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II. Meta-Analysis of Alendronate for the Treatment of Postmenopausal Women

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A. Abstract

Objective: To review the effect of alendronate on bone density and fractures in postmenopausal women.

Data Source: We searched MEDLINE, EMBASE, Current Contents, and the Cochrane Controlled trials registry from 1980 to 1999, and we examined citations of relevant articles and proceedings of international meetings.

Study Selection: We included 11 trials that randomized women to alendronate or placebo and measured bone density for at least 1 yr.

Data Extraction: For each trial, three independent reviewers assessed the methodological quality and abstracted data.

Data Synthesis: The pooled relative risk (RR) for vertebral fractures in patients given 5 mg or more of alendronate was 0.52 [95% confidence interval (CI), 0.43–0.65]. The RR of nonvertebral fractures in patients given 10 mg or more of alendronate was 0.51 (95% CI 0.38–0.69), an appreciably greater effect than for the 5 mg dose. We found a similar reduction in RR across nonvertebral fracture types; in particular, RR reductions for fractures traditionally thought to be "osteoporotic," such as hip and forearm, were very similar to RR reductions for "nonosteoporotic" fractures. Individual studies showed similar results, reflected in the *P* values of the test of heterogeneity ($P = 0.99$ for vertebral and 0.88 for nonvertebral fractures).

Alendronate produced positive effects on the percentage change in bone density, which increased with both dose and time. After 3 yr of treatment with 10 mg of alendronate or more, the pooled estimate of the difference in percentage change between alendronate and placebo was 7.48% (95% CI 6.12–8.85) for the lumbar spine (2–3 yr), 5.60% (95% CI 4.80–6.39) for the hip (3–4 yr), 2.08% (95% CI 1.53–2.63) for the forearm (2–4 yr), and 2.73% (95% CI 2.27–3.20) for the total body (3 yr). Heterogeneity of the treatment effect of alendronate was not consistently explained by any of our *a priori* hypotheses; in particular, the effect was very similar in prevention and treatment studies.

The pooled RR for discontinuing medication due to adverse effects for 5 mg or greater of alendronate was 1.15 (95% CI 0.93–1.42). The pooled RR for discontinuing medication due to gastro-intestinal (GI) side effects for 5 mg or greater was 1.03 (0.81–1.30, $P = 0.83$), and the pooled RR for GI adverse effects with continuation of medication was 1.03 (0.98 to 1.07) $P = 0.23$.

Conclusions: Alendronate increases bone density in both early postmenopausal women and those with established osteoporosis while reducing the rate of vertebral fracture over 2–3 yr of treatment. Reductions in nonvertebral fractures are evident among postmenopausal women without prevalent fractures and have bone mineral density (BMD) levels below the World Health Organization threshold for osteoporosis. The impact on fractures appears consistent across all fracture types, casting doubt on traditional distinctions between osteoporotic and nonosteoporotic fractures.

B. Background

ALENDRONATE SODIUM, a bisphosphonate and antiresorptive agent, was developed and marketed as an intervention to reduce vertebral and nonvertebral fractures in postmenopausal women (1–3). Alendronate does not impair bone mineralization at doses that maximally inhibit bone resorption (4). A previous systematic review examining the effect of alendronate on nonvertebral fractures (2) did not clearly report their search methods, address the methodological quality of the individual trials, include unpublished data, or examine the effect on vertebral fractures or BMD. Furthermore, the 95% CI on the RR bordered on no effect (0.50–1.0). We therefore undertook a systematic review and meta-analysis of the effect of alendronate on bone density and fractures. An additional motivation for the review was to explore whether the effect of alendronate was consistent across studies, and whether results differed in those with milder *vs.* more severe osteoporosis, those ingesting more or less calcium or vitamin D, across different doses and durations of alendronate therapy, and in different fracture sites.

C. Methods

We followed the procedures defined by the Cochrane Collaboration for conducting a systematic review (5).

1. Inclusion criteria. Trials satisfied the following inclusion criteria: 1) randomized placebo-controlled trials (RCTs) comparing postmenopausal women receiving alendronate to those not receiving alendronate with follow-up of at least 1 yr; and 2) fracture incidence, or BMD data (including percentage change from baseline and a measure of variance) available. We made no restriction by country in which the

Abbreviations: BMD, Bone mineral density; CI, confidence interval; GI, gastro-intestinal; RCT, randomized placebo-controlled trial; RR, relative risk.

trial occurred, nor did we limit the language to English. Eleven trials total met our inclusion criteria (1, 3, 6–14).

2. Study search and selection. To identify relevant studies of alendronate therapy, we used the search strategy outlined in *Section I* and used the following key and text words: bisphosphonates, diphosphonates, osteoporosis, postmenopausal, and alendronate (15). We reviewed citations of relevant articles and conference proceedings. Two reviewers (A.C., V.R.) examined each title generated from the search and identified potentially eligible articles for which we obtained the abstracts. For abstracts consistent with study eligibility, we obtained the full article text.

3. Reproducibility. Three reviewers judged study eligibility, assessed the methodological quality, and abstracted the data. We achieved a high level of chance corrected agreement in our rating of methodological quality for blinding (κ 1.0) and moderate agreement for loss to follow-up (κ 0.6).

4. Outcomes and explanations for variability in alendronate effect across studies. We examined the effect of alendronate on vertebral and nonvertebral fractures, bone density of the total body, lumbar spine, hip, and forearm, as well as adverse effects of the drug as manifested in patients unable to continue study medication. We developed, for fractures and bone density, *a priori* hypotheses that might explain heterogeneity of study results as outlined in *Section I*. Specifically, we compared groups according to 1) prevention *vs.* treatment; 2) concurrent treatments including total calcium intake (1250 mg of total calcium *vs.* <1250 mg); 3) vitamin D supplementation; 4) for nonvertebral fractures, sites in which fractures are strongly associated with low bone density and those not as strongly associated; and 5) individual components of the quality assessment, including concealed randomization, blinding, loss to follow-up, and intention-to-treat analysis. *Section I* includes a full description of the methodology used to separate prevention from treatment studies. To further evaluate heterogeneity of the severity of osteoporosis in women with BMD 2 SD values below the mean, we grouped trials with a prevalent vertebral fracture rate of greater than 10% at study inclusion (1, 3, 8, 12, 13), in comparison to those without fractures or prevalence below 10% (6, 7, 9, 10, 14). We chose the 10% cut because there was a cluster of studies just less than 10%, and a number of studies with fracture rates much greater than 10%. We also evaluated whether the treatment effect varied depending on baseline total calcium intake (cut point of 1250 mg) and presence of vitamin D supplementation.

5. Data collection. Reviewers abstracted data regarding study design, patient characteristics, treatment duration, dosage, mean change, and SD values for bone density, and number of fractures, both vertebral and nonvertebral. We did not include data from the calcitonin treatment arm of Adami *et al.* (9) or the hormone replacement arm of the Hosking *et al.* (7) trial. We sought data missing from the original reports through correspondence with the primary investigators and with the company, Merck, that sponsored the trials. Merck provided us with the clinical study reports for all of the published trials included in this meta-analysis (1, 3, 6–10). For the trials not yet published at the time we collected data, we were able to obtain the clinical studies reports from Merck for the Clinical Fracture Arm of the Fracture Intervention Trial (FIT) (14), the draft manuscript of two trials (Refs. 11 and 12; both have since been published), and the data from the most recently completed RCT (13).

6. Analysis. When we found duplicate reports of the same study in preliminary abstracts and articles (16–18), we analyzed data from the most complete data set (1, 9). A random effects model provided the strategy for final estimates of all treatment effects, whether for fractures, bone density, or toxicity (19). We only used data on one fracture per person in the analysis.

We conducted separate analyses using regression models for each bone density site (lumbar spine, combined hip, forearm, and total body) using the difference between the change in bone density for each dose group and the change in the placebo arm.

Across both fractures and bone density, the dominant parsimonious models generally allowed combining doses of 1 and 2.5 mg, almost invariably allowed combining the results from 10-, 20-, and 40-mg doses, and sometimes allowed combining the 5-mg dose with doses of 10–40 mg. Because the effect was smallest with doses of 1–2.5 mg, and because clinicians are not using doses lower than 5 mg, we present data only from arms using doses of 5–40 mg. Although clinicians are not using doses of 20–40 mg, in all but one instance we found their effect is similar to 10 mg, and including these trials allows a more precise estimate of the treatment effect associated with doses of 10–40 mg.

With regard to the duration of therapy, the dominant parsimonious model for bone density kept all years separate. In the one exception, we found we could combine yr 2 and 3 for total body bone density. Because clinicians should appropriately offer alendronate therapy for at least 2 yr, we present only data from two or more years of follow-up. For the bone density analysis, if there was statistically significant heterogeneity between studies ($P < 0.05$), we divided the studies into two groups according to *a priori* hypotheses and tested whether the effect sizes differed in the two groups of studies (20).

For each fracture analysis, we calculated a RR and tested for heterogeneity using a χ^2 procedure (19). The same analytic strategy was used to deal with the proportion of patients who discontinued medication because of adverse effects.

D. Results

1. Trial characteristics. We reviewed a total of 358 articles and abstracts. Of these, 46 warranted closer examination, and 19 proved to be possible RCTs (Fig. 1). Of these 19, we excluded 8 for the following reasons: duplicate report or earlier report of another study (16–18), lack of a control group (21), duration less than 1 yr (22–24), and outcomes limited to histomorphometric data (25).

Table 1 presents the characteristics of the 11 trials that met our eligibility criteria. The trials included a total of 12,855 women, of whom 5,561 received placebo. Two trials dealt with prevention (6, 7), and the other nine trials involved women whose densitometry showed low bone density (1, 3,

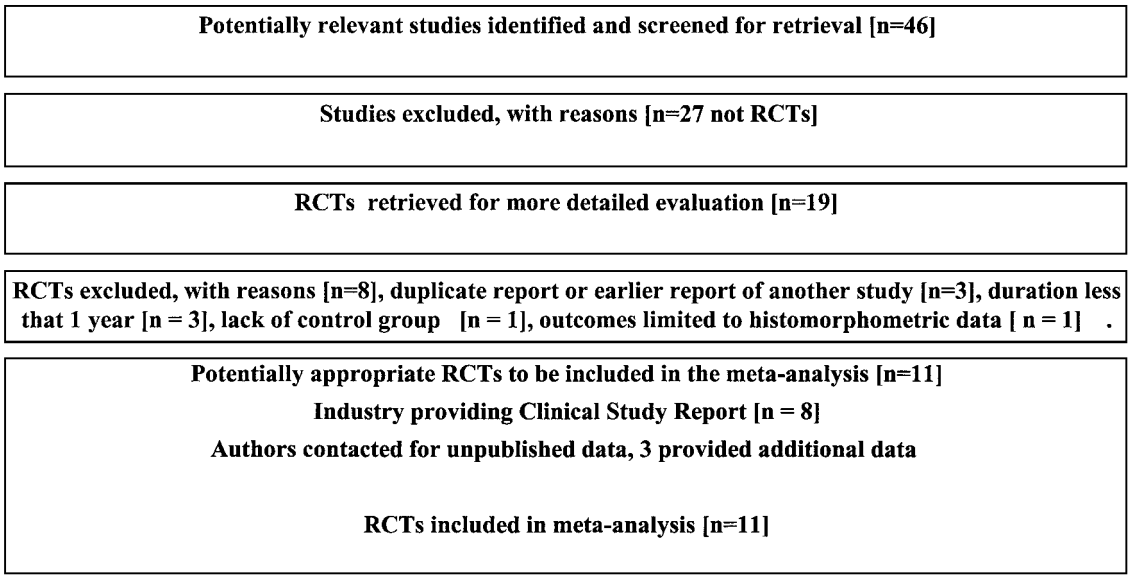

FIG. 1. Search results for alendronate review.

8–14). Of the nine trials in women with low bone density, six included women with a prevalence of vertebral fractures at the beginning of the study of over 10% (Table 1). The Fracture Intervention Trial, which was the largest treatment trial, used a dose of 5 mg for the initial 2 yr and then switched to a 10-mg dose for the third year.

All of the trials effectively concealed randomization, and blinded patients, clinicians, and those assessing outcome. Heterogeneity in study methodological quality was restricted to loss to follow-up. Two trials achieved loss to follow-up of less then 5%, losses to follow-up varied between 5 and 20% in six trials, and three trials had losses to follow-up over 20% (Table 1).

2. Fractures. For vertebral fractures, our analysis failed to reject pooling across the entire range of doses from 5 to 40 mg. The pooled estimate of the RR of vertebral fractures with alendronate from 8 trials randomizing patients to a dose of 5 mg of alendronate or greater (1, 3, 6–10, 14) showed a RR of 0.52 (95% CI 0.43–0.65), which was consistent across trials (heterogeneity *P* value 0.99; Fig. 2). Thus, it is not surprising that, of our five *a priori* hypotheses, none showed statistically significant differences between subgroups. In particular, the point estimates for the reduction in fracture risk was similar for the prevention trials (RR of 0.45, 95% CI 0.06–3.15) and treatment trials (RR of 0.53, 95% CI 0.43–0.65. *P* value on difference between estimates 0.87).

Table 2 presents the RR for fracture with alendronate in the groupings of the nonvertebral fractures we examined. We found statistically significantly smaller effect sizes for 5 mg than for 10–40 mg of alendronate in every fracture category. At doses in the 10- to 40-mg range, the effect on each fracture category is similar, with the RRs varying from 0.45 to 0.57. The results across studies are quite similar, reflected in both the heterogeneity *P* values in Table 2 and Fig. 3, which presents the results of doses of 10 mg or more for individual studies for total nonvertebral fractures. Once again, the nonsignificant reduction in risk of all nonvertebral fractures in the one prevention trial (RR of 0.79, 95% CI 0.28–2.24) was not clearly different from the five treatment trials (RR 0.49, 95% CI 0.36–0.67, *P* value on difference between estimates 0.40). These results did not change for the 10- to 40-mg dose if we used a femoral neck T-score cut point of −2.5, instead of −2.0, to classify the trials into prevention and treatment. When we pooled across studies using 5 mg and greater for outcome of hip fracture, the pooled RR is 0.63 (0.43,0.92). The point estimate lies between the 5 mg and 10 to 40 mg estimates, and the 95% CI excludes no effect.

3. Bone density. The methods of densitometry included dual x-ray absorptiometry—Hologic, Lunar, and Norland. Table 3 presents the results of the pooled estimates of effect of alendronate on bone density across the four sites. All sites had a significant positive response to treatment with alendronate ($P < 0.01$), but we found consistently larger effects with the higher doses of alendronate than with the 5-mg dose, and larger effects as duration of follow-up increased in the lumbar spine (Fig. 4) and forearm and hip sites. For combined forearm, we found no statistically significant heterogeneity, whereas for total body, lumbar spine, and hip there were differences in the treatment effect between trials in some subgroups (Table 3). Even when statistically significant heterogeneity existed, all studies still demonstrated appreciable differences in favor of alendronate.

