Safety and Efficacy of Risedronate in Reducing Fracture Risk in Osteoporotic Women Aged 80 and Older: Implications for the Use of Antiresorptive Agents in the Old and Oldest Old

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OBJECTIVES: To determine the efficacy of risedronate in reducing vertebral fracture risk in women aged 80 and older with osteoporosis.

DESIGN: Pooled analysis of data from three randomized, double-blind, controlled, 3-year-fracture-endpoint trials conducted from November 1993 to April 1998: Hip Intervention Program (HIP), Vertebral Efficacy with Risedronate Therapy—Multinational (VERT-MN), and VERT-North America (NA).

SETTING: Office-based practices, research centers, and osteoporosis clinics in Europe, North America, and Australia.

PARTICIPANTS: Osteoporotic (femoral neck bone mineral density T-score < -2.5 standard deviations or at least one prevalent vertebral fracture) women aged 80 and older.

INTERVENTION: Patients received placebo (n = 688) or risedronate 5 mg/d (n = 704) for up to 3 years. All patients received 1,000 mg/d calcium and, if baseline levels were low, up to 500 IU/d vitamin D.

MEASUREMENTS: Cumulative incidence of new vertebral fractures.

RESULTS: After 1 year, the risk of new vertebral fractures in the risedronate group was 81% lower than with placebo (95% confidence interval = 60–91%; $P < .001$). The number of women who needed to be treated to prevent one new vertebral fracture after 1 year was 12. This early onset of efficacy was consistent across the clinical programs, and antifracture efficacy was confirmed over 3 years. Risedronate was well tolerated, with a safety profile comparable with that of placebo.

CONCLUSION: These findings provide the first evidence that, even in the very old, reducing bone resorption rate remains an effective treatment strategy for osteoporosis. Because each therapeutic agent used for the treatment of osteoporosis may have unique characteristics, the observations made in this study should not be assumed to apply to other bisphosphonates. **J Am Geriatr Soc 52:1832–1839, 2004.**

Key words: postmenopausal osteoporosis; risedronate; fractures; aged; aged 80 and older

Vertebral fractures are the most common serious complication of osteoporosis, and their incidence increases steadily with age.[1–5] The prevalence of vertebral deformities, which is 5% to 10% in women aged 50 to 54, increases to about 45% to 55% in women aged 80 to 89.[1,6] Because the elderly are the fastest-growing segment of the population, the number of individuals affected with vertebral fractures can be expected to increase dramatically in coming decades.

Although hip fractures are considered to be the most severe and economically important osteoporotic fracture,[7] vertebral fractures also lead to adverse health outcomes, including back pain,[8,9] height loss,[8] and kyphosis.[10] These changes may result in significant declines in physical performance and function and ultimately loss of independence.[11,12] Vertebral fractures frequently require hospitalization or prolongation of hospital stays, particularly in elderly individuals.[13–15] Each additional vertebral fracture leads to further functional limitation[9,16] and substantially increases the risk of additional vertebral and hip fractures.[17–21] Vertebral fractures are even associated with

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an excess rate of mortality,[4,22–25] and relative survival rates after fracture decline with age at the time of fracture.[24]

Despite the debilitating effects of vertebral fractures and the availability of therapies to reduce fracture occurrence,[26] only a small percentage of women with osteoporotic fractures receive treatment,[27–31] and this percentage decreases with age.[27] One explanation for this decrease is that clinicians presume that it is too late to alter the course of disease in its late stage.[27] Treatment of very elderly women with combined calcium and vitamin D supplements has been shown to reduce the risk of fracture,[32,33] but there is no published evidence in persons aged 80 and older that further reducing bone turnover by adding an antiresorptive agent provides protection against osteoporotic fractures in addition to that provided by calcium and vitamin D.

The effectiveness of risedronate, a pyridinyl bisphosphonate, in reducing the risk of vertebral and nonvertebral fractures in osteoporotic women is well established across a wide range of ages.[34–36] The risedronate database includes almost 1,400 individuals aged 80 and older with confirmed osteoporosis and thus provides a unique opportunity to study the antifracture effect of antiresorptive treatment from a geriatric perspective. Given the high prevalence of osteoporosis in elderly women, the underuse of antiresorptive treatment in these patients, and the paucity of information about antiresorptive treatment of osteoporosis in the very old, a retrospective analysis was conducted to determine the efficacy and safety of risedronate in reducing the risk of vertebral fractures in women aged 80 and older with osteoporosis. To this end, data from three large clinical trials with fracture as the primary endpoint were evaluated.[34–36]

PATIENTS AND METHODS

Studies Included in the Analysis

The analysis was based on combined data from three randomized, double-blind, placebo-controlled, parallel-group, phase-3 clinical studies from the risedronate clinical program conducted in parallel: the Vertebral Efficacy with Risedronate Therapy North America (VERT-NA) and Multinational (VERT-MN) studies and the Hip Intervention Program (HIP) study. The three studies were conducted in multiple office-based practices, academic research centers, and regional osteoporosis clinics in Europe, North America, and Australia from November 1993 to April 1998. The VERT studies were designed to determine the effect of risedronate on vertebral fractures in women with postmenopausal osteoporosis, and the HIP study was designed to evaluate the effect of risedronate on hip fractures in elderly women. In all three studies, patients received risedronate 2.5 mg, risedronate 5 mg, or placebo daily for up to 3 years. All patients received calcium 1,000 mg/d, and patients whose serum 25-hydroxyvitamin D levels were below 40 nmol/L also received up to 500 IU vitamin D daily. The investigator, not the sponsor, provided vitamin D supplements; vitamin D_2 or vitamin D_3 could be administered. Patients were permitted to continue use of their other medications (except for other osteoporosis treatments), including aspirin, nonsteroidal antiinflammatory drugs (NSAIDs), histamine$_2$-receptor antagonists (H_2-RAs), and proton pump inhibitors (PPIs). All studies were conducted according to the Declaration of Helsinki and approved by the appropriate ethics committee. All patients gave written informed consent. The study design, patients studied, and methods have been described in detail elsewhere.[34–36]

Measurements

Lateral and thoracolumbar (T4–L4) radiographs were obtained at baseline and annually throughout the studies. Prevalent and incident vertebral fractures were assessed quantitatively and semiquantitatively at a central facility. An incident new vertebral fracture was defined quantitatively as a loss of 15% or more in the anterior, posterior, or middle vertebral height in a vertebra that was normal at baseline and semiquantitatively as a change from Grade 0 (normal) to Grades 1 (mild), 2 (moderate), or 3 (severe).[1,37] Independent radiologists adjudicated discrepancies in the results of quantitative and semiquantitative methods for prevalent and incident vertebral fractures. The radiologists remained blinded to treatment while performing all vertebral fracture assessments.

Assessments of radiographically confirmed osteoporosis-related nonvertebral fractures, defined as fractures of the clavicle, humerus, wrist, pelvis, hip, or leg, whether or not associated with trauma, were performed every 3 months from baseline to Month 36.

Bone turnover markers (urinary deoxypyridinoline/creatinine and pyridinoline/creatine ratios and bone alkaline phosphatase) were measured at 1, 3, 6, 12, and 36 months, and bone mineral density (BMD) of the lumbar spine and femoral neck and trochanter was measured using dual-energy x-ray absorptiometry at 6, 12, 18, 24, and 36 months.

Adverse event information was collected at the study visits made every 3 months during the trials. The investigator recorded adverse events reported by the patients, as well as adverse events observed on examination of the patient.

Statistical Analysis

The analysis population consisted of patients aged 80 and older at the time of enrollment who had osteoporosis and had received at least one dose of placebo or risedronate 5 mg in the VERT or HIP programs. Patients were considered to have osteoporosis if they had a femoral neck BMD T-score of -2.5 standard deviation (SD) or less or one or more prevalent vertebral fractures. These criteria were used to define osteoporosis because there is evidence that they best identify those patients most likely to have fracture reduction with bisphosphonate therapy.[38,39] The analysis was based on data from patients who received the risedronate 5 mg dose because that is the marketed daily dose.

Combining the data from the two fracture clinical programs was possible because the same patient population criteria were used to select the patients for the analysis (i.e., women aged 80 with osteoporosis). In addition, the treatment-by-trial interaction for the efficacy (Cox regression) and safety (Breslow-Day test) parameters was not statistically significant ($P > .1$), showing that the treatment effect was consistent across programs and further indicating that pooling of the data was appropriate.

Table 1. Characteristics of Patients Treated with Placebo or Risedronate 5 mg in the Vertebral Efficacy with Risedronate Therapy and Hip Intervention Program Clinical Programs (Patients Aged 80 and Older)

Characteristic	Placebo (n = 688)	Risedronate 5 mg (n = 704)
Age, mean ± SD (range)	83.0 ± 3.0 (80–98)	83.0 ± 3.1 (80–100)
Height, cm, mean ± SD	154.0 ± 7.0	154.0 ± 7.4
Weight, kg, mean ± SD	58.0 ± 10.4	58.0 ± 11.2
Body mass index, m/kg^2, mean ± SD	24.5 ± 4.1	24.9 ± 4.6
Femoral neck bone mineral density T-score, mean ± SD*	−3.1 ± 0.6	−3.0 ± 0.7
Prevalent vertebral fractures, n (%)		
0	100 (17)	94 (16)
≥1	493 (83)	511 (84)
History of gastrointestinal tract disease, n (%)	430 (63)	456 (65)
Active gastrointestinal tract disease, n (%)	282 (41)	324 (46)
Concomitant use of aspirin or nonsteroidal antiinflammatory drugs, n (%)	423 (62)	446 (63)
Concomitant use of histamine$_2$-receptor antagonists or proton pump inhibitors, n (%)	143 (21)	146 (21)

* Based on National Health and Nutrition Examination Survey, Third Revision reference database.[40]
SD = standard deviation.

Within the group of patients aged 80 and or older, descriptive statistics were used to determine whether the baseline characteristics of the risedronate and placebo treatment groups were similar. To determine whether the baseline characteristics of the group of patients aged 80 and older differed from those of patients younger than 80, these two groups were compared using the two-sample *t*-test, chi-square test, or Wilcoxon rank-sum test as appropriate.

The endpoint of primary interest in this analysis was the cumulative incidence of new vertebral fractures. This analysis included data from patients with a known vertebral fracture status at baseline and over the 3 years of the study. Reductions in fracture risk were investigated for the group of patients aged 80 and older. The fracture incidence (Kaplan-Meier) was computed for each treatment group and hazard ratio (HR) (Cox proportional hazards regression, stratified for trial, allowing for separate underlying hazard functions) with associated *P*-value (stratified log-rank test, stratified for trial) for the treatment comparison at the 5% level of significance. The same analyses were performed for nonvertebral osteoporosis-related fractures. The number of patients who would need to be treated to prevent one additional new vertebral fracture (number needed to treat) was calculated for 1 and 3 years by determining the reciprocal of the absolute risk reduction.

The analysis of longitudinal measures of bone turnover markers and BMD was based on the percentage change from baseline in each treatment group. These analyses were performed for the group of patients aged 80 and older. Within- and between-treatment group differences in bone turnover markers were investigated using nonparametric statistics because these data were not normally distributed.

Table 2. Characteristics of Patients Treated with Placebo or Risedronate 5 mg in the Vertebral Efficacy with Risedronate Therapy and Hip Intervention Program Clinical Programs (Patients Aged <80 and ≥80)

Characteristic	<80 (n = 4,734)	≥80 (n = 1,392)	*P*-value
Age, mean ± SD (range)	72 ± 5.5 (41–79)	83 ± 3.0 (80–100)	—
Height, cm, mean ± SD	157 ± 6.9	154 ± 7.2	<.001
Weight, kg, mean ± SD	62 ± 11.7	58 ± 10.8	<.001
Body mass index, m/kg^2, mean ± SD	25.2 ± 4.42	24.7 ± 4.36	<.001
Femoral neck bone mineral density T-score, mean ± SD*	−2.69 ± 0.696	−3.05 ± 0.632	<.001
Prevalent vertebral fractures, n (%)			
0	1,186 (28)	194 (16)	<.001
≥1	3,026 (72)	1,004 (84)	
Selected comorbidities, n (%)			
Active gastrointestinal tract disease	1,851 (39)	606 (44)	.003
Cataract	1,089 (23)	553 (40)	<.001
Cardiovascular dysrhythmia	234 (5)	111 (8)	<.001
Glaucoma	167 (4)	88 (6)	<.001

* Based on National Health and Nutrition Examination Survey, Third Revision reference database.[40]
SD = standard deviation.

