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Original Article

Randomized Trial of the Effects of Risedronate on Vertebral Fractures in Women with Established Postmenopausal Osteoporosis

J.-Y. Reginster[1], H. W. Minne[2], O. H. Sorensen[3], M. Hooper[4], C. Roux[5], M. L. Brandi[6], B. Lund[7], D. Ethgen[8], S. Pack[8], I. Roumagnac[8], R. Eastell,[9] on behalf of the Vertebral Efficacy with Risedronate Therapy (VERT) Study Group*

[1]Centre Universitaire d'Investigation du Métabolisme Osseux et du Cartilage Articulaire, University of Liège, Belgium; [2]Clinic for Metabolic Bone Disease, Bad Pyrmont, Germany; [3]Copenhagen Municipal Hospital, Copenhagen, Denmark; [4]University of Sydney and Concord Repatriation General Hospital, Sydney, Australia; [5]Cochin Hospital, René Descartes University, Paris, France; [6]University of Florence, Florence, Italy; [7]Copenhagen, Denmark; [8]Procter & Gamble Pharmaceuticals, Cincinnati, Ohio, USA; and [9] University of Sheffield, Sheffield, UK

Abstract. The purpose of this randomized, double-masked, placebo-controlled study was to determine the efficacy and safety of risedronate in the prevention of vertebral fractures in postmenopausal women with established osteoporosis. The study was conducted at 80 study centers in Europe and Australia. Postmenopausal women (n = 1226) with two or more prevalent vertebral fractures received risedronate 2.5 or 5 mg/day or placebo; all subjects also received elemental calcium 1000 mg/day, and up to 500 IU/day vitamin D if baseline levels were low. The study duration was 3 years; however, the 2.5 mg group was discontinued by protocol amendment after 2 years. Lateral spinal radiographs were taken annually for assessment of vertebral fractures, and bone mineral density was measured by dual-energy X-ray absorptiometry at 6-month intervals. Risedronate 5 mg reduced the risk of new vertebral fractures by 49% over 3 years compared with control ($p < 0.001$). A significant reduction of 61% was seen within the first year (p = 0.001). The fracture reduction with risedronate 2.5 mg was similar to that in the 5 mg group over 2 years. The risk of nonvertebral fractures was reduced by 33% compared with control over 3 years (p = 0.06). Risedronate significantly increased bone mineral density at the spine and hip within 6 months. The adverse-event profile of risedronate, including gastrointestinal adverse events, was similar to that of control. Risedronate 5 mg provides effective and well-tolerated therapy for severe postmenopausal osteoporosis, reducing the incidence of vertebral fractures and improving bone density in women with established disease.

Keywords: Bisphosphonates; Bone mineral density; Osteoporosis; Postmenopausal women; Risedronate; Vertebral fracture

Introduction

Osteoporosis, characterized by low bone mass and microarchitectural deterioration, increases the risk of fractures. The annual cost of treating osteoporotic fractures in the UK has been estimated to be £942 million [1]. Effective treatments include estrogen replacement therapy [2,3] and bisphosphonates [4–6]. Some studies showing that bisphosphonates reduce vertebral fracture incidence were complicated by subgroup analyses, data pooling or changes in treatment doses [4-6]. In addition, gastrointestinal adverse events affect the tolerability of some bisphosphonates [7–9].

*The full list of VERT Study Group investigators is provided in the Appendix.

Correspondence and offprint requests to: Prof. Richard Eastell, Department of Human Metabolism and Clinical Biochemistry, Clinical Sciences Centre, Northern General Hospital, Herries Road, Sheffield S5 7AU, UK. Tel: +44 (0)114 271 4705. Fax: +44 (0)114 261 8775.

Risedronate [1-hydroxy-2-(3-pyridinyl)ethylidene bisphosphonic acid monosodium salt] is a pyridinyl bisphosphonate that has been assessed as a treatment for various metabolic bone diseases in several clinical trials [10–16]. We report a European and Australian (multinational) study of its efficacy and tolerability in postmenopausal women with established osteoporosis.

Patients and Methods

This randomized, double-masked, placebo-controlled, parallel-group study was performed at 80 European and Australian centers. Patients gave written, informed consent before entering the study, which was conducted according to the Declaration of Helsinki and approved by the local ethics committees.

The study duration was 3 years; the risedronate 2.5 mg group was discontinued after 2 years, because of other data showing that the 5 mg dose produced a more consistent effect in increasing BMD while having a similar safety profile to the 2.5 mg dose [10].

Later data have confirmed the similar safety profile of the two doses [11].

Patients

Ambulatory women up to 85 years old and at least 5 years postmenopausal were eligible if they had at least two radiographically confirmed vertebral (T4–L4) fractures. Exclusion criteria included conditions that might interfere with evaluation of spinal osteoporosis, and use of calcitonin, calcitriol or vitamin D supplements within 1 month, anabolic steroids, estrogen, estrogen-related drugs or progestogen within 3 months, or bisphosphonates, fluoride or subcutaneous estrogen implant within 6 months. Women were not excluded because of previous or current gastrointestinal illness or use of medications associated with gastrointestinal intolerance, such as nonsteroidal anti-inflammatory drugs (NSAIDs) or aspirin.

Treatment

Patients were randomized to receive risedronate 2.5 or 5 mg/day, or placebo. Patients were instructed to take their medication with 240 ml water, 30–60 min before breakfast. All patients received calcium 1000 mg/day in a single dose with lunch or the evening meal and up to 500 IU/day vitamin D if baseline 25-hydroxyvitamin D levels were below 40 nmol/l.

Measurements

The primary efficacy measure was vertebral fracture incidence over 3 years, expressed as the proportion of patients with at least one incident fracture. Lateral thoracolumbar (T4–L4) radiographs were obtained at baseline and annually during the study. Radiographic assessments were made at the Department of Experimental Radiology, Erasmus University, Rotterdam.

Prevalent (baseline) and incident vertebral fractures were diagnosed quantitatively and semiquantitatively. In the quantitative assessment [17], an incident new vertebral fracture was diagnosed if the anterior, posterior or middle vertebral height had decreased by at least 15% in a vertebra that was normal at baseline. In the semiquantitative assessment, a new fracture was diagnosed if the grade changed from 0 (normal) to 1 (mild), 2 (moderate) or 3 (severe) [18]. Radiographs were taken at 1, 2 and 3 years and were read in the order in which they were taken. An independent radiologist adjudicated discrepancies between the methods.

Other efficacy measures included radiographically confirmed nonvertebral osteoporosis-related fractures (fractures of the clavicle, humerus, wrist, pelvis, hip or leg, regardless of relationship to trauma), standing height, and bone mineral density (BMD) at the lumbar spine, femoral neck, femoral trochanter, and midshaft (1/3) radius. Bone turnover markers were measured at baseline and after 1, 3, 6, 12, 24 and 36 months in subjects enrolled at a subset of study centers. Serum bone-specific alkaline phosphatase (BAP) was measured using the Hybritech Tandem-R Ostase immunoradiometric assay [19], and urinary deoxypyridinoline/creatinine (Dpd/Cr) ratio using high-performance liquid chromatography [20]. The urine samples were to be 2-hr, fasting collections, obtained in the morning. Serum samples were also to be collected in the morning after an overnight fast.

BMD was measured by dual-energy X-ray absorptiometry with Lunar (Madison, WI) or Hologic (Waltham, MA) densitometers at 6-month intervals. Scans were analyzed at the Department of Radiology, University of California, San Francisco, USA. Standardized lumbar spine BMD was calculated at baseline to adjust for instrument differences [21,22]. Subjects were required to have at least two evaluable lumbar vertebrae at baseline. Vertebrae that were fractured or otherwise nonevaluable were excluded from the BMD analyses at all time points.

Patient-reported adverse events were monitored. Physical examinations were performed at baseline and after 36 months of treatment or at discontinuation. Vital signs were recorded at 3-month intervals, and standard hematology and clinical chemistry tests at 6, 12, 24 and 36 months. Endoscopy was performed at the investigator's discretion in patients reporting moderate-to-severe gastrointestinal adverse events.

Statistical Analysis

The sample size was based on an expected annual vertebral fracture incidence of 17% in the control group. Assuming a 50% dropout rate over 3 years, the study had at least 90% power to detect a 40% reduction in fracture risk with a two-sided $\alpha = 0.05$ significance level. The prospectively defined primary analysis compared the

risedronate 5 mg and control groups at the 5% significance level after withdrawal of the risedronate 2.5 mg group. Analyses were performed on an intent-to-treat basis.

Continuous baseline variables were compared by analysis of variance (ANOVA), with treatment, pooled center, and stratum as factors. Discrete variables were compared by the Cochran–Mantel–Haenszel test stratified by pooled center and stratum.

Analyses of fracture incidence (vertebral and non-vertebral) compared the control and risedronate 5 mg groups on the basis of time to first diagnosed fracture using a stratified log-rank test. A stratified Cox proportional hazards regression model was used to estimate the relative risk of fracture between the risedronate 5 mg and control groups. Fracture incidence was calculated using the Kaplan–Meier method. Analyses to explore the onset of effect were performed over 0–1, 0–2 and 0–3 years.

BMD, height and bone turnover markers were analyzed by ANOVA. Nonparametric methods were used if model assumptions were not met.

Results

Of the women screened for study eligibility, approximately 2500 were studied radiologically to assess the number of prevalent vertebral fractures; 38% of these women did not meet the radiologic criteria for study entry. Patients (n = 1226) were randomized to three treatment groups (Fig. 1), which had similar demo-

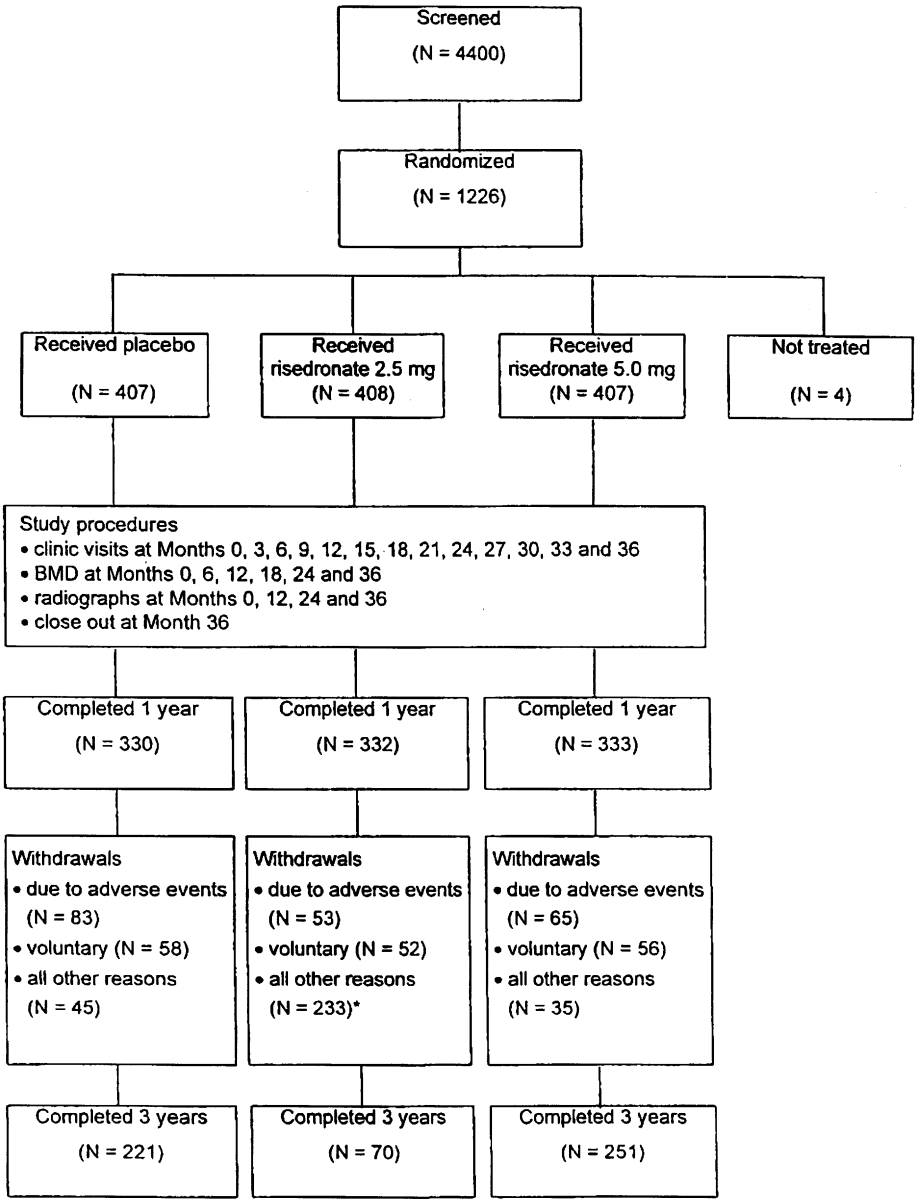

Fig. 1. Trial profile. *Includes those discontinued by protocol amendment.

graphic and baseline characteristics (Table 1). Patients had established osteoporosis (mean number of vertebral fractures 4, mean lumbar spine *T*-score −2.8). Supplemental vitamin D was required by 35% of patients; the proportion of patients requiring supplementation was similar across treatment groups. Follow-up serum 25-hydroxyvitamin D levels after 6 months showed that the number of subjects with below-normal levels had decreased to 25% and remained balanced across treatment groups. Eighty-six percent of patients were determined to be compliant with study medication (risedronate or placebo) on the basis of tablet counts, with compliance being defined as taking at least 80% of the tablets.

Over 3 years, the new vertebral fracture risk in the risedronate 5 mg group was reduced by 49% versus control ($p < 0.001$) (Table 2). The incidence over 3 years was 18% in the risedronate 5 mg group and 29% in the control group (Fig. 2a). In the first year fracture risk was reduced by 61%. Over the 2 years for which data are available, risedronate 2.5 and 5 mg reduced the fracture risk by similar amounts. Among patients who withdrew, 34% receiving placebo and 19% receiving risedronate 5 mg experienced at least one vertebral fracture. The incidence of vertebral fracture was higher in those subjects with more prevalent vertebral fractures at baseline (16% in control patients with fewer than three prevalent fractures compared with 47% in those with three or more).

There was a reduction in nonvertebral osteoporosis-related fractures in the risedronate 5 mg group compared with control over 3 years (Table 2), resulting in a 33%

Table 1. Demographic characteristics, bone mineral density (BMD) and vertebral fractures at baseline

	Treatment group		
	Control	2.5 mg risedronate	5 mg risedroanate
Patients (*n*)	408	410	408
Age (years)[a]	71 ± 7.0	71 ± 6.9	71 ± 7.0
Time since menopause (years)[a]	25 ± 8.7	24 ± 8.3	25 ± 8.6
Height (cm)	155.5 ± 7.1	155.3 ± 6.8	154.9 ± 7.3
Median number of vertebral fractures per patient [range][b]	3 [0–13]	3 [0–13]	4 [0–13]
Standardized lumbar spine BMD (mg/cm^2)[a]	787 ± 140	792 ± 154	776 ± 155
Lumbar spine *T*-score[a]	−2.77 ± 1.28	−2.69 ± 1.37	−2.84 ± 1.39
Femoral neck BMD (g/cm^2)[a]	0.576 ± 0.093	0.583 ± 0.105	0.573 ± 0.098
Serum 25-hydroxyvitamin D levels below 40 nmol/l: number of subjects (%)[c]	148 (37)	142 (36)	134 (34)

[a]Data are presented as the means ± SD.
[b]All patients had two or more baseline vertebral fractures based upon the initial screening radiographic assessment, which included documentation of the fractures at the study site and verification at the screening center. Two percent of patients had no vertebral fractures and 6% had one fracture based upon post-study serial quantitative and qualitative assessments.
[c]Percentage is based upon the number of subjects with baseline measurements: placebo, 403; risedronate 2.5 mg, 399; risedronate 5 mg, 400.

Table 2. Incidence of vertebral and nonvertebral osteoporosis-related fractures

	Patients (*n*)	Patients with incident fracture [*n* (%)][a]	Relative risk (95% CI)[b]	*p* value[c]	No. needed to treat[d]
New vertebral fracture					
Year 0–1					
Control	334	45 (13)	—	—	—
Risedronate 2.5 mg	329	24 (7.1)	0.50 (0.30, 0.84)	0.012	17
Risedronate 5 mg	333	19 (5.6)	0.39 (0.22, 0.68)	0.001	14
Year 0–3					
Control	346	89 (29.0)	—	—	—
Risedronate 5 mg	344	53 (18.1)	0.51 (0.36, 0.73)	<0.001	10
Osteoporosis-related nonvertebral fracture					
Year 0–3					
Control	406	51 (16.0)	—	—	—
Risedronate 5 mg	406	36 (10.9)	0.67 (0.44, 1.04)	0.063	20

For vertebral fractures, *n* represents the number of patients with radiographs at baseline and at the indicated visit.
[a]Based upon Kaplan–Meier estimate of the survival function.
[b]Based upon Cox regression model.
[c]Log-rank test.
[d]Number of patients who would need to be treated to prevent one patient from experiencing a fracture.

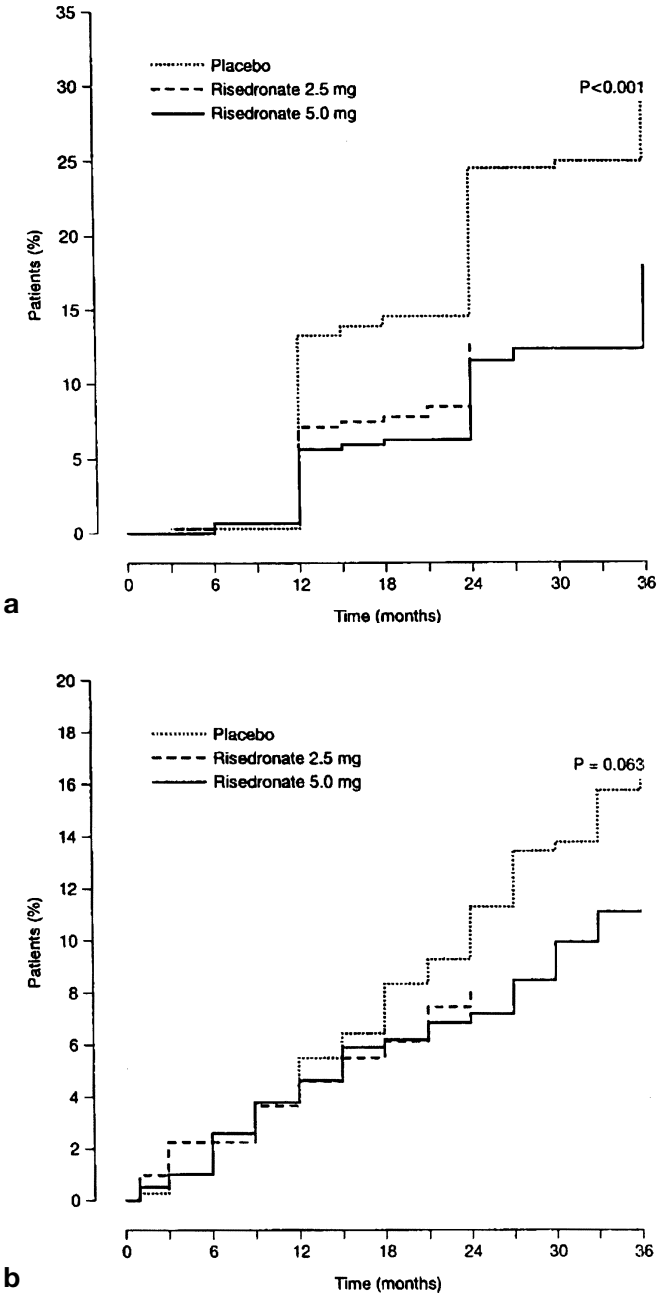

Fig. 2. Incidence of **a** new vertebral fractures and **b** nonvertebral osteoporosis-related fractures, in patients receiving control, risedronate 2.5 mg or risedronate 5 mg.

reduction in fracture risk (p = 0.06) (Fig. 2b). The number of nonvertebral fractures by skeletal site in the placebo and risedronate 5 mg groups, respectively, was 21 and 15 at the wrist, 14 and 7 at the humerus, 11 and 9 at the hip, eight and five at the pelvis, five and seven at the leg, and one and two at the clavicle.

The rate of height loss was lower in the risedronate 5 mg group compared with control, both overall (−1.3 vs (−2.4 mm/year, p = 0.003) and in patients with an incident vertebral fracture(s) (−3.2 vs −5.7 mm/year, p = 0.001). In the overall population, the median change in height after 36 months was −0.68 cm in the placebo group and −0.50 cm in the risedronate 5 mg group; the changes in subjects with at least one incident vertebral fracture were −1.61 cm and −1.25 cm, respectively.

There were significant differences in spine and hip BMD between the risedronate 5 mg and control groups after 6 months, the earliest time point measured (Fig. 3). At 3 years, treatment differences were 5.9% (95% CI: 4.5, 7.3) at the spine and 6.4% (95% CI: 4.9, 7.8) at the femoral trochanter ($p < 0.001$). Treatment differences of 3.1% (95% CI: 1.8, 4.5) and 2.1% (95% CI: 1.1, 3.2) were recorded at the femoral neck and midshaft radius, respectively ($p < 0.001$). At 3 years, BMD in the risedronate 5 mg group was significantly increased from baseline at the spine, femoral neck and trochanter, and was maintained at the midshaft radius. In the control group at 3 years, BMD increased significantly at the spine, was unchanged at the femoral neck, and decreased significantly at the femoral trochanter and midshaft radius.

Dpd/Cr decreased in both risedronate treatment groups in the first month of treatment ($p \leqslant 0.05$, each group, paired t-test), and reached nadirs of −26% and −33% median change from baseline at 6 months for risedronate 2.5 and 5 mg, respectively. The median change in BAP activity from baseline with risedronate 5 mg reached a nadir at 6 months of −37%, compared with −26% with risedronate 2.5 mg ($p \leqslant 0.05$, each group). In the control group, a transient decrease from baseline in the median Dpd/Cr and BAP levels of up to 10% was observed during the first few months of the study. Overall, the differences between the control and risedronate groups were maintained throughout the treatment period.

There were no clinically meaningful differences in the incidence of individual adverse events. The incidence of serious and drug-related adverse events was similar among the treatment groups (Table 3).

Overall, the incidence of upper gastrointestinal adverse events was similar in the three groups, and most adverse events were of mild or moderate severity, despite approximately 35% of the patients having current upper gastrointestinal disorders at study entry. No increase in upper gastrointestinal adverse events was found in the 45% of patients using NSAIDs or the 25% using aspirin-containing medications during the study (data not presented).

Twenty-six patients in the control group and 21 in the risedronate 5 mg group underwent endoscopies after complaints of moderate-to-severe gastrointestinal symptoms. Findings in the esophagus, stomach, and duodenum were similar in the control and risedronate 5 mg groups.

Discussion

Preventing vertebral fractures is the principal aim of osteoporosis treatment, and this study demonstrates that

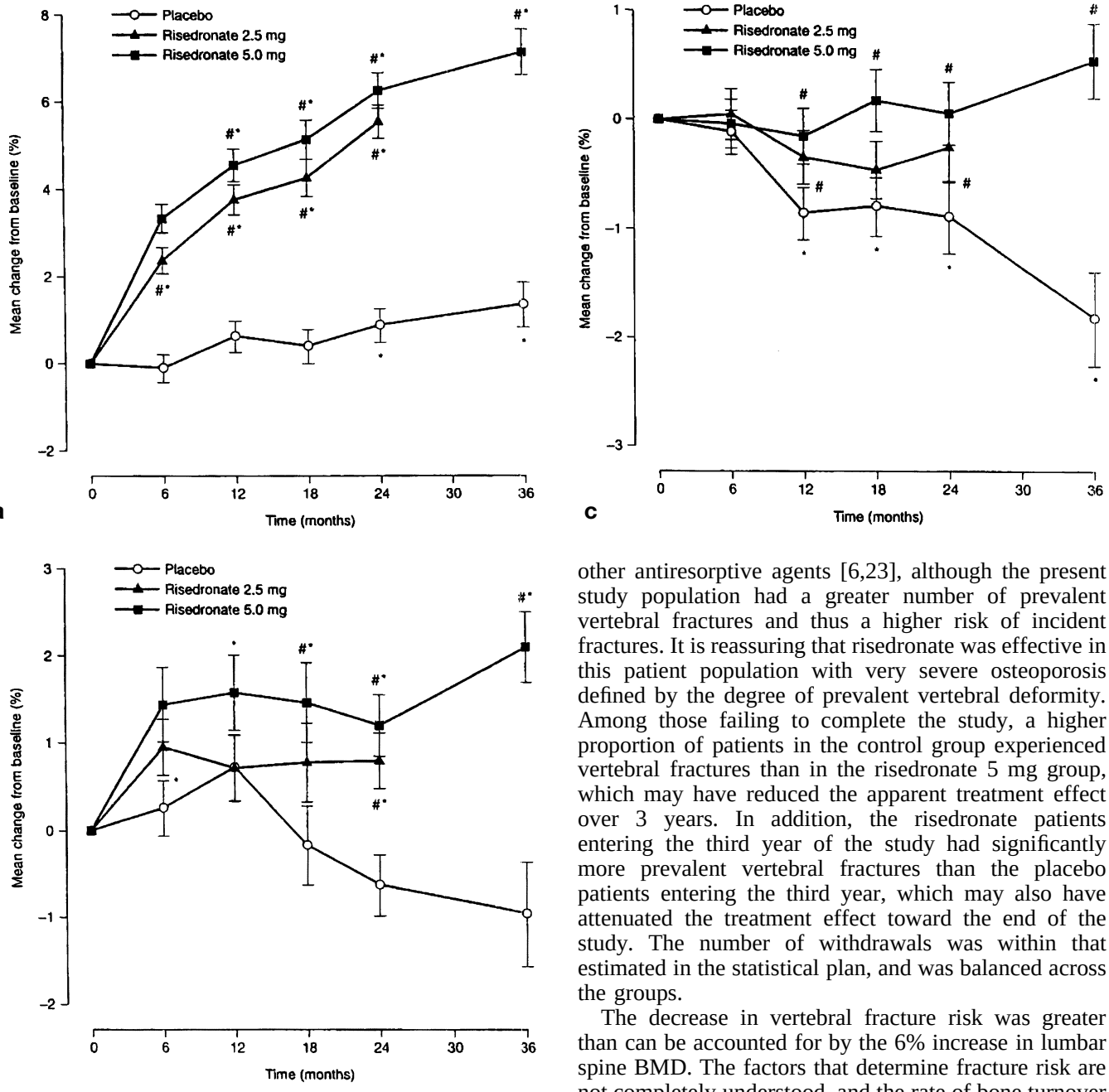

Fig. 3. Percentage change from baseline in bone mineral density of **a** lumbar spine, **b** femoral neck and **c** midshaft radius in patients receiving placebo (control), risedronate 2.5 mg or risedronate 5 mg. #Significantly different from control ($p < 0.05$; three-way analysis of variance model); *significantly different from baseline ($p < 0.05$; paired *t*-test). Data at months 6, 12 and 18 are drawn from additional measurements made at a subset of centers. The risedronate 2.5 mg group was discontinued after 24 months.

risedronate reduces the incidence of vertebral fractures in women with two or more prevalent fractures. Risedronate reduced the risk of vertebral fractures by 61% over 12 months and by 49% over 3 years. The risk reduction over 3 years is similar to that produced by other antiresorptive agents [6,23], although the present study population had a greater number of prevalent vertebral fractures and thus a higher risk of incident fractures. It is reassuring that risedronate was effective in this patient population with very severe osteoporosis defined by the degree of prevalent vertebral deformity. Among those failing to complete the study, a higher proportion of patients in the control group experienced vertebral fractures than in the risedronate 5 mg group, which may have reduced the apparent treatment effect over 3 years. In addition, the risedronate patients entering the third year of the study had significantly more prevalent vertebral fractures than the placebo patients entering the third year, which may also have attenuated the treatment effect toward the end of the study. The number of withdrawals was within that estimated in the statistical plan, and was balanced across the groups.

The decrease in vertebral fracture risk was greater than can be accounted for by the 6% increase in lumbar spine BMD. The factors that determine fracture risk are not completely understood, and the rate of bone turnover may also be important [24,25]. We found that 6 months of treatment with risedronate 5 mg reduced bone resorption by 33% and bone formation by 37%. The reductions in bone turnover occurred rapidly, with significant effects after 1 month of therapy that were sustained over 3 years. In preclinical models, risedronate reduced bone turnover and was associated with maintenance of bone strength [26,27].

The efficacy of risedronate in reducing vertebral fracture risk is supported by the assessments of nonvertebral fractures. Although not powered to examine nonvertebral fractures, the study revealed a reduced incidence, with a 33% risk reduction over 3 years ($p = 0.06$). A significant 39% reduction in nonvertebral

Table 3. Summary of adverse events (AEs)

	Treatment group		
	Control (n = 407)	2.5 mg risedronate (n = 408)	5 mg risedronate (n = 407)
	n (%)	n (%)	n (%)
Any clinical event	370 (91)	374 (92)	374 (92)
Drug-related AE[a]	129 (32)	109 (27)	116 (28)
Withdrawals due to AEs	81 (20)	51 (13)	63 (15)
Serious AE[b]	135 (33)	124 (30)	151 (37)
Cardiovascular	38 (9.3)	30 (7.4)	38 (9.3)
Bone fracture (traumatic)[c]	31 (7.6)	18 (4.4)	26 (6.4)
Bone fracture (atraumatic)[c]	7 (1.7)	3 (0.7)	3 (0.7)
Cancer	17 (4.2)	12 (2.9)	19 (4.7)
Upper gastrointestinal symptoms			
Any	104 (26)	94 (23)	109 (27)
Abdominal pain	32 (8)	36 (9)	50 (12)
Dyspepsia	44 (11)	38 (9)	36 (9)
Esophagitis	11 (3)	8 (2)	10 (2)
Gastritis	14 (3)	14 (3)	9 (2)
Stomach ulcer	2 (0.5)	5 (1)	6 (1)
Duodenitis	0	1 (0.5)	2 (0.5)
Esophageal ulcer	3 (1)	4 (1)	2 (0.5)
Duodenal ulcer	1 (0.5)	2 (0.5)	2 (0.5)

[a]Based upon the investigator's masked assessment.
[b]Serious adverse events included all events that were life-threatening, fatal, permanently disabling, required intervention to prevent permanent impairment or led to hospitalization, and included all cancers or cases of overdose.
[c]Bone fractures reported as adverse events did not require radiographic confirmation. Mean exposure (months) to study medication was 28 (control), 25 (risedronate 2.5 mg)and 28 (risedronate 5 mg).

fracture risk was observed in a North American risedronate trial, which included twice as many patients as the present study [28].

Risedronate increased BMD at the lumbar spine, femoral neck and femoral trochanter at the first assessment (6 months), showing that it promotes rapid increases in BMD at sites of cortical and trabecular bone. Risedronate 5 mg was more effective than 2.5 mg at increasing BMD, but the reductions in fracture risk were similar at 2 years. No data were available to confirm that fracture reduction was sustained for 2.5 mg beyond 2 years. There were no differences in safety or tolerability between the two doses.

Consistent with published data [29], 35% of patients had low baseline vitamin D levels. All patients received calcium 1000 mg/day (and vitamin D, if needed); modest increases in spinal BMD due to calcium supplementation is a well-documented finding [28] and probably accounts for the increase in spinal BMD seen in the control group. At the same time, bone density at the trochanter and midshaft radius decreased in this group, indicating that calcium and vitamin D alone do not prevent bone loss in this patient population.

Risedronate was well tolerated. Esophageal erosions and ulcerative esophagitis have been reported during clinical use of some bisphosphonates [8,9,30–32]. Because gastrointestinal side effects have been an issue with some bisphosphonates, we included patients with previous or current gastrointestinal disease or who were users of NSAIDs or aspirin. Despite the inclusion of such patients, risedronate was not associated with an increase in the incidence of upper gastrointestinal events, including esophagitis, compared with control. Although further studies and surveillance during clinical use will be needed fully to characterize the gastrointestinal safety profile of risedronate, we are encouraged by the results observed in our study.

In summary, risedronate 5 mg rapidly reduces the incidence of new vertebral fractures, sustains this fracture reduction, and increases BMD in postmenopausal women with established osteoporosis. Risedronate was well tolerated, even in patients with gastrointestinal disease or using NSAIDs or aspirin.

Appendix. The Risedronate Multinational Study Group

The principal investigators at each center were: J.-Y. Reginster, Université de Liège, Liège, Belgium; J. P. Devogelaer, UCL, Brussels, Belgium; B. Pornel, Brussels Menopause Center, Brussels, Belgium; J. Dequeker, Pellenberg, Belgium; P. Geusens, Dr Willems Instituut, Diepenbeek, Belgium; J.M. Kaufman, U.Z. Gent, Gent, Belgium; O.H. Sorensen, Copenhagen Municipal Hospital, Copenhagen, Denmark; S.P. Nielsen, Hillerød Sygehus, Hillerød, Denmark; H. Beck-Nielsen, Odense University Hospital, Odense C, Denmark; B. Lund, Copenhagen, Denmark; P. Salmela, Oulu University Central Hospital, Oulu, Finland; M.

Välimäki, Third Department of Medicine, Helsingfors, Finland; J. Salmni, Universitetsjukhuset, Tammerfors, Finland; C.-J. Menkes, Hôpital Cochin, Paris, France; C. Roux, Hôpital Cochin, Paris, France; J.-L. Sebert, Hopital Nord, Amiens, France; R. Dingler, Munich, Germany; D. Felsenberg, Klinikum Steglitz, Berlin, Germany; T.H. Ittel, RWTH Aachen, Aachen, Germany; H. Stracke, Medizinische Poliklinik Giessen, Giessen, Germany; G. Sigurdsson, Borgarspitalinn, Fossvogi, Iceland; B. Bresnihan, St Vincent's Private Hospital, Dublin, Ireland; H. Taggart, Belfast City Hospital, Belfast, UK; M.J. McKenna, St Michael's Hospital, Dublin, Ireland; M.G. Molloy, Cork Regional Hospital, Cork, Ireland; G.H. Tomkin, Adelaide Hospital, Dublin, Ireland; C. Gennari, Università deglie Studi di Siena, Siena, Italy; L. Tessari, Istituto Scientifico San Raffaele, Milan, Italy; M.L. Brandi, Università di Firenze, Florence, Italy; S. Adami, Centro Ospedaliero, Valeggio, Italy; H. Mulder, Good Clinical Practice, Rotterdam, Netherlands; R. Lorenc, Memorial Hospital, Warsaw, Poland; E. Marcinowska-Suchowierska, Postgraduate Medical Center, Warsaw, Poland; J. Przedlacki, Krajowe Centrum Osteoporozy, Warsaw, Poland; A.Z. Sawicki, Warsaw Centre of Osteoporosis and Calcium Metabolism, Warsaw, Poland; W. Tlustockowicz, Centralny Szpital Kliniczny, Warsaw, Poland; C. Lozano, Hospital Universitario San Carlos, Madrid, Spain; J. Farrerons, Hospital Santa Creu y Sant Pau, Barcelona, Spain; J. Munoz, Hospital Clinic I Provincial, Barcelona, Spain; J.B. Rubiò, Servicio de Reumatologia Hospital del Mar, Barcelona, Spain; J.M. Rodriguez, Hospital de Belvitge, Barcelona, Spain; S. Ljunghall, Medicinska Kliniken, Uppsala, Sweden; M. Palmér, Örebro Lasarett, Örebro, Sweden; D. Mellström, Osteroporos kliniken, Göteborg, Sweden; O. Johnell, Ortopediska kliniken, Malmö, Sweden; R. Burwood, Sussex Diagnostic Centre, Hove, UK; M. Cawley, Rheumatology Research Unit, Southampton, UK; G.M. Crawford, Community Pharmacology Services Ltd, Glasgow, UK; M.W.J. Davie, NHS Trust Hospital, Oswestry, UK; J. Davies, Royal National Hospital for Rheumatic Diseases, Bath, UK; S. Doherty, Hull Royal Infirmary, Hull, UK; W. Dodds, Lancaster Moor Hospital, Lancaster, UK; D.V. Doyle, Silverthorn Centre, Chingford, UK; R. Eastell, University of Sheffield, Sheffield, UK; A. Fairney, St Mary's Hospital Medical School, London, UK; A. Frank, Northwick Park Hospital, Harrow, UK; J. Ginsburg, Royal Free Hospital, London, UK; D. Hosking, Nottingham City Hospital and NHS Trust, Nottingham, UK; R. Hughes, St Peters Hospital, Chertsey, UK; G. Nuki, University of Edinburgh, Edinburgh, UK; A. Parsons, University of Warwick, Coventry, UK; T. Price, Cannock Chase Hospital, Cannock, UK; D. Reid, University of Aberdeen, Aberdeen, UK; I.G. Smith, Wrightington Hospital & NHS Trust, Wigan, UK; J.G. Spiro, Harwell Laboratories, Didcot, UK; P. Thompson, Poole Hospital, Poole, UK; K.W. Woodhouse, University of Wales, Penarth, UK; T.J. Wilkin, University of Plymouth, Plymouth, UK; A. Woolf, Royal Cornwall Hospital, Truro, UK; D. Calligeros, Randwick Osteoporosis Centre, Randwick, Australia; D. Cameron, Princess Alexandra Hