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III. Meta-Analysis of Risedronate for the Treatment of Postmenopausal Osteoporosis

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A. Abstract

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

Data Sources: We searched MEDLINE from 1966 to the end of 2000 and examined citations of relevant articles and the proceedings of international osteoporosis meetings.

Study Selection: We included eight randomized, placebo-controlled trials of postmenopausal women receiving risedronate or placebo with a follow-up of at least one year and providing data on bone density or fracture rate.

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

Data Synthesis: The major methodological limitation of the trials was the loss to follow-up, which was over 20% in most trials and over 35% in the largest study. However, the magnitude of the treatment effect was unrelated to loss to follow-up, and in one of the largest trials, more high-risk patients were lost to follow-up in the control than in the treatment group. The pooled relative risk (RR) for vertebral fractures in women given 2.5 mg or more of risedronate was 0.64 [95% confidence interval (CI) 0.54, 0.77]. The pooled RR of nonvertebral fractures in patients given 2.5 mg or more of risedronate was 0.73 (95% CI 0.61, 0.87).

Risedronate produced positive effects on the percentage change in bone density of the lumbar spine, combined forearm, and femoral neck that were generally larger with the 5-mg daily dose than with cyclical administration or the 2.5-mg dose. The pooled estimate of the difference in percentage change between 5 mg risedronate and placebo after the final year of treatment (1.5–3 yr) was 4.54% (95% CI 4.12, 4.97) for the lumbar spine, and 2.75% (95% CI 2.32, 3.17) at the femoral neck.

Conclusions: Risedronate substantially reduces the risk of both vertebral and nonvertebral fractures. This fracture reduction is accompanied by an increase in bone density of the lumbar spine and femoral neck in both early postmenopausal women and those with established osteoporosis.

B. Background

RECENT STUDIES SUGGEST that risedronate, a third-generation bisphosphonate with antiresorptive activity, decreases vertebral and nonvertebral fracture risk in postmenopausal osteoporosis (1, 2). The Federal Drug Administration has recently approved risedronate at a dose of 5 mg daily for the prevention and treatment of postmenopausal osteoporosis.

We performed a systematic review and meta-analysis of the effect of the risedronate on bone density and fractures. We endeavored to include all published and unpublished randomized control trials that measured the effect of risedronate on vertebral and nonvertebral fractures or on bone density. Our goals included determining the impact of risedronate dose and duration of therapy on fractures and bone density, and the relative effect in the prevention and treatment of osteoporosis.

As described in *Section I*, Merck, the makers of alendronate, provided partial funding for this series of systematic reviews. The source of funding could introduce a possible threat to our objectivity, particularly in a systematic review of a directly competing bisphosphonate. Aware of this threat, we have endeavored to be scrupulous both in our methods and our conclusions. Our efforts included obtaining a review of this manuscript from Procter & Gamble, the manufacturers of risedronate.

C. Methods

a. Eligibility criteria. We selected trials that satisfied the following inclusion criteria: 1) randomized, placebo-controlled trials of risedronate for osteoporosis in postmenopausal women (defined as greater than 6 months postmenopausal); 2) follow-up of at least one year; and 3) fracture incidence or bone mineral density data available.

b. Search and selection. To identify relevant studies of risedronate therapy, we used the Cochrane Collaboration search strategy, which was modified for the Cochrane Musculoskeletal group (see *Section I*) and used the following key and text words: risedronate, actonel, osteoporosis, postmenopausal, bisphosphonates, randomized control trial. For published data, this included a search of electronic databases including MEDLINE, EMBASE, Current Contents, and the Cochrane Controlled trials registry using a time frame from 1966 to December 2000. There were no language restrictions applied to the search strategy. We hand-searched conference abstract books from international meetings and the results of Food and Drug Administration proceedings, reviewed citations of relevant articles, and successfully enlisted the collaboration of Procter & Gamble, makers of risedronate. The

Abbreviation: CI, Confidence interval.

introductory paper fully describes our search and selection process (see *Section I*).

Two reviewers (N.Z., A.C.) examined all potentially relevant trials. For abstracts consistent with study eligibility, we obtained the full text.

c. Methodological quality. Two reviewers (N.Z., A.P.) independently evaluated each trial for four characteristics: concealment, intention to treat analysis, blinding, and the completeness of follow-up.

d. Data collection. Two reviewers independently extracted all data, including study population characteristics, treatment duration, baseline demographic data, and the baseline and end-of-study outcomes.

e. A priori hypotheses regarding heterogeneity. As outlined in detail in the introductory paper, we developed *a priori* hypotheses that might explain the heterogeneity of study results. Specifically, we compared groups according to: 1) prevention *vs.* treatment; 2) concurrent treatments including total calcium intake (<500 mg/d *vs.* ≥500 mg), and vitamin D; 3) individual components of the quality assessment; 4) the dose-administration regimen (daily *vs.* cyclical); 5) loss to follow-up (<20% *vs.* >20%); and 6) for bone density, the year of follow-up.

f. Analysis. A random-effects model guided the calculation of final estimates of treatment effects on bone density and fractures. For bone density, we conducted separate analyses for each site (lumbar spine, femoral neck, and combined forearm) using the difference between the change in bone density for each dose group and the change in the placebo arm. We constructed regression models as outlined in *Section I*.

The first full regression model with lumbar spine data included a parameter for each year of follow-up and each dose. We compared this full model to a reduced model with all year parameters removed (Table 1). For the lumbar spine, the proportion of variance explained by the full model was not significantly greater than the proportion explained by the reduced model; therefore we pooled across all years, examining the final year of data (Table 1).

In seeking the most parsimonious model with respect to dose, we found we could not pool all doses (Table 1). Subsequent model comparisons led to our adopting a model in which we pooled both 2.5-mg and 5.0-mg cyclical doses with a 2.5-mg daily dose, and we considered the 5.0-mg daily dose separately. Similar regression techniques provided the most parsimonious model for femoral neck.

To calculate the weighted mean percent difference in bone density between treatment and control groups, we followed the methodology outlined in the *Section I*.

For fractures, a RR was determined using a method described by Fleiss (3). We used the person as the unit of analysis, rather than fractures. For instance, a person with two new vertebral fractures was counted as having a single event, a recurrent fracture. When the necessary data were absent or ambiguous in the original papers, we contacted the author or company for clarification. We constructed two-by-two tables for both vertebral and nonvertebral fractures and calculated and subsequently pooled the associated risk ratios using a random-effects model. A similar analytic strategy was used to deal with the proportion of patients who discontinued medication because of adverse effects.

A χ^2 test (3) provided the statistical basis for examining possible sources of heterogeneity between studies. Irrespective of whether there was statistically significant heterogeneity between studies, we divided the studies into two groups based on the *a priori* hypotheses and tested whether the treatment effects were different between the two groups (4). For instance, for the fracture analyses, we compared effects in studies that used the 5-mg dose *vs.* other doses, prevention *vs.* treatment studies, studies that met and did not meet individual components of the quality assessment, and so on according to our *a priori* hypotheses regarding sources of heterogeneity.

We constructed plots of the relationship between sample size and the magnitude of the treatment effect (funnel plots). We looked for asymmetry in the distribution of results of the small trials in relation to results of the larger trials. We examined funnel plots for each outcome for each of the meta-analyses we undertook and noted instances in which the results suggested possible publication bias.

The original draft of this paper emphasized the threat to validity represented by the large proportion of patients lost to follow-up in these studies. After their review of the paper, the manufacturer provided us with data concerning baseline characteristics of patients lost to follow-up in the 5-mg daily and control groups in the two largest studies that measured vertebral fracture incidence (1, 2).

TABLE 1. Summary of regression analysis to determine a parsimonious summary of the effect of risedronate on lumbar spine bone mineral density

Site	Parameters				χ^2	*P* value[a]	Decision
	More complex model		Simpler model				
	Dose	Time	Dose	Time			
Lumbar spine	1 2 3 4	1 2 3 4	1 2 3 4	[1 2 3 4][b]	3.41	0.33	Pool all times
	1 2 3 4	[1 2 3 4]	[1 2 3 4]	[1 2 3 4]	26.29	<0.01	Do not pool all doses
	1 2 3 4	[1 2 3 4]	1 2 [3 4]	[1 2 3 4]	24.19	<0.01	Do not pool doses 3 and 4
	1 2 3 4	[1 2 3 4]	[1 2] 3 4	[1 2 3 4]	0.002	0.97	Pool doses 1 and 2
	[1 2] 3 4	[1 2 3 4]	[1 2 3] 4	[1 2 3 4]	0.49	0.48	Pool doses 1, 2, and 3
Model chosen	Pool all years.						
	Pool doses 2.5 mg cyclical, 5.0 mg cyclical, and 2.5 mg daily keeping 5.0 mg daily separate.						

[a] *P* value is for a test on the difference in variance explained by the two models.

[b] *Brackets* indicate pooling of doses *within brackets*. Dose 1, 2.5 mg cyclical; dose 2, 5.0 cyclical; dose 3, 2.5 mg; dose 4, 5.0 mg. Time 1 = 1 yr; time 2 = 1.5 yr; time 3 = 2 yr; time 4 = 3 yr.

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D. Results

a. Trial characteristics. We identified 12 potential articles through the electronic-search strategy and 6 from hand searching. We excluded 10 for the following reasons: use of risedronate for other clinical conditions such as breast cancer (5), review articles (6–10), lack of a control arm (11), and duplication of data (Refs. 12–14, see also Fig. 1).

Table 2 presents the characteristics of the eight eligible studies. Six trials were treatment trials (1, 2, 15–18), and two were classified as prevention studies (19, 20). Two studies were available in abstract form only (18, 20). All the trials were randomized and placebo controlled. All eight trials used an intention to treat analysis and concealed allocation.

Seven trials had losses to follow-up of greater than 20%, and three of those had losses to follow-up of over 30% (Table 2) (1, 2, 16). In one of the largest trials that measured vertebral fracture incidence (1), 41.4% of the 331 placebo patients lost to follow-up had sustained two or more vertebral fractures at baseline, whereas 33.4% of 488 patients who completed the trial had two or more fractures. In the treatment group, 37.9% of the 317 patients lost to follow-up had sustained two or more vertebral fractures at baseline, whereas 35.5% of 502 patients who completed the trial had two or more fractures. These results suggest that in comparison to treatment, higher risk patients in the control group were lost to follow-up. If this is so, any bias introduced by loss to follow-up would favor the placebo group. In the other, largest, trial that measured vertebral fractures, 68.3% of 142 control patients lost to follow-up, and 64.3% of 265 followed successfully, had suffered more than two vertebral fractures. Parallel numbers in the treated patients were 69.9% of 133 lost to follow-up and 67.3% of 275 treated patients.

b. Fractures. The pooled estimate of the RR (all doses combined) from the five trials reporting results of vertebral fractures (1, 2, 15, 17, 19) was 0.64 (95% CI 0.54, 0.77; Table 3 and Fig. 2). The results were consistent across studies (Fig. 2), reflected in the high *P* value of the test of heterogeneity, 0.89; and none of our *a priori* hypotheses explained the variability that did exist. Analyses restricted to patients who received 5 mg showed a very similar RR to the entire data set (0.62, 95% CI 0.51, 0.76).

Seven trials reported nonvertebral fractures (1, 2, 15–19), and the pooled RR for the final year for all doses combined was 0.73 (95% CI 0.61, 0.87). The results were consistent across trials (heterogeneity *P* value of 0.81), and our *a priori* hypotheses did not explain any of the variability (Table 3 and Fig. 3). Once again, results restricted to patients who received the 5-mg dose were very similar to the entire data set (0.68, 95% CI 0.53, 0.87).

c. Bone mineral density. Table 4 presents the results of the pooled estimates for lumbar spine, distal radius, and femoral neck. Risedronate produced positive effects on percentage change in bone mineral density of the lumbar spine and femoral neck. The 5-mg daily dose demonstrated larger effects than the 2.5-mg dose or the cyclical administration in both lumbar spine and femoral neck bone density. After 1½-3 yr of therapy with risedronate, the pooled estimate of treatment effect was 4.54% (95% CI 4.12, 4.97) for the lumbar spine (Fig. 4).

For femoral neck, the results were generally consistent across studies, as reflected in the high *P* values associated with the tests of heterogeneity. However, results for the lumbar spine measurements from final year for the 2.5-mg and the cyclical doses combined group showed a highly significant test of heterogeneity (Table 4). None of our *a priori* hypotheses explained variability in the final year results (Table 5).

d. Publication bias. We found no persuasive evidence of publication bias from review of the funnel plots.

e. Adverse effects and withdrawals. Eight studies provided data regarding dropouts and withdrawals. Treatment had little or no impact on the risk of discontinuing medication (RR 0.94; 95% CI 0.80, 1.10). For discontinuation due to gastrointestinal side effects, the pooled RR was 0.97 (95% CI 0.90, 1.04). The pooled RRs for dyspepsia and abdominal pain were similar. For esophagitis, the pooled RR from five trials was 0.91 (95% CI 0.70, 1.18). It is important to note that the risedronate trials did not exclude patients with a history of or ongoing gastrointestinal disease *a priori*, as seen in other bisphosphonate trials.

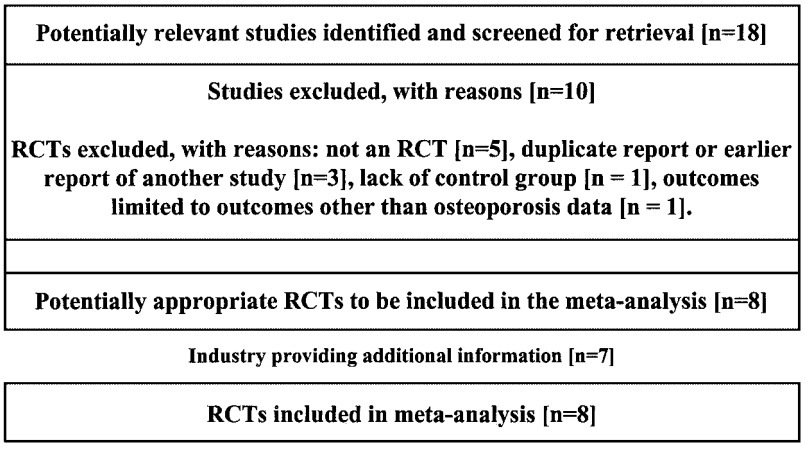

FIG. 1. Search results for the risedronate review.

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TABLE 2. Risedronate trial characteristics

Trial year prevention/treatment[a] (Ref.)	No. of patients (Tx/Control)	Mean age (SD) Years postmenopausal [Baseline Ca^{2+}] LS-BMD g/cm^2 t-score	Intervention (calcium or vitamin D supplementation)	Duration (years)	Outcomes measured Vertebral fractures rate (Tx/N *vs.* Cnrtl /N) Nonvertebral fracture rate (Tx/N vs Cnrtl /N)	Lost to follow-up (%)[b]
Reginster *et al.*, 2000 (treatment) (2)	1226 819/407	71.0 (7.0) 24.4 (8.5) [Not collected] 0.79 g/cm^2 (0.15) −2.7	Risedronate 2.5 mg/d or risedronate 5 mg/d *vs.* placebo (1000 mg calcium daily and 500 IU vitamin D if 25-hydroxyvitamin levels were low)	3 (2.5 mg/dose discontinued at 2 yr)	BMD: Lumbar spine, femoral neck, and trochanter Fracture: Vertebral (53/344 *vs.* 89/346) and nonvertebral (36/406 *vs.* 51/406)	231/1226 (1st yr) (18.8%) 191/663 (3rd yr) (28.9%)
Harris *et al.*, 1999 (treatment) (1)	2458 1638/820	69 (7.3) 24 (9.9) [Not collected] 0.83 g/cm^2 (0.16) −2.4	Risedronate 2.5 mg/d or risedronate 5 mg/d *vs.* placebo (1000 mg calcium daily and 500 IU vitamin D if 25-hydroxyvitamin levels were low)	3 (2.5 mg/d dose discontinued at 1 yr)	BMD: Lumbar spine, femoral neck, trochanter, and mid-radius Fractures: Vertebral (61/696 *vs.* 93/678) and nonvertebral (33/812 *vs.* 52/815)	601/2458 (1st yr) (24.5%) 708/1647 (3rd yr) (43%)
Mortensen *et al.*, 1998 (prevention) (19)	111 75/36	51.2 (3.8) 2.7 (1.7) [977 (535) mg/d] 0.94 (0.11) g/cm^2 −1.0	Risedronate 5 mg/d daily or cyclical risedronate 5 mg/d for 1st 2 wk of every calendar month then placebo for remainder *vs.* placebo	3 (Patients given option to continue after 1st yr, 3-yr follow-up only no tx provided)	BMD: Lumbar spine, femoral neck, trochanter Fractures: Vertebral (2/75 *vs.* 0/36) and nonvertebral (3/75 *vs.* 3/36)	15/111 (1st yr) (13.5%) 6/68 (2nd yr) (8.8%) 0/61 (3rd yr) (0%)
Clemmesen *et al.*, 1997 (treatment) (15)	132 88/44	68.3 (5.7) 20.3 (7.3) [753 (311) mg/d] 0.78 (0.14) g/cm^2 −2.4	Risedronate 2.5 mg/d daily or cyclical risedronate 2.5 mg/d for 2 wk then off for 10 wk *vs.* placebo (1000 mg calcium/d)	3 (last year follow-up only)	BMD: Lumbar spine and femoral neck Fractures: Vertebral (28/88 *vs.* 20/44) and nonvertebral (13/88 *vs.* 4/44)	39/132 (29.5%)
Fogelman *et al.*, 2000 (treatment) (17)	543 363/180	64.7 (7.2) 17.7 (9.4) [Not collected] 0.74 (0.08) −2.9	Risedronate 2.5 mg/d or risedronate 5 mg/d *vs.* placebo (1000 mg calcium daily)	2 (2.5 mg group discontinued at 1 year)	BMD: Lumbar spine, femoral neck, and trochanter Fractures: Vertebral (16/172 *vs.* 17/125) and nonvertebral (11/172 *vs.* 13/125)	112/543 (20.6%) 76 patients withdrawn from 2.5 mg group prior 2 yr)
Hooper *et al.*, 1999 Abs (prevention) (20)	383 257/126	52.7 (3.2) 3.9 [–] 1.08 g/cm^2 −0.4	Risedronate 2.5 mg/d or risedronate 5 mg/d *vs.* placebo (1000 mg calcium daily)	2	BMD: Lumbar spine, femoral neck, and trochanter	87/383 (23%)
McClung *et al.*, 2001 (treatment) (16)	9331 6197/3134	78.0 (9.7) 31.8 (19.3) [–] −2.8	Risedronate 2.5 mg/d or risedronate 5 mg/d *vs.* placebo (1000 mg calcium daily and 500 IU vitamin D if 25-hydroxyvitamin levels were low)	3	BMD: Femoral neck and trochanter Fractures: Hip (130/6197 *vs.* 86/3134)[c]	3324/9331 (35.6%)
McClung *et al.*, Low BMD study, 1999 Abs treatment (18)	648 428/220	62.5 (0.3) 16.4 (0.4) [–] 0.80 g/cm^2 −2.8	Risedronate 2.5 mg/d or risedronate 5 mg/d *vs.* placebo (1000 mg calcium daily)	1.5	BMD: Lumbar spine, femoral neck, trochanter, distal radius, and mid-radius Fractures: Nonvertebral (18/428 *vs.* 13/220)	246/648 (38%)

LS-BMD, Lumbar spine bone mineral density. Tx, Treatment.

[a] Definition of prevention and treatment outlined in *Section I*.

[b] Number of patients available for last visit of study close-out.

[c] Not all nonvertebral fractures were reported; hip fractures only.

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TABLE 3. Weighted RR with 95% CI after treatment with risedronate

Fracture sites	Dose	No. of trials	No. of patients	RR (95% CI)	RR *P* value	Heterogeneity *P* value
Vertebral	All	5	2604	0.64 (0.54, 0.77)	<0.01	0.89
Nonvertebral	All	7	12958	0.73 (0.61, 0.87)	<0.01	0.81

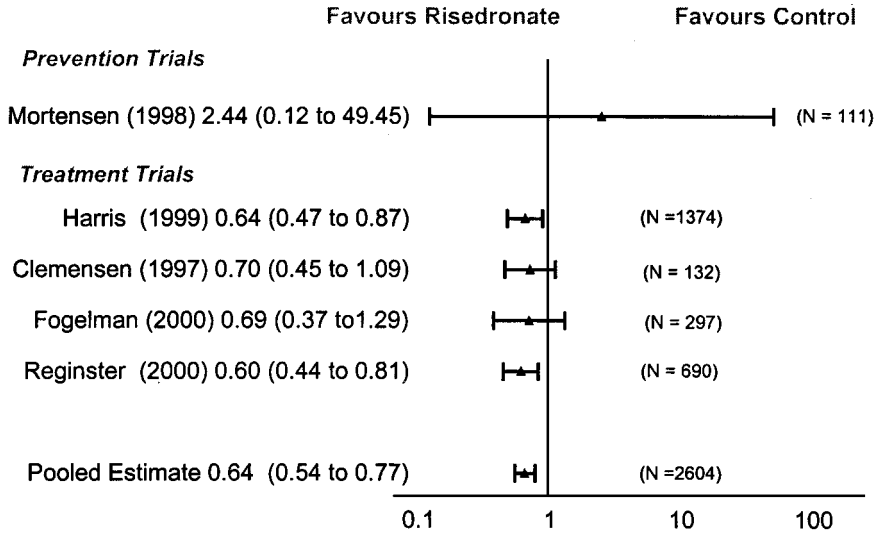

FIG. 2. Relative risk with 95% CI for vertebral fractures after treatment with risedronate.

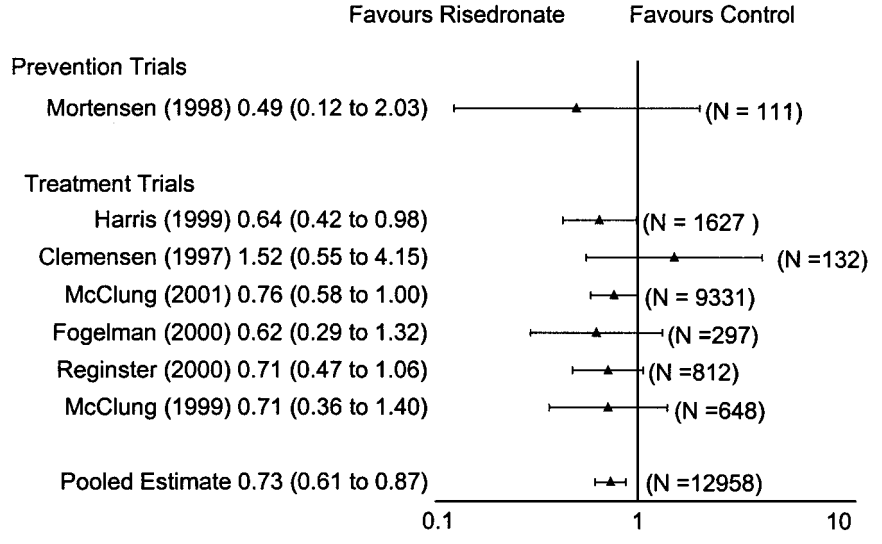

FIG. 3. Relative risk with 95% CI for nonvertebral fractures after treatment with risedronate.

E. Discussion

The primary finding of this systematic review is that the best estimate of risedronate's effect is a reduction in the RR of vertebral fractures of slightly more than a third, and of nonvertebral fractures of slightly more than a quarter (Table 3 and Figs. 2 and 3). The upper boundary of the CI representing the smallest plausible treatment effect suggests a RR reduction of at least 23% for vertebral fractures, and 13% for nonvertebral fractures. The substantial increase in bone density associated with risedronate therapy provides, at least in part, a biological mechanism for the reduction in fractures. The 5-mg daily dose of risedronate, the formulation now available to clinicians, tended to show a larger impact on bone density than did the 2.5-mg dose or cyclic administration, and longer duration of therapy produced larger effects (Table 4).

The most serious methodological limitation of these studies is the consistently very high loss to follow-up (Table 2). Loss to follow-up threatens the validity of a trial because the distribution of prognostic factors, and thus the event rate, may be very different in those lost to follow-up than in those who complete the trial. In other words, a large loss to follow-up places a trial at great risk of losing the balance of prognostic factors initially achieved by randomization (21).

Fortunately, there are reasons to think that loss to follow-up is unlikely to bias upward our estimate of the risedronate treatment effect. First, the proportion lost to fol-

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TABLE 4. Weighted mean difference of bone density after treatment with risedronate

Bone density site	Dose	Trial year	No. of trials	Sample size (n)	Weighted mean difference (95% CI)	*P* value	Test of heterogeneity *P* value
Lumbar spine	2.5 mg cyclical, 5.0 mg cyclical, and 2.5 mg daily	Final	7	1842	2.94 (1.55, 4.34)	<0.01	<0.01
	5.0 mg daily	Final	6	2138	4.54 (4.12, 4.97)	<0.01	0.42
Distal Radius	2.5 mg daily and 5.0 mg daily	1.5 yr	1	648	0.70 (−0.60, 2.00)	0.29	–
Femoral Neck	2.5 mg cyclical, 5.0 mg cyclical, and 2.5 mg daily	1	6	1606	0.63 (0.20, 1.06)	<0.01	0.59
	5.0 mg daily	1	5	1509	1.55 (1.08, 2.02)	<0.01	0.50
	2.5 mg cyclical, 5.0 mg cyclical, and 2.5 mg daily	1.5–3	6	1380	1.71 (1.17, 2.25)	<0.01	0.66
	5.0 mg daily	1.5–3	6	2337	2.75 (2.32, 3.17)	<0.01	0.77

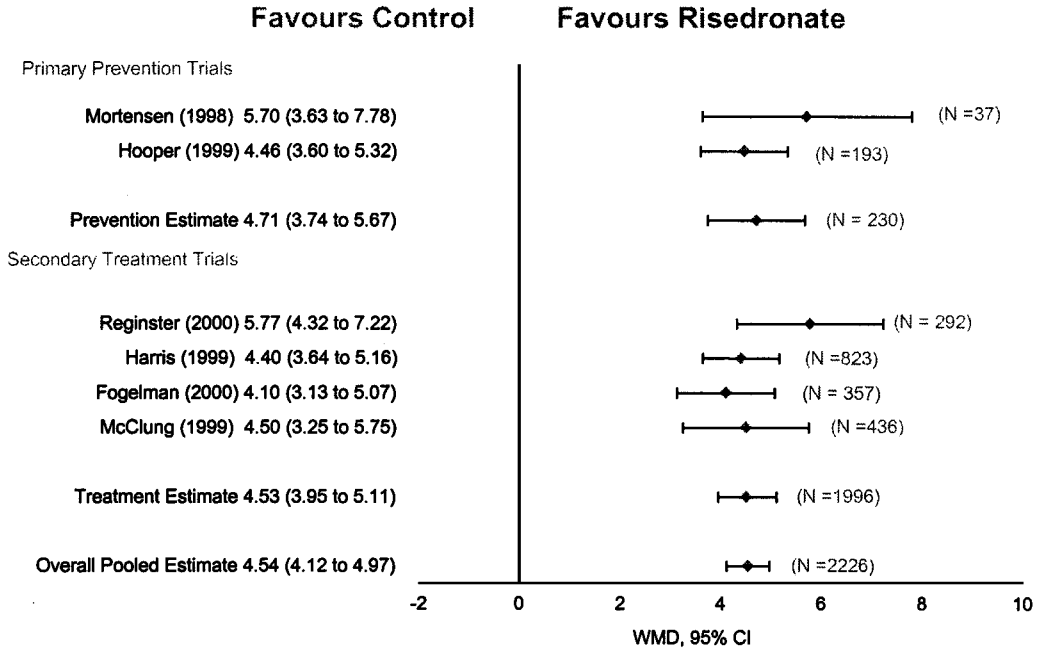

FIG. 4. Weighted mean difference for lumbar spine after treatment with risedronate (5 mg daily).