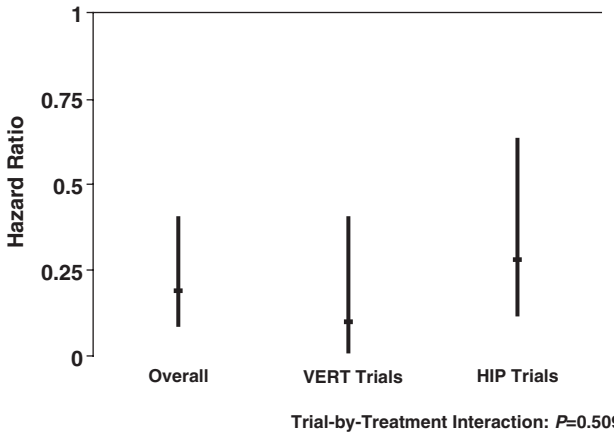

Figure 1. Risk of new vertebral fracture during 1 year of treatment with risedronate 5 mg relative to the risk during treatment with placebo in patients with osteoporosis (aged ≥80) in the overall analysis population and in the Vertebral Efficacy with Risedronate Therapy (VERT) and Hip Intervention Program (HIP) trials. Bars represent 95% confidence intervals.

Within- and between-treatment group differences in BMD were investigated using parametric statistics.

Adverse events, withdrawals, deaths, and upper gastrointestinal (GI) symptoms were summarized by treatment group. Differences in the proportions of patients between the treatment groups were tested using the Fisher exact test.

All statistical analyses were performed using SAS statistical software, version 8.02 (SAS Institute, Inc., Cary, NC).

RESULTS

Patients

Of the 8,680 patients from the intent-to-treat populations of the VERT and HIP studies, 6,126 (71%) met the criteria for osteoporosis (i.e., femoral neck T-score ≥ -2.5 SD or ≥1 prevalent vertebral fractures). A total of 1,392 patients were included in the analysis of patients aged 80 and older. Within this population of elderly patients, the treatment groups were comparable at baseline with respect to demographic and disease characteristics and concomitant use of NSAIDs or aspirin and H_2-RAs or PPIs ($P > .13$) (Table 1[40]). At baseline, 212 of 1,338 (16%) patients were considered to have low vitamin D levels. At 6 months, of the 153 patients who had low vitamin D levels at baseline and for whom 6-month data were available, vitamin D levels had normalized in 122 (80%).

Comparison of this group of very old patients with patients younger than 80 showed that the older patients were significantly shorter, weighed significantly less, had significantly lower BMD, and had a significantly greater frequency of prevalent vertebral fractures (Table 2). In addition, patients aged 80 and older were at greater risk for comorbidities than patients younger than 80, including active GI tract disease (relative risk (RR) = 1.1, 95% confidence interval (CI) = 1.0–1.2; $P = .003$), cataract (RR = 1.7, 95% CI = 1.6–1.9; $P < .001$), cardiovascular dysrhythmia (RR = 1.7, 95% CI = 1.3–2.1; $P < .001$), and glaucoma (RR = 1.8, 95% CI = 1.4–2.3; $P < 001$) (Table 2).

Antifracture Efficacy

In patients aged 80 and older, after 1 year, the incidence of new vertebral fractures was 2.5% in the risedronate 5 mg group, compared with 10.9% in the placebo group. This represents a reduction in the risk of fractures in the risedronate 5 mg group of 81% versus control (HR = 0.19, 95% CI = 0.09–0.40; $P < .001$) (Figure 1). After 3 years, the incidence of new vertebral fractures was 18.2% in the risedronate 5 mg group, compared with 24.6% in the placebo group. This represents a reduction in the risk of fractures in the risedronate 5 mg group of 44% versus control (HR = 0.56, 95% CI = 0.39–0.81; $P = .003$). After 1 and 3 years, the number-needed-to-treat values were 12 and 16, respectively.

After 3 years, the incidence of osteoporosis-related nonvertebral fractures in patients aged 80 and older in the risedronate 5 mg group (14%) was not significantly less than that in the placebo group (16.2%) ($P = .66$).

Because of the discrepancy between the effects of treatment on vertebral and nonvertebral fractures in the patients aged 80 and older, supplementary efficacy analyses were conducted in patients younger than 80 (mean age ± SD = 72.0 ± 5.5; range 41–79) to further investigate this difference. In patients younger than 80, risedronate significantly reduced the risk of new vertebral fractures after 1 year (HR = 0.45,; 95% CI = 0.32–0.63; $P < .001$) and

Table 3. Median Percentage Change from Baseline in Bone Turnover Markers in Patients Treated with Placebo or Risedronate 5 mg (Patients Aged 80 and Older)

	Deoxypyridinoline/Creatinine		Alkaline Phosphatase	
	Placebo	Risedronate 5 mg	Placebo	Risedronate 5 mg
Month	%			
1	−9.06*	−27.41*†	−6.44*	−3.60
3	−10.85	−30.68*†	−10.09*	−24.24*†
6	−10.14	−30.87*†	−15.81*	−30.87*†
12	−9.92	−24.35*†	−15.33	−33.06*†
36	3.05	−20.54*†	0.00	−25.00*†

* Significantly different from baseline, $P < .05$ (Wilcoxon signed-rank test).
† Significantly different from placebo, $P < .01$ (Wilcoxon rank sum test).

Table 4. Summary of Adverse Events in Patients Treated with Placebo or Risedronate 5 mg in the Vertebral Efficacy with Risedronate Therapy and Hip Intervention Program Clinical Programs (Patients Aged 80 and Older)

Patients	Placebo (n = 688)	Risedronate 5 mg (n = 704)	*P*-value*
	n (%)		
Patients with any adverse event	617 (89.7)	640 (90.9)	.469
Patients withdrew due to adverse events	140 (20.3)	145 (20.6)	.947
Patients died	49 (7.1)	40 (5.7)	.276
Patients with any upper gastrointestinal adverse event	182 (26.5)	203 (28.8)	.338
Patients with nausea†	57 (8.3)	66 (9.4)	.509
Patients with abdominal pain†	53 (7.7)	58 (8.2)	.767
Patients with dyspepsia†	47 (6.8)	48 (6.8)	1.000
Patients with vomiting†	23 (3.3)	29 (4.1)	.482
Patients with gastrointestinal disorder†	15 (2.2)	24 (3.4)	.194
Patients with serious upper gastrointestinal adverse events	17 (2.5)	23 (3.3)	.424

* *P*-value based on two-tailed Fisher exact test.
† Adverse events with an incidence of $\geq 2\%$.

3 years (HR = 0.61, 95% CI = 0.51–0.74; $P < .001$) and nonvertebral osteoporosis-related fractures after 3 years (HR = 0.79, 95% CI = 0.65–0.97; $P = .025$).

Effects on Bone Turnover and BMD

The changes from baseline in the risedronate 5 mg group were statistically significantly greater than those in the placebo group for urinary deoxypyridinoline/creatinine at 1 month and each subsequent time point ($P < .01$) and for alkaline phosphatase at 3 months and each subsequent time point ($P < .001$) (Table 3). In addition, the changes from baseline in BMD in the risedronate 5 mg group were significantly greater than those in the placebo group as early as 6 months at the lumbar spine ($P < .001$), femoral neck ($P < .05$), and femoral trochanter ($P < .01$).

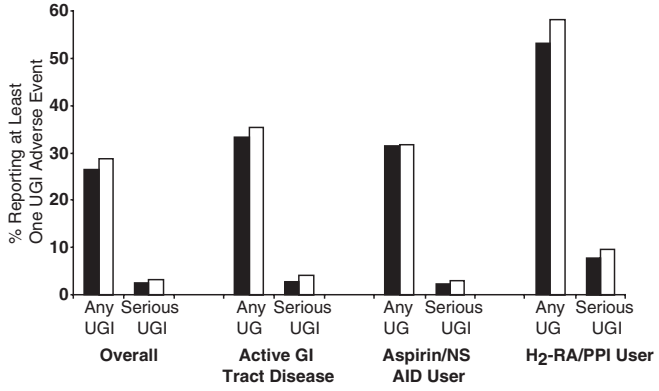

Figure 2. Incidence of any upper gastrointestinal (UGI) adverse events and serious UGI adverse events associated with placebo (black bars) or risedronate 5 mg (white bars) treatment in all patients aged 80 and older (overall) and in subgroups of patients aged 80 and older who had active gastrointestinal (GI) disease, who were using aspirin or nonsteroidal antiinflammatory drugs (NSAIDs), or who were using histamine$_2$-receptor antagonists (H_2-RAs) or proton pump inhibitors (PPIs).