None of the possible explanations satisfactorily explained significant heterogeneity. In three comparisons (lumbar spine 10–40 mg, 2–3 yr; combined hip 5 mg and 10–40 mg, 2 yr), we found larger effects in trials in which neither treatment nor control received vitamin D. The magnitude of the effect was very similar in prevention and treatment studies. In the one instance (total body bone density) in which it differed, the effect was greater in the prevention trials.

TABLE 1. Study characteristics for Alendronate trials

Study (first author/year/Ref.)[a] (treatment/ prevention)	Sample size (alendronate/ control)	Study sample Mean age (SD) BMD[b] g/cm^2 [c] t-score Fracture prevalence (%)	Baseline dietary calcium intake (SD)	Intervention (calcium/vitamin D supplements during trial)	Duration (yr)	Outcomes measured	Loss to follow-up (%)Tx/N Control/N
Adami, 1995 (9) (treatment)	140/71	59.5 (5.8) yr 0.67 g/cm^2 (0.10) −2.3 5% with prevalent vertebral fractures	571 (256) mg/d	Alendronate 10, 20 mg *vs.* placebo (500 mg calcium/d)	2	BMD: lumbar spine, femoral neck, trochanter, total body. Fractures: Vertebral, nonvertebral	32/211 (15.2%) 21/140 11/71
Black, 1996 (3) (treatment)	1022/1005	71.0 (5.6) yr 0.57 g/cm^2 (0.07) −3.3 100% prevalent vertebral fractures	636 (407) mg/d	Alendronate 5 mg × 2 yr then 10 mg × 1 yr *vs.* placebo (If intake < 1000 mg–500 mg Ca and 250 IU vitamin D)	3	BMD: lumbar spine, femoral neck, total hip, trochater, total body. Fractures: vertebral, nonvertebral; hip wrist	81/2027 (4.0%) 44/1022 37/1005
Bone, 1997 (8) (treatment)	268/91	70.4 (5.6) yr 0.60 g/cm^2 (0.09) −3.0 30.7% prevalent vertebral fractures	891 (629) mg/d	Alendronate 1, 2.5, 5 mg or placebo (500 mg calcium/d)	2	BMD: lumbar spine, femoral neck, total body, distal and proximal forearm. Fractures: vertebral and nonvertebral	19/359 (5.3%) 13/268 6/91
Chesnut, 1995 (10) (treatment)	126/31	63.04 (6.27) yr 0.62 g/cm^2 (0.10) −2.8 0% prevalent vertebral fractures	853 (516) mg/d	Alendronate 5, 10, 20/0, 40/0 mg *vs.* placebo (500 mg calcium/d)	2	BMD: lumbar spine, total body, femoral neck, trochanter, total hip. Fractures: vertebral, nonvertebral	26/157 (16.6%) 21/126 5/31
Hosking, 1998 (7) (prevention)	997/502 (HRT group not included)	53 (4) yr 0.72 g/cm^2 (0.11) −1.8 <10% prevalent vertebral fractures	923 (505) mg/d	Alendronate 2.5, 5 mg *vs.* placebo (<500 mg calcium intake encouraged to increase)	2	BMD: lumbar spine, femoral neck, distal forearm, trochanter, total body. Fractures: vertebral and nonvertebral	287/1499 (19.1%) 194/997 93/502
Liberman, 1995 (1) (treatment)	597/397	64 (7) yr 0.62 (0.09) −2.8 21% prevalent vertebral fractures	739 (537) mg/d	Alendronate 5, 10, or 20/5 mg *vs.* placebo (500 mg calcium/d)	3	BMD: lumbar spine, femoral neck, trochanter, total body, distal forearm. Fractures: vertebral and nonvertebral	170/994 (17.1%) 101/597 69/397
McClung, 1998 (6) (prevention)	357/90	51.8 (3.4) yr 0.72 g/cm^2 (0.10) −1.8 0% prevalent vertebral fractures	996 (494) mg/d	Alendronate 1, 5, 10, or 20/0 mg *vs.* placebo. (500 mg calcium/d if intake < 1000 mg)	3	BMD: lumbar spine, femoral neck, total body, trochanter, total hip, distal forearm. Fractures: vertebral, nonvertebral	136/447 (30.4%) 109/357 27/90
Greenspan, 1998 (11) (treatment)	60/60	70 (4.6) yr 0.63 g/cm^2 (0.09) −2.7 Entry criteria not based on BMD or fracture prevalence	719 (465) mg/d	Alendronate 5 mg × 1.5 yr then increased to 10 × 1 yr *vs.* placebo (if Ca intake < 1000 mg–250 mg Ca and/or 125 IU vitamin D/d)	2.5	BMD: lumbar spine, femoral neck, total hip, trochanter, total body, distal forearm. Fractures: nonvertebral	33/120 (27.5%) 15/60 18/60
Pols, 1999 (12) (treatment)	950/958	62.8 (7.4) yr 0.63 g/cm^2 (0.09) −2.7 18.3% prevalent fracture history	Not available	Alendronate 10 mg, *vs.* placebo (500 mg calcium/d)	1	BMD: lumbar, femoral neck, trochanter, total hip. Fracture: nonvertebral	211/1908 (11.1%) 118/950 93/958
Bonnick (13) (treatment)	563/138	66.2 (8.8) yr 0.65 g/cm^2 (0.10) −2.5 55.9% prevalent fracture history	Not available	Alendronate 10 mg, 10 mg with 1000 mg calcium, *vs.* 1000 mg calcium (400 IU vitamin D/d)	2	BMD: lumbar spine, femoral neck, trochanter, wards' triangle. Fracture: nonvertebral	217/701 (31.0%) 175/563 42/138
Cummings, 1998 (14) (treatment)	2214/2218	67.6 (6.1) 0.59 g/cm^2 (0.06) −2.2 0% prevalent vertebral fractures	636 (400) mg/d	Alendronate 5 mg for 2 yr then increased to 10 mg *vs.* placebo (If intake <1000 mg–500 mg Ca and 250 IU vitamin D)	4	BMD: lumbar spine, femoral neck, total hip, trochanter, distal forearm. Fractures: vertebral, nonvertebral	179/4432 (4.0%) 95/2214 84/2218

[a] Refer to *a priori* hypotheses defining prevention and treatment.
[b] Mean BMD of femoral neck site.
[c] BMD g/cm^2 corrected to Hologic measurements with SD *in parentheses*.

4. Publication bias. Funnel plots provided no suggestion of publication bias for any of bone density or vertebral or nonvertebral fractures.

5. Adverse effects. Our pooled estimate of the RR of discontinuing medication as a result of adverse effects from 9 trials using 5 mg of alendronate or more of 1.15 (95% CI 0.93–1.42)

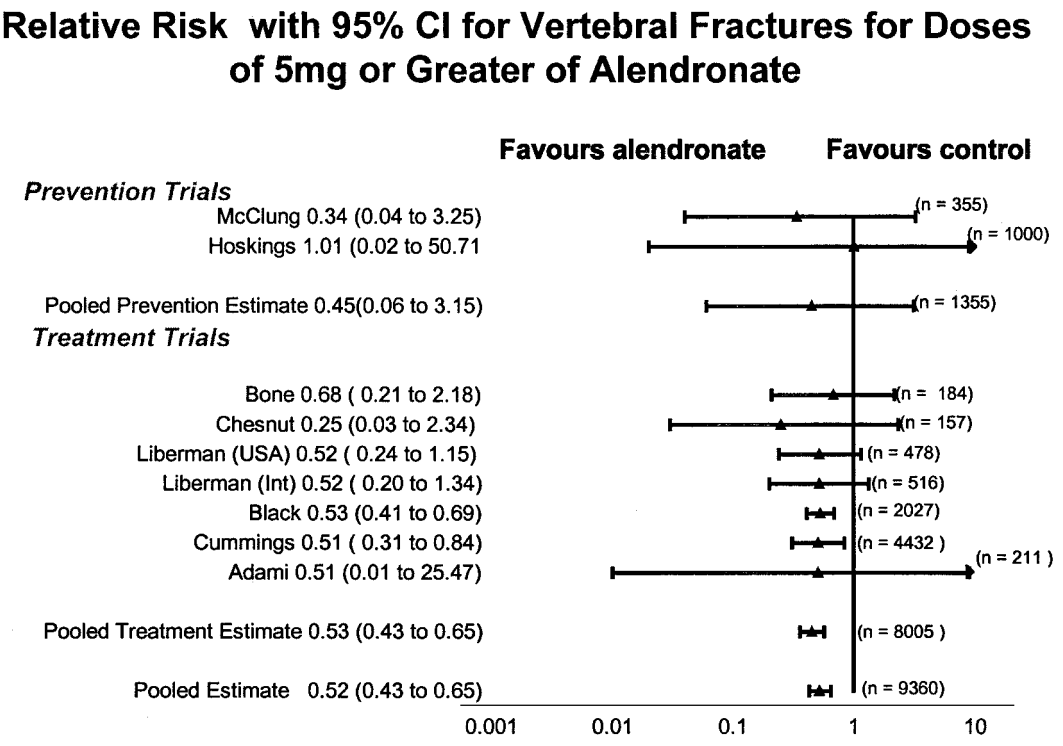

FIG. 2. RR for vertebral fractures with alendronate (5 mg and greater).

TABLE 2. Weighted mean difference of bone density after treatment with alendronate

Fracture sites	No. of Trials	Sample size	Dose (mg)	RR (95% CI)	RR *P* value	Heterogeneity *P* value
All nonvertebral	8	8603	5	0.87 (0.73, 1.02)	0.09	0.31
	6	3723	10–40	0.51 (0.38, 0.69)	<0.01	0.88
Hip	8	8603	5	0.70 (0.46, 1.05)	0.08	0.96
	6	3723	10–40	0.45 (0.18, 1.13)	0.09	0.98
	11	11808	5–40	0.63 (0.43, 0.92)	0.02	0.98
Forearm	8	8603	5	0.84 (0.51, 1.40)	0.51	0.10
	6	3723	10–40	0.48 (0.29, 0.78)	<0.01	0.65
Hip and Forearm	8	8603	5	0.87 (0.52, 1.45)	0.58	0.02
	6	3723	10–40	0.47 (0.30, 0.73)	<0.01	0.72
Osteoporotic[a]	8	8603	5	0.81 (0.65, 1.01)	0.06	0.29
	6	3723	10–40	0.46 (0.32, 0.66)	<0.01	0.85
Nonosteoporotic[b]	8	8603	5	1.05 (0.72, 1.53)	0.79	0.08
	6	3723	10–40	0.57 (0.32, 1.02)	0.06	0.83

We interpreted the heterogeneity $P \leq 0.05$ as indicating important between-study differences in results.

[a] Osteoporotic fractures defined by all fractures in which calcaneal bone density was associated with a RR of fracture of 1.5 or greater in a prior study (forearm, hip, rib, leg, femur, tibia and fibula, patella, pelvis, and hands) (29).

[b] Nonosteoporotic fractures defined by all fractures in which the RR of fracture was less than 1.5 in a prior study (29).

was very consistent across trials (heterogeneity *P* value 0.82). The pooled RR for discontinuing medication to GI side effects for 5 mg or greater from 7 trials was 1.03 (0.81–1.30, heterogeneity $P = 0.83$). The pooled RR for GI adverse effects from 10 trials with continuation of medication was 1.03 (0.98–1.07, heterogeneity $P = 0.23$).

E. Discussion

This meta-analysis confirms that alendronate results in a large reduction in the RR of vertebral and nonvertebral fractures. For nonvertebral fractures, the effect was substantially larger at doses of 10 mg or greater than for lower doses. Although we found a similar trend toward larger risk reductions for vertebral fractures with doses of 10 mg or greater, we could not exclude chance as the explanation for this trend.

Our statistical power to detect heterogeneity was extremely limited for some tests due to the low number of fractures in some categories. Of particular concern in this regard is our exploration of differences in effect between treatment and prevention trials. We found very similar effects on bone density in prevention and treatment trials and a similar RR of fracture in trials with varying baseline levels of bone density. Although our bone density results are relatively robust, the number of fractures in the prevention trials was very small and the CIs very wide. As a result, our analyses have very little power to detect differences in relative risk reduction of fracture with alen-

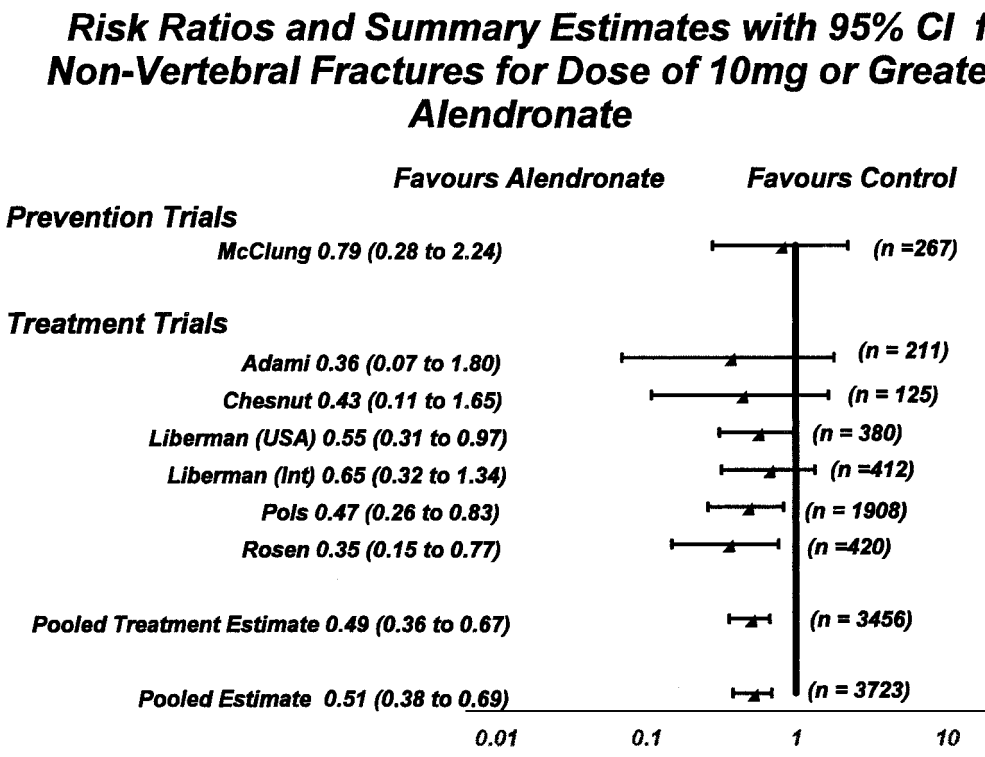

FIG. 3. Risk ratios for nonvertebral fractures with alendronate (10 mg and greater).

TABLE 3. Weighted mean difference of bone density after treatment with alendronate

Bone density site	Dose (mg)	No. of trials	Sample size (n)	Trial duration (yr)	Weighted mean difference (95% CI)	Test of heterogeneity *P* value
Total body	5	6	1619	2	1.77 (1.25, 2.30)	<0.01
	5	3	2497	3	1.84 (1.46, 2.21)	0.23
	10–40	4	712	2	2.43 (1.85, 3.01)	0.09
	10–40	2	469	3	2.73 (2.27, 3.20)	0.35
Lumbar spine	5	8	8219	2 or 3	5.81 (5.32, 6.29)	<0.01
	10–40	5	1613	2 or 3	7.48 (6.12, 8.85)	<0.01
Combined forearm[a]	5	6	2646	2	1.15 (0.93, 1.36)	0.95
	5	3	1581	3 or 4	1.83 (1.47, 2.20)	0.56
	10–20	2	565	2 to 4	2.08 (1.53, 2.63)	0.30
Combined hip[b]	5	8	8146	2	3.37 (3.05, 3.69)	0.04
	5	4	6962	3–4	4.64 (4.27, 5.01)	0.23
	10–40	5	1443	2	4.24 (3.45, 5.02)	0.05
	10–40	2	599	3–4	5.60 (4.80, 6.39)	0.65

We interpreted the heterogeneity $P \leq 0.05$ as indicating important between-study differences in results.
[a] If a trial reported more than one forearm site, our order of preference was 1/3 distal radius and ulna and then 1/3 distal radius.
[b] If a trial reported more than one hip site, our order of preference was total hip, femoral neck, and then trochanter.

dronate and control across prevention and treatment groups.

Our lack of access to individual patient data limited our power to explore this issue further. An analysis from one study (26) suggested that alendronate's effect in reducing nonvertebral fractures is greater in patients who begin treatment with lower bone density. Similar findings have been noted in clinical trials with other bisphosphonates, including etidronate and risedronate (27, 28). In conclusion, the existing data have not resolved the question of whether important differences in risk reduction across groups of patients with varying degrees of osteoporosis exist. The impact of alendronate on the relative risk of nonvertebral fracture in populations without major decrease in bone density merits further investigation.

Turning to the question of whether our estimates of alendronate effect apply to all nonvertebral fractures, most investigators have intuitively assumed that antiosteoporotic drugs will reduce fracture rates that are associated with low bone density and minimal trauma. In keeping with this line of thinking, we made *a priori* hypotheses that we might find larger alendronate-induced reduction in the RR of fractures of the hip, spine, forearm, or other fractures previously associated with reduced bone density. However, we found that the RR reduction with alendronate doses of 10 mg or greater was extremely consistent—for wrist, hip, vertebral, and indeed for fractures traditionally considered "nonosteoporotic." To us, this provides strong evidence that our pooled estimate of RR (0.51) and the associated CI (0.38–0.69) applies to all nonvertebral fractures. Our failure to find an

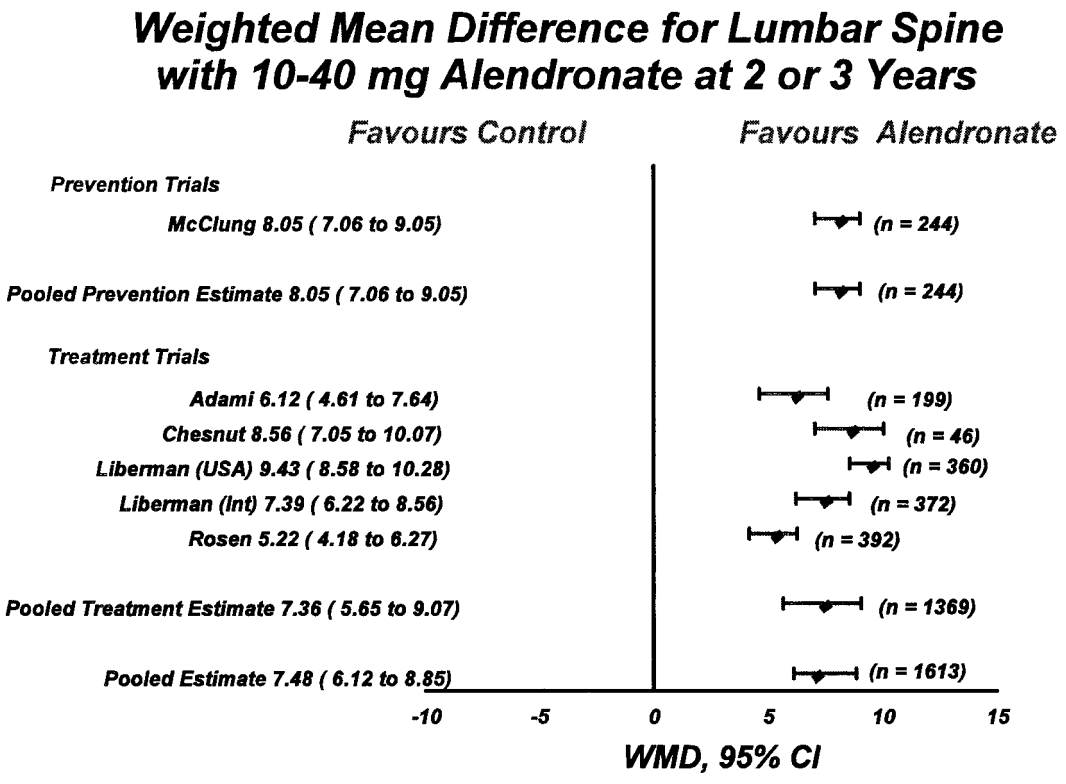

FIG. 4. Weighted mean difference for lumbar spine with alendronate (10–40 mg).

appreciable gradient across osteoporotic and nonosteoporotic fractures challenges prior assumptions in this area.

With respect to bone density, we found that doses of alendronate 10 mg or greater had larger effects on bone density than smaller doses. Alendronate at doses of 10–40 mg increased bone density substantially, with larger increments in sites with a relatively high proportion of cancellous bone. Although we observed larger effects as time passed, the incremental gain of treatment over control in bone density decreased progressively with each succeeding year.

In analyses of differences in percentage change in bone mineral density, even where there was substantial inconsistency with statistically significant heterogeneity, alendronate increased bone density in all trials. When significant heterogeneity was present, we failed to uncover a compelling explanation.

Regarding the long-term impact of alendronate on fractures, we do not feel confident extrapolating beyond the duration of follow-up of the trials in our review. Data from longer term trials that are ongoing will help establish whether the effect on vertebral fractures is maintained, increased, or diminished.

Merck's collaboration greatly facilitated our obtaining complete data from all published and unpublished studies. As a result, we were largely successful in obtaining relevant data. Our success in obtaining near-complete data constitutes a strength of this systematic review.

In general, the trials were methodologically strong. Their major methodological limitation was the loss to follow-up (Table 1). However, two trials achieved loss to follow-up of less than 5% (3, 14). It is reassuring that the proportion of patients lost to follow-up did not appear to influence the magnitude of the treatment effect in any analyses. Another limitation is the length of follow-up, 4 yr or less in all studies to date.

TABLE 4. Pooled RR reduction and number needed to treat for all estimates of morphometric vertebral and nonvertebral fractures

Study population	Risk of fracture without treatment over 2 yr (%)	Absolute risk reduction in fractures with treatment	Number needed to treat to prevent one fracture (95% CI)
Morphometric vertebral fracture			
Low risk	0.12	0.0006	1790 (1507, 2455)
High risk	2.88	0.014	72 (61, 99)
Nonvertebral fractures			
High risk	8.65	0.042	24 (19, 37)
Hip fractures			
High risk	0.86	0.004	237 (188, 375)

Using pooled RR of 0.52 for vertebral fractures and 0.51 for nonvertebral and hip fractures.

The RR for discontinuing alendronate due to adverse effects was 1.15 (95% CI 0.93–1.42). One of the limitations of evaluating data on adverse effects from summary meta-analyses is that participants in RCTs tend to be healthier with fewer co-morbid diseases, and the results may not be generalizable to clinical practice. For example, in a number of the alendronate trials, women were excluded if they had a history of peptic ulcer disease, or esophageal disease within a year of study entry. In addition, RCTs are underpowered for rare effects, and meta-analyses of RCTs generally cannot provide definitive information about drug toxicity.

Table 4 presents the absolute reductions in fracture risk we could anticipate over a 2-yr period in women with varying fracture risk receiving a dose of alendronate of 5 mg or greater for vertebral fractures. To make these calculations, we have estimated baseline risk from pooled estimates from the prevention trials of patients with normal bone density (low risk) and from the treatment trials that enrolled women with low BMD (high risk). Table 4 also presents the absolute reduction in fracture risk for high risk women receiving 10 mg or greater for nonvertebral fractures. We have not included the absolute reduction for the low risk population because, as we have noted previously, the magnitude of the RR reduction in nonvertebral fractures with alendronate in low-risk populations remains open to question.

With the pooling of data in this analysis, we have provided a much more precise estimate of the magnitude in reduction of not only vertebral but nonvertebral fracture with alendronate than was previously available. Furthermore, our conservative random-effects model resulted in the upper boundary of the CI of approximately 0.69, still a 31% reduction in RR of nonvertebral fracture. Subsequent studies should focus on issues such as whether alendronate reduces nonvertebral fractures in younger women with osteopenia, and whether supplemental calcium can increase alendronate's effect on fractures.

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