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Changes in Bone Density and Turnover Explain the Reductions in Incidence of Nonvertebral Fractures that Occur during Treatment with Antiresorptive Agents

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Some, but not all, antiresorptive agents have been shown to reduce the risk of nonvertebral fractures. Agents that significantly reduced nonvertebral fracture risk also appear to produce larger mean increases in bone mineral density (BMD) and reductions in biochemical markers (BCM) of bone turnover, compared with other agents. To examine the extent to which increases in BMD and reductions in BCM during antiresorptive therapy are associated with reductions in risk of nonvertebral fractures, we performed a meta-analysis of all randomized, placebo-controlled trials of antiresorptive agents conducted in postmenopausal women with osteoporosis (*i.e.* prior vertebral fracture or low BMD) with available relevant data. A total of 18 such trials with usable data were identified, including a total of 2,415 women with incident nonvertebral fractures over 69,369 women-years of follow-up. Poisson regression was used to estimate the association between changes in BMD or BCM during the first year and overall reductions in risk of nonvertebral fractures (*vs.* the placebo group) across all trials. Larger increases in BMD and larger reductions in BCM were significantly associated with greater reductions in nonvertebral fracture risk. For example, each 1% increase in spine BMD at 1 yr was associated with an 8% reduction in nonvertebral fracture risk ($P = 0.02$). Mean BMD changes at the hip were smaller than at the spine, but the predicted net effect on fracture risk was the same; an agent that increases spine BMD by 6% at 1 yr reduces nonvertebral fracture risk by about 39%, and an agent that increases hip BMD by 3% at 1 yr reduces nonvertebral fracture risk by about 46%. The results also predict that a 70% reduction in resorption BCM would reduce risk by 40%, and a 50% reduction in formation BCM would reduce risk by 44%. It appears that either BMD or BCM changes are able to explain the effect of treatment, because a separate variable for treatment was not independently significant in any models. These data demonstrate that larger increases in BMD at both the spine and hip and larger reductions in both formation and resorption BCM are associated with greater reductions in the risk of nonvertebral fractures. Antiresorptive agents that do not produce large increases in BMD or large reductions in BCM do not appear to and would not be expected to decrease the risk of nonvertebral fractures. (*J Clin Endocrinol Metab* 87: 1586–1592, 2002)

BONE MINERAL DENSITY (BMD) is a major determinant of bone strength and fracture risk. Most of the variability in bone strength is related to BMD *in vitro*, and low BMD is an important predictor of fracture risk in prospective studies of people (1–3). The relationship between BMD and fracture risk is nonlinear in that small reductions in BMD are associated with greater proportional increases in fracture risk (1, 4). There is also evidence that increased levels of bone turnover, as measured by biochemical markers (BCMs) of either bone formation or resorption, are associated with increased fracture risk (5, 6).

Antiresorptive agents reduce the rate of bone turnover and increase BMD to varying degrees, and a number of these agents have been approved for the treatment of osteoporosis in the United States (7–13). Some agents have been shown to reduce the incidence of radiographic and clinical vertebral fractures (14). Alendronate and risedronate have been shown to significantly reduce the risk of nonvertebral fractures, whereas other agents such as raloxifene and calcitonin have not (14).

Abbreviations: BCM, Biochemical markers; BMD, bone mineral density; RR, relative risk.

Prior analyses of data from randomized placebo-controlled clinical trials conducted in postmenopausal women suggest that increases in BMD during antiresorptive therapy account for much of the reduction in risk of radiographic vertebral fractures (15, 16). Despite these analyses, there continues to be a debate regarding the extent to which reductions in fracture risk during antiresorptive therapy may be related to changes in BMD (1, 17). For example, it has been proposed that some antiresorptive agents might reduce vertebral fracture risk substantially by reducing rates of bone resorption while having little or no effect on BMD (9, 17). Part of the rationale for this hypothesis is that maximum effects on BCM are generally achieved within the first 6–12 months, and substantial reductions in fracture risk have also been reported within the first 12–18 months (14). However, a large proportion of the observed increases in BMD also occurs within the first 18 months, although BMD continues to increase progressively over time up to at least 7 yr in some studies (18). Although one study reported that reductions in bone turnover during treatment were associated with a reduction in vertebral fracture risk, the analyses did not directly evaluate the extent to which changes in turnover could

explain the effect of treatment, nor did they evaluate the extent to which changes in turnover were related to changes in BMD (19).

The analyses described here further explore these issues for the outcome of symptomatic nonvertebral fractures, and for early (1 yr) changes in BMD and BCM. The objective of this study was to examine the associations between changes in BMD and BCM with reductions in the risk of symptomatic nonvertebral fractures by conducting a meta-analysis of randomized placebo-controlled clinical trials of antiresorptive agents in postmenopausal women with osteoporosis.

Materials and Methods

Randomized, placebo-controlled, double-blind, clinical trials of antiresorptive agents that reported both changes in BMD (or BCM) and incidence of nonvertebral fractures were identified from a systematic literature review and from abstracts in conference proceedings (Table 1) (14, 20). The analysis was limited to studies that recruited postmenopausal women with osteoporosis (those with existing vertebral fractures and/or low BMD). Trials that compared calcium or vitamin D to placebo were not considered, because most of the trials of pharmacological agents provided calcium and/or vitamin D to participants, so the effects of the pharmacological agents are above and beyond those of calcium or vitamin D.

Poisson regression was used to pool the data across all trials and to examine the associations of treatment and changes in BMD (or BCM) during the first year with reduction in risk of nonvertebral fracture over the duration of each study. The Poisson model gives greater weight to larger studies with higher numbers of fracture events and appropriately calculates associations for studies that include more than one active treatment group compared with a single placebo group. The independent (predictor) variables were change in BMD (or BCM), treatment assignment, and an indicator variable for each trial. The dependent (outcome) variable was nonvertebral fracture incidence. Where not provided in the original report, patient-years of follow-up were calculated by multiplying the number of patients with follow-up by the duration of the study. When a substantial proportion of participants dropped out of a study, follow-up was calculated by linear interpolation between the number of women at baseline and at completion.

A separate model was used for each measure of BMD and BCM at 1 yr: one each for change in spine and change in hip BMD, and one each for change in resorption and change in formation BCM. Models were also examined using BMD changes at the end of each study. We also tested models that included combinations of BMD change and BCM change. The sensitivity of the results to individual trials was evaluated by excluding trials singly and repeating the analysis. The sensitivity of the results to individual pharmacological agents was evaluated by excluding all trials of that specific agent and repeating the analysis. The site of hip BMD measurements varied among studies (Table 2). For BCM, the types of assays varied among studies; the resorption markers included urinary deoxypyridinoline, collagen type I cross-linked N-telopeptide, and collagen type I cross-linked C-telopeptide (one small study (21) reported urinary hydroxyproline); formation markers included serum osteocalcin and bone-specific alkaline phosphatase. The differences in hip BMD measurements are unlikely to substantially influence the findings, because the same measurements were used for both the placebo and treatment groups in each study, and changes in total hip and femoral neck BMD were generally similar within each study when both were measured. Although the same assay was used for both the placebo and treatment groups within each study, differences in BCM assays among studies may have greater potential to influence the findings, with uncertain consequences.

Results

A total of 18 studies were identified that satisfied the inclusion criteria (7–9, 13, 21–34). These studies enrolled 26,494 women and accumulated a total follow-up of 69,369 woman-years, during which 2,415 women experienced one or more new nonvertebral fractures (Table 2). The eight largest studies accounted for 92% of follow-up time and 90% of all new fracture cases.

The relative risk (RR) and percentage reduction in RR of nonvertebral fracture is plotted against the changes in BMD and BCM (relative to placebo) for the treatment group in each trial in Figs. 1-4. Most, but not all, studies observed reductions in risk of nonvertebral fractures. For studies with small numbers of events, however, these RR estimates are unstable with wide confidence intervals (confidence intervals are not shown). On the other hand, studies with large numbers of events have relatively stable estimates with narrower confidence intervals.

Poisson regression models were used to pool data across all trials and obtain the best fit, giving greater weight to larger studies (Figs. 1–4). Larger increases in BMD at both the lumbar spine and hip during treatment were significantly associated with greater reductions in the risk of nonvertebral fracture ($P = 0.02$ and 0.006, respectively). Larger increases

TABLE 1. Descriptive characteristics for the randomized trials

Study (reference no.)	N: initial/final	Duration (yr)	Age: mean; range (yr)	Baseline vertebral fracture (%)	Spine BMD (T-score)	Hip BMD (T-score)	Incident fracture types
7	7,705/5,901	3	67; 31–80	59	−2.6	−2.5	Excluded if violent, finger, or skull
22	3,658/3,585	3.5	70; 54–81	55	−2.3	−2.7	Excluded if violent, face, or skull
33	5,445/3,086	3	74; 70–79	39		−3.7	Wrist, leg, humerus, hip, pelvis, clavicle
8	1,628/939	3	69; ≤85	100	−2.4	−2.6	Clavicle, humerus, wrist, pelvis, hip, leg
9	1,255/626 (at 3 yr)	5	68	79	−2.3		Not stated
10, 25	994/881	3	64; 45–80	20	−3.1	−2.5	No exclusions
13	1,226/472	3	71; ≤85	100	−2.7		Clavicle, humerus, wrist, pelvis, hip, leg
23	1,908/1,697	1	63; 39–84	Not stated	−3.0	−2.1	No exclusions
24	423/289	3	65; <75	100	−2.8		All fractures; nonviolent, non-metastatic
28	359/341	2	71; 60–85	38	−3.0		No exclusions
30	425/320	2	62; 42–82	Not stated	−2.5		No exclusions
21	208/164	2	70; 68–72	Not stated	−3.1		Nonviolent
29	286/260	2	59; 48–76	5	−2.9	−1.8	Not stated
27	66/40	3	68; 56–75	100			No exclusions
31	143/130	1	68; 45–75	100	−2.5	−2.2	Atraumatic
32	132/93	3	68; 53–81	100	−2.5	−2.2	No exclusions
34	188/154	2	63; 42–75	Not stated	−2.7	−1.8	All fractures
26	488/424	2	62; 50–80	0	−2.9		Low energy fractures

TABLE 2. Nonvertebral fracture incidence and changes in BMD and BCM from the randomized trials

Study (reference no.)	Agent	Dose	1 yr spine BMD (%)[a]	Final spine BMD (%)[a]	1 yr hip BMD (%)[a]	Final hip BMD (%)[a]	Resorption marker (%)[a]	Formation marker (%)[a]	Fracture cases (n)	Patient-years	RR
7	Raloxifene	60 and 120 mg	2.6	2.7	1.3[b]	2.3[b]	−25 (at 3 yr)	−20 (at 3 yr)	677	23,115	0.91
22	Alendronate	5 and 10 mg	3.6	6.6	1.8	4.9	−39	−29	518	12,729	0.71[c]
33	Risedronate	2.5 and 5 mg				2.8[b]			499	12,523	0.79[c]
8	Risedronate	5 mg	3.0	4.1	1.7[b]	2.0[b]	−30 (at 6 months)	−23 (at 6 months)	85	4,881	0.64[c]
9	Calcitonin	100 IU	1.0	0.5			−11		32	999	0.67[c]
9	Calcitonin	200 IU	1.2	0.7			−12		46	999	0.96
9	Calcitonin	400 IU	1.0	1.1			−16		41	999	0.85
									PBO, 48	PBO, 999	
10, 25	Alendronate	5–20 mg	5.7	7.6	1.9[b]	3.6[b]	−49	−38	83	2,540	0.79
13	Risedronate	5 mg	3.9	5.9	0.8[b]	4.0[b]	−37 (at 6 months)	−33 (at 6 months)	87	2,436	0.71
23	Alendronate	10 mg	4.9	4.9	3.0	3.0	−53	−41	56	1,697	0.53[c]
24	Etidronate	200 mg	2.4	4.1	1.2	2.0			67	1,140	1.40
28	Alendronate	1 mg	0.9	0.7	0.3[b]	1.2[b]	1	−8	15	148	1.09
	Alendronate	2.5 mg	2.2	3.5	0.6[b]	1.5[b]	−42	−36	9	149	0.59
	Alendronate	5 mg	4.2	5.7	1.5[b]	3.4[b]	−51	−42	9	149	0.57
									PBO,16	PBO, 154	
30	Alendronate	10 mg	4.0	6.6	2.3	3.7	−63	−46	5	184	0.68
	Estrogen		4.9	6.6	2.2	3.1	−53	−46	10	286	0.87
	Alendronate + estrogen	10 mg	5.8	8.9	3.1	4.4	−70	−56	8	280	0.71
									PBO, 4	PBO, 100	
21	Calcitonin	50 IU	1.6	1.1			−8	−12	0	80	0.0
		100 IU	0	1.1			−8	−8	1	86	0.47
		200 IU	2.2	1.1			−7	−6	1	82	0.49
									PBO, 2	PBO, 80	
29	Calcitonin	100 IU	0.6	−0.8	0.9[b]	0.8[b]	10	−11	1	150	0.31
	Alendronate	10 mg	4.8	5.2	2.6[b]	3.8[b]	−31	−37	1	146	0.33
	Alendronate	20 mg	6.0	7.3	2.2[b]	4.6[b]	−34	−35	1	144	0.33
									PBO, 3	PBO, 142	
27	Etidronate	200 mg	2.3	8.0					11	115	0.83
31	Raloxifene	60 mg	0.8	0.8	1.7	1.7	−25	−15	0	43	0
		120 mg	1.1	1.1	1.2	1.2	−31	−9	4	45	1.33
									PBO, 3	PBO, 45	
32	Risedronate	2.5 mg cyclical	0.8	−0.1	1.2[b]	1.8[b]	−28	7	9	142	2.25
	Risedronate	2.5 mg continuous	1.5	−0.9	3.1[b]	4.2[b]	−37	4	4	142	1.00
									PBO, 4	PBO, 142	
34	Alendronate	5–40 mg	5.8	7.7	2.0	4.7	−40 (at 6 months)	−52 (at 6 months)	11	210	0.83
26	Tiludronate	50 mg		1.0					14	324	0.74
	Tiludronate	200 mg		0.7					10	324	0.52
									PBO, 19	PBO, 328	
Totals									2415	69,369	

PBO, Placebo group. The sample size of the placebo group is shown only when more than one treatment group was analyzed; for other studies, the numbers of fracture cases and patient-years are given for the total sample (placebo plus treatment combined).

[a] Change *vs.* placebo.

[b] Femoral neck BMD (otherwise, total hip BMD was measured).

[c] $P < 0.05$.

in hip BMD at the end of each trial (instead of change at 1 yr) were also significantly ($P = 0.022$) associated with fracture risk reductions, but the association did not quite reach significance for spine BMD ($P = 0.065$). Changes in resorption and formation BCM were also significantly associated with nonvertebral fracture risk ($P = 0.047$ and 0.009, respectively). The models are multiplicative in nature; the resulting plots are almost straight, but not perfectly linear. Additional analyses, including the square and cube of BMD or BCM changes, did not improve the models (data not shown). The variable for treatment was not significant in any models that included variables for change in BMD or BCM. Thus, changes in BMD or BCM appeared to explain a significant part of the risk reduction and indicate that there is no significant effect of treatment on fracture risk for treatments that were not associated with increases in BMD or moderate-to-large reductions in BCM (Figs. 1–4).