Safety

The adverse event profiles of patients aged 80 and older were similar in the two treatment groups (Table 4). The incidences of esophagitis (placebo 1.3%; risedronate 1.7%), stomach ulcer (placebo 1.0%; risedronate 1.4%), and duodenal ulcer (placebo 0.6%; risedronate 0.4%) were low and similar between the two treatment groups. In fact, the incidence of upper GI and serious upper GI adverse events were similar in the two treatment groups even in patients who had active GI tract disease at baseline, who took concomitant aspirin or NSAIDs, and who took H_2-RAs or PPIs (Figure 2).

DISCUSSION

In this study in elderly women (aged ≤ 100) with osteoporosis, risedronate 5 mg significantly reduced the risk of new vertebral fractures over 1 and 3 years. The reductions in fracture risk in the risedronate-treated women were seen within 1 year of treatment and were in addition to any benefit experienced as a result of calcium and, if needed, vitamin D supplementation, which has been shown to significantly decrease the risk of osteoporotic fractures in older individuals.[32,33,41,42] The reductions in fracture risk in this group of very old patients were consistent with those in the overall populations of patients in the VERT and HIP studies, whose ages spanned a wide range.[34–36] To the authors' knowledge, this study is the first to document a benefit of antiresorptive treatment in addition to that afforded by calcium and vitamin D in a population of women aged 80 and older with osteoporosis.

These findings support the concept that reducing the bone remodeling rate remains an effective osteoporosis treatment strategy even in the oldest patients, although it remains to be determined whether similar results would be seen for other antiresorptives. The findings are particularly relevant given the aging population. The prevalence of vertebral deformities in women increases markedly between the ages of 50 and 90, and epidemiological data suggest that

half or more of women aged 80 and older have vertebral fractures.[1]

In this study, patients aged 80 and older had significantly lower femoral neck BMD and body mass index values and a greater frequency of prevalent fractures at baseline than younger patients and were therefore at greater risk for fracture than their younger counterparts,[18] suggesting that the risk of fracture continues to increase with age, even in the very old. These findings underscore the need to arrest bone loss and prevent fracture in elderly patients and the importance of a rapid-treatment effect. As noted previously, osteoporosis is vastly undertreated, and the percentage of patients who do not receive treatment increases significantly with age.[27–31] This study suggests that adding antiresorptive treatment to calcium and vitamin D could significantly decrease the incidence of vertebral fractures in elderly women with osteoporosis and thereby reduce the public health burden associated with these fractures. A consistent treatment effect of risedronate was observed in reducing vertebral fracture risk in those younger than 80 (HR = 0.61; $P < .001$) and those aged 80 and older (HR = 0.56; $P = .003$). The absence of a significant treatment-by-age group interaction supported this ($P = .722$).

The treatment effect of risedronate appears numerically larger during the first year of treatment. The findings showing a beneficial antifracture effect of risedronate over the first year are consistent with other reports,[34,35,43] but the magnitude of the reduction in fracture risk at 1 year for patients aged 80 and older (80%) was higher than that previously reported (i.e., 60–70%). In this analysis, the incidence of vertebral fractures is greater in the older patients than in the younger patients in each treatment group at each time interval except in the risedronate 5 mg group in the first year (2.5%). The incidence of vertebral fractures in this group of patients (2.5%) is lower than that observed in risedronate-treated patients aged 70 and older (4.4%) in the original clinical programs, whereas the fracture incidences in the placebo groups were about the same (10.8% and 10.9%).[44] These comparisons suggest that the incidence of fractures in the risedronate 5 mg group in the current analysis of patients aged 80 and older was unexpectedly low during the first year of treatment and that this low rate of fracture was the factor driving the apparent large treatment effect in the first year. It is difficult to comment on possible reasons for this result because of the lack of published controlled data in patients aged 80 and older, but it is reassuring to observe this early and significant effect of treatment in this elderly group. The most important finding from this post hoc analysis is that risedronate provides a statistically significant and clinically relevant antivertebral fracture effect over the 3 years of observation in patients aged 80 and older.

The reduction in nonvertebral fractures in patients younger than 80 was statistically significant, but a treatment effect was not seen in patients aged 80 and older. Although risedronate has been shown to effectively reduce the risk of nonvertebral fractures across a wide range of ages,[34–36] little evidence currently exists to support the efficacy of bisphosphonates in reducing the risk of nonvertebral fractures in women aged 80 and older. Most studies have not enrolled such elderly subjects.[45–47] The HIP trial enrolled two groups of patients; Group 1 consisted of women aged 70 to 79 with osteoporosis, and Group 2 consisted of women aged 80 and older who had at least one nonskeletal risk factor for hip fracture or low BMD. In the HIP trial, no effect on nonvertebral fracture risk was observed in Group 2 patients, but those patients were not selected on the basis of low BMD and may not have been osteoporotic.[36] However, the patients aged 80 and over included in the analyses presented in this article met the criteria for osteoporosis and, as noted previously, had an even more severe degree of osteoporosis than the younger patients in the analyses. Thus, the failure to demonstrate an effect of treatment on nonvertebral fracture risk cannot be attributed to selection of very old patients with less skeletal fragility. Nor can a greater effect of calcium and vitamin D in patients aged 80 and older explain it, because the calcium- and vitamin D–associated changes in bone turnover markers in the placebo groups were similar in patients aged 80 and older and patients younger than 80 (data not shown). The robust effect of risedronate treatment on vertebral fractures in patients aged 80 and older suggests that risedronate treatment addressed the skeletal fragility component of fracture risk, even in these very old patients. The significant effects of treatment on bone turnover and BMD and the statistical similarity of these effects in the two age groups further support the suggestion, although changes in BMD or bone turnover account for only a portion of the antifracture efficacy of antiresorptive agents.

Therefore, it is possible that the reduced effect of treatment on nonvertebral fractures in patients aged 80 and older may reflect the increasing influence of nonskeletal risk factors for these types of fractures, such as falling, with increasing age.[48,49] In the current study, the frequency of comorbidities, including conditions likely to increase patients' risk of falling, was significantly higher in patients aged 80 and older, confirming an age-associated increase in comorbid conditions. Although falls and the prevalence of many of the more typical and significant comorbidities in this age group were not assessed, it is likely that patients aged 80 and older were at greater risk of falling because of their higher prevalence of comorbidities. It is also possible that this increase in risk may have offset the benefit of antiresorptive intervention on skeletal strength. Finally, inadequate statistical power is likely to have contributed to the failure to demonstrate a significant effect. Under the assumption that the treatment effect in women aged 80 and older would be similar to that in women younger than 80 (a 21% reduction in nonvertebral fracture risk), this trial had only 30% power to show an effect in these oldest patients.

Risedronate was well tolerated in the elderly patients in this analysis. Evaluation of baseline characteristics in the study showed that the individuals aged 80 and older had a higher prevalence of underlying GI diseases than younger individuals. Thus, the GI tolerability of long-term antiresorptive treatment may be especially important in elderly patients. Although some bisphosphonates have been associated with adverse GI effects,[50–52] the trials in the risedronate clinical program did not exclude patients because of active GI disease or treatment with agents that could irritate the GI tract. Evaluation of upper GI adverse events in patients aged 80 and older who were at risk for these events because of active GI disease or use of concomitant medications showed that risedronate was not associated

with an increased frequency of adverse GI events even in these older patients at high risk for these events.

Risedronate treatment provides an antivertebral-fracture benefit in addition to that afforded by calcium and vitamin D in women aged 80 and older with documented osteoporosis. These findings provide the first evidence that, even in the very old, reducing bone resorption rate remains an effective treatment strategy for osteoporosis. Because each therapeutic agent used for the treatment of osteoporosis may have unique characteristics, our observations should not be assumed to apply to other bisphosphonates.

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