probability of the hypothesis of treatment effect given the observed data. *p* value is known to be a poor measure for evaluating evidence and making clinical decisions[34,35] and is often misinterpreted.[34] Even the CI that has been advocated as a better measure than the *p* value is not without its shortcomings.[36–38] In contrast, the Bayesian method does not depend on, and bypasses, the shortcomings associated with *p* values for inference. The Bayesian analysis allows the reporting of direct probability statements about any magnitude of difference that is of clinical interest. For instance, based on traditional *p* value and CI criteria, the effect of alendronate on hip fracture may be deemed to be "nonsignificant"; however, the Bayesian analysis suggested that there is a 90% probability that alendronate reduced fracture risk by at least 20%.

However, results of a Bayesian analysis can be dependent on the prior distribution of the parameter of interest. In this study, four prior distributions (two γ distributions and two uniform distributions with various distributional parameters) of the between-study variance were considered, and the overall estimates of RR changed little, suggesting that the estimates were robust.

As with any meta-analysis, exclusion of pertinent unpublished trials represents a threat to the validity of the analy-

sis. In this analysis, we found no evidence of publication bias. Because bisphosphonates are relatively recent agents for the treatment of osteoporosis, any clinical trials can be confidently captured by our automatic search procedure and personal knowledge in the field. However, it should be noted that data from the ibandronate study[39] was not available for analysis because of industrial difficulty. In the ibandronate study, a posthoc analysis in those high-risk individuals found a significant reduction in hip fracture risk, but there was no statistically significant reduction in the entire study sample (the latest personal communication with Dr Chesnut was on March 5, 2005). Therefore, it is unlikely that the addition of these data will alter the overall estimate of treatment effect reported in this paper.

In conclusion, regardless of the meta-analytic method used, there was evidence that bisphosphonates as a group could reduce the incidence of hip fracture in postmenopausal women with osteoporosis or low BMD. The probability that bisphosphonates reduce hip fracture risk by at least 30% was estimated to be 90%. The transition of randomized clinical trial results to clinical practice is a long and complex process.[40] Bayesian meta-analysis that represents the cumulative experience of randomized trials is expected to most influence medical decision-making and practice patterns. It is hoped that this meta-analysis will thereby assist in bridging any gap between research and practice in the use of bisphosphonates for the treatment of all eligible patients with high risk of hip fracture.

ACKNOWLEDGMENTS

NDN and TVN were supported by a grant from the National Health and Medical Research Council.

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Received in original form February 21, 2005; revised form August 2, 2005; accepted August 31, 2005.