The regression coefficients (SE) corresponding to a 1% change at 1 yr were: −0.0816 (0.0349) for spine BMD, −0.267 (0.0976) for hip BMD, 0.0067 (0.0034) for resorption BCM, and 0.0134 (0.0051) for formation BCM. Taking into account the nonlinear nature of the models and the effect of treatment (this is necessary despite the lack of significance), the results predict that treatments with the largest increases in lumbar

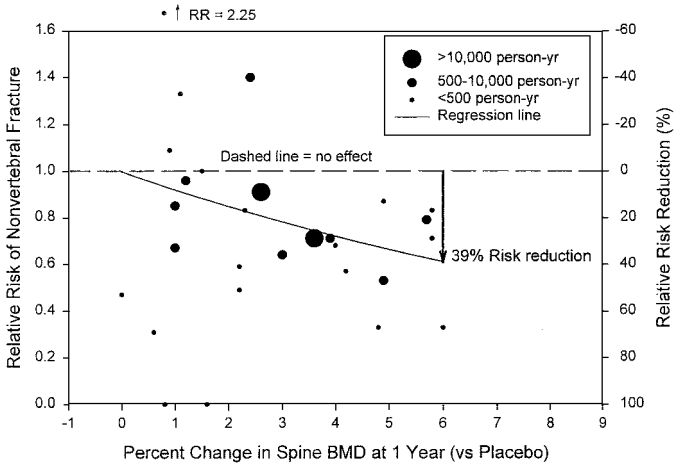

FIG. 1. RR of new nonvertebral fracture *vs.* change in spine BMD at 1 yr (*vs.* placebo) for randomized controlled trials of antiresorptive agents listed in Table 2. One point was off-scale, as indicated by the *arrow* (RR = 2.25). The *solid line* represents the Poisson regression results in Figs. 1–4.

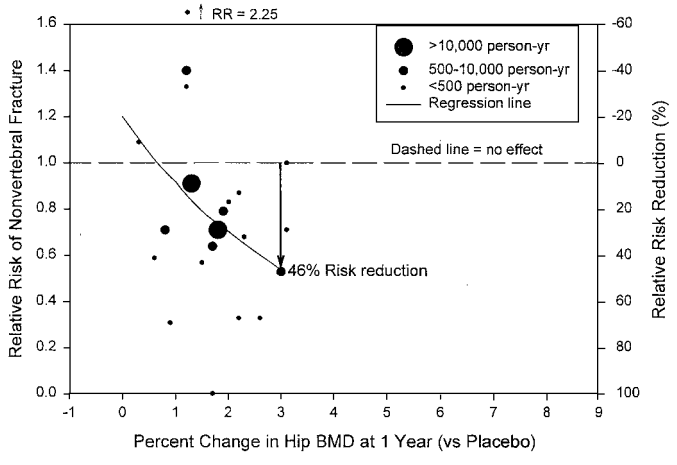

FIG. 2. RR of new nonvertebral fracture *vs.* change in hip BMD at 1 yr (*vs.* placebo) for randomized controlled trials of antiresorptive agents listed in Table 2. One point was off-scale, as indicated by the *arrow* (RR = 2.25).

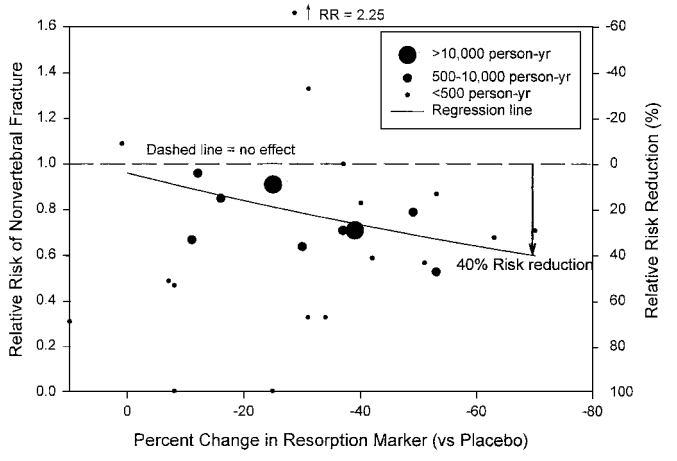

FIG. 3. RR of new nonvertebral fracture *vs.* change in resorption BCM at 1 yr (*vs.* placebo) for randomized controlled trials of antiresorptive agents listed in Table 2. One point was off-scale, as indicated by the *arrow* (RR = 2.25).

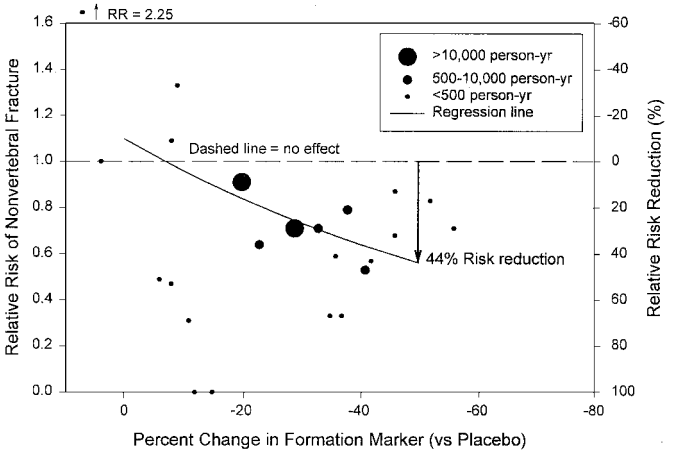

FIG. 4. RR of new nonvertebral fracture *vs.* change in formation BCM at 1 yr (*vs.* placebo), for randomized controlled trials of antiresorptive agents listed in Table 2. One point was off-scale, as indicated by the *arrow* (RR = 2.25).

spine BMD at 1 yr, 6% *vs.* placebo, are associated with a 39% reduction in nonvertebral fracture risk (Fig. 1). The results also predict a 46% risk reduction for treatments that increase hip BMD by 3% *vs.* placebo at 1 yr, a 40% risk reduction for treatments that decrease resorption BCM by 70% *vs.* placebo at 1 yr, and a 44% risk reduction for treatments that decrease formation BCM by 50% *vs.* placebo at 1 yr (Figs. 2–4).

The changes in BMD were significantly ($P \leq 0.002$) correlated with changes in BCM. The r^2 values for changes in spine BMD at 1 yr were 0.80 *vs.* resorption BCM and 0.85 *vs.* formation BCM. The r^2 values for changes in hip BMD at 1 yr were 0.58 *vs.* resorption BCM and 0.41 *vs.* formation BCM.

The Poisson regression results were generally robust in the sensitivity analysis. The results were basically unchanged when individual trials were removed singly (yielding 18 sensitivity models for each predictor, one model for each trial that was dropped). One exception was that the association for change in hip BMD remained significant, but the associations for change in BCM (formation and resorption) and for spine BMD were not quite significant ($P = 0.09–0.17$) after excluding the large raloxifene study (7). Also, the association for change in resorption BCM was not quite significant ($P = 0.11–0.15$) when any one of three alendronate trials was excluded (22, 23, 28).

The results were also basically unchanged when all trials of the individual drugs calcitonin, etidronate, and risedronate were removed singly from the models. When the two raloxifene studies were removed from the models, the association for change in hip BMD remained significant, but the other associations were not quite significant ($P = 0.08–0.16$). When all alendronate studies were removed from the models, however, the associations were no longer significant. The alendronate trials contributed 22% of follow-up time and 29% of all fractures, whereas the raloxifene trials contributed 33% of follow-up time and 28% of all fractures. Thus, the loss of statistical significance is probably due to the large reduction in sampling units when these studies were dropped.

Discussion

Osteoporosis is defined as a condition characterized by low BMD and increased fracture risk (35). Indeed, low BMD is a major determinant of increased fracture risk and is sufficient to justify treatment (1, 36). Osteoporosis in postmenopausal women is also associated with an elevated rate of bone turnover. This increase in bone turnover is accompanied by an imbalance in the ratio of bone resorption to formation, leading to decreases in the quantity or mass of bone, reflected by declines in BMD, loss of trabecular connectivity, and decreases in bone mineralization (37). High turnover is also accompanied by increased numbers of resorption lacunae, which represent focal areas of weakness. The structural defects coupled with the loss of bone mass result in decreased bone strength and increased fracture risk.

A number of antiresorptive agents, including alendronate, calcitonin, raloxifene, and risedronate, have been approved by the U.S. Food and Drug Administration for the treatment of osteoporosis in postmenopausal women (36). There is evidence from randomized placebo-controlled clinical trials that these agents reduce the risk of radiographic vertebral fractures, although the evidence is weaker for calcitonin than for the other agents. However, not all of these agents have been shown to reduce the risk of nonvertebral fractures. In a meta-analysis of these and other randomized placebo-controlled clinical trials, Wasnich and Miller (15) noted a significant association between the amount of increase in BMD at both the lumbar spine and hip and the reduction in risk of new radiographic vertebral fractures, with a significant, independent effect of treatment. In the present meta-analysis, we report a significant association between the amount of increase in BMD at both the lumbar spine and hip during the first year of treatment and the reduction in risk of incident nonvertebral fractures without an independent effect of treatment. As with BMD, changes in markers of bone turnover during the first year of treatment were also significantly associated with fracture risk reductions, and without an independent effect of treatment. It was not possible to include both BMD and BCM in models, because they were correlated too highly. The results suggest that changes in BMD and BCM both provide similar information regarding reductions in nonvertebral fracture risk during treatment.

Both the earlier report (15) and the current meta-analyses found a significant association between increases in BMD and reductions in fracture risk during treatment with antiresorptive agents. How might one explain the differences in the results of the meta-analyses with regard to the independent effect of treatment? Specifically, there was an independent effect of treatment with an antiresorptive agent after adjusting for the effects of treatment on bone mineral density for vertebral fractures, but not for nonvertebral fractures. There are several potential mechanisms by which antiresorptive agents might reduce the risk of vertebral fractures to a greater extent than nonvertebral fractures: 1) a reduction in activation frequency with antiresorptive agents would lead to fewer, and possibly shallower, resorption sites; 2) the inhibition of excessive resorption allows compromised bone to respond to mechanical demands, preferentially thickening critical trabeculae; 3) reduction in bone turnover might prevent perforation of trabecular plates and loss of trabecular connectivity in the vertebral bodies; and 4) reduction in bone turnover allows mineralization to proceed fully (38). Vertebral bodies have a larger proportion of trabecular bone than tubular appendicular bones. The rate of turnover in trabecular bone is approximately 30% per year, which is approximately 10 times greater than the rate for cortical bone. Small, but clinically significant reductions in bone turnover may produce significant reductions in vertebral fracture risk with albeit relatively small increases in BMD. Larger clinically significant changes in both bone turnover and BMD may be better indicators of effects on cortical bone and reductions in risk of nonvertebral fractures where cortical bone strength is involved to a greater extent. Indeed, in the present meta-analysis, there also was not an independent effect of treatment with an antiresorptive agent after adjusting for the effects of treatment on BCMs for nonvertebral fractures. The effects of antiresorptive therapy on parameters of bone geometry, which may affect fracture risk independently of both bone turnover and BMD, have not been explored as yet in clinical trials.

Considering that 18 sensitivity models were run for each predictor variable (one model for each dropped trial), the consistency of the results is reassuring. In almost all cases, most of the associations remained significant. The only exception was that the associations were no longer significant when all trials of alendronate were excluded. This is probably because a large number of sampling units were lost when the alendronate trials were excluded. Excluding the alendronate trials would also reduce the ability to detect an association by reducing the variability among studies, because many of the largest changes in BMD and BCM, and large reductions in fracture incidence, were observed in these trials.

Many studies were too small to have sufficient power to individually detect a significant effect on nonvertebral fracture risk or to provide estimates of effect size with meaningful confidence intervals. It is difficult to interpret the relationship with BMD or BCM changes by comparing individual studies because of the large variability in fracture risk reduction among studies, which may be related to chance, especially in the smaller studies. The variability in the magnitude of risk reductions among studies, together with the relatively large uncertainties for individual estimates, especially among smaller studies, makes it difficult to interpret whether reductions in risk during antiresorptive therapy are related to changes in BMD. The apparently large risk reductions in the absence of large BMD increases in some studies are probably due to chance, rather than real effects. Therefore, this meta-analysis pooled the data from all studies to obtain the best-fit estimate of the true relationship between changes in BMD and reductions in fracture risk. In general, our findings are consistent with those of large trials; there were no significant reductions in nonvertebral fracture risk for agents with smaller increases in BMD and smaller reductions in BCM (7, 9).

Our results have clinical implications for helping to determine which agents are most effective for reducing the risk of nonvertebral fractures. Our analyses indicate that agents which produce the largest increases in BMD and the largest

decreases in BCM are those which are most effective for reducing the risk of nonvertebral fractures and are in general agreement with the earlier analysis of BMD changes and reductions in vertebral fracture risk (15). These findings should not be used to attempt to predict antifracture benefits from changes in BMD or BCM of individual patients. Data on changes in BMD and BMC for individual patients were not available for the current analysis, and we did not explore how individual patient changes might relate to fracture risk. Individual patients may benefit from treatment even if BMD does not appear to increase initially; such patients may have experienced greater bone loss and fracture risk in the absence of treatment (39, 40). Also, one cannot extrapolate the findings observed here to agents other than antiresorptive compounds, such as PTH or fluoride. Increases in BMD with agents such as PTH are accompanied by increased, rather than decreased, BCM, suggesting a different mechanism of action (41).

Our study has some potential limitations, but the consequences, if any, are uncertain. There is a possibility that publication bias may have influenced the results. Trials that observed positive or significant results may tend to be published more often than those that did not. In this regard, results suggesting a possible reduction in nonvertebral fracture incidence in a clinical trial of tiludronate were reported for one small arm (used in our analysis), but comparable results were not provided for a much larger arm in the same trial (26). Differences in BCM assays among the trials also may have potential to influence the findings.

Our analysis illustrates the usefulness of meta-analysis for interpreting associations when results appear to be discordant. On the basis of these results, we conclude that the antifracture efficacy of antiresorptive agents is associated with changes in BMD for both nonvertebral and vertebral fractures. Agents that produce larger increases in BMD tend to provide greater reductions in both vertebral and nonvertebral fracture risk. In contrast to results seen with vertebral fractures, changes in BMD during treatment appear to explain all of the reduction in risk of nonvertebral fractures. Changes in BMD were highly correlated with changes in BCM, and we could not distinguish between the two in our analyses; there was no independent treatment effect after taking into account changes in either BMD or BCM. Thus, physicians treating patients with osteoporosis should choose agents that provide the greatest increases in BMD or reductions in BCM relative to placebo to reduce their patient's risk of both vertebral and nonvertebral fractures.

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