TABLE 5. Heterogeneity of difference of bone mineral density after treatment with risedronate

Bone density site Study year Dose	Study population Prevention *vs.* treatment Difference (95% CI) *P* value	Dose administered Cyclical *vs.* daily administration Difference (95% CI) *P* value	Calcium supplementation <500 mg *vs.* >500 mg Difference (95% CI) *P* value	Vitamin D supplementation No *vs.* yes Difference (95% CI) *P* value	Lost to follow-up <20% *vs.* >20% Difference (95% CI) *P* value
Lumbar Spine Final Year 2.5 mg cyclical, 5.0 mg cyclical, and 2.5 mg	2.29; 3.14 0.86 (−1.24, 2.95) *P* = 0.42	2.70; 3.33 0.63 (−2.21, 3.48) *P* = 0.66	2.70; 2.98 0.28 (−2.49, 3.04) *P* = 0.85	2.67; 3.35 0.68 (−1.48, 2.83) *P* = 0.54	2.70; 2.98 0.28 (−2.49, 3.04) *P* = 0.85

low-up appears unrelated to the magnitude of the treatment effect. Second, in one of the two largest studies that measured vertebral fracture incidence (1), the patients lost to follow-up in the placebo arm are a particularly high-risk group, as reflected in a disproportionately large number of patients who had a vertebral fracture at baseline. Thus, it is particularly unlikely that loss to follow-up has created a bias in favor of risedronate in this study.

In some trials, our estimates of the RR differ from those reported in the primary publications. In some instances, a differing analytic approach explains the discrepancy. We took a uniform approach to analysis in all our systematic reviews. We were limited in that we generally did not have access to timing of events, and therefore made our estimates of RR on the basis of the proportion of patients who sustained a fracture, irrespective of when the events occurred. A time-to-event or survival analysis that investigators prospectively planned and used in some of the risedronate studies (1, 2, 18) is a generally more powerful and informative analysis. To the extent that treatment not only reduces the proportion of patients who suffer an event, but also delays the occurrence of the events that do take place, an analysis that looks only at the proportion of patients who suffer an event underestimates the treatment effect. For instance, in the study by

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Harris *et al.* (1), the survival analysis suggested a pooled estimate of RR of vertebral fractures of 0.59 with a 95% CI of 0.43–0.82, whereas our analysis, using only numbers of events, generated a pooled estimate of RR of 0.64 (95% CI 0.47–0.87). We did not generally have access to the primary data, and this represents a limitation of our meta-analyses.

With respect to other aspects of methodological quality, the risedronate trials are all described as double-blind; additional information provided by Procter & Gamble noted that this included patients, clinicians, those collecting outcome data, those adjudicating outcome events, and data analysts. We were able to confirm concealment of allocation in the eight trials. In general, the methodological quality of the studies was high, and the primary limitation of large loss to follow-up is unlikely to have substantially biased the treatment effect upward.

The short duration of follow-up, at most 3 yr, further limits the inferences one can make from the data. The impact of continued bisphosphonate therapy over the long-term remains speculative.

This systematic review shares the strengths of other reviews in this series, including explicit eligibility criteria, assessment of the methodological quality of the studies, reproducibility of judgements regarding eligibility and study quality, and a comprehensive search for published and unpublished data. For risedronate, we were able to obtain most of the relevant data. Procter & Gamble provided us with some unpublished data [SD values of bone density estimates from one trial (20) and methodological details from two trials (18, 20)], but we were not able to access bone density or vertebral fracture data from the risedronate hip fracture trial (16).

Some limitations of inferences from these trials apply, to a lesser or greater degree, to all the drugs for osteoporosis we have reviewed. The magnitude of impact on quality of life associated with reduction in vertebral fractures remains uncertain. The impact of risedronate on the reduction of vertebral and nonvertebral fractures in low-risk women without osteoporosis is less certain due to limitations in sample size and a relatively small number of events. The impact of risedronate on events beyond 3 yr of follow-up remains uncertain.

In relation to other bisphosphonates tested in randomized trials focusing on fracture reduction, risedronate showed a reduction in nonvertebral fractures that etidronate failed to produce. The magnitude of the RR reduction of risedronate in comparison to other bisphosphonates must await head-to-head comparisons between the drugs. In comparison to placebo, risedronate did not demonstrate an increase in discontinuation due to gastrointestinal adverse events.

In summary, risedronate produces a substantial reduction of vertebral and nonvertebral fractures. Clinicians should consider these results when choosing a treatment for women suffering from postmenopausal osteoporosis.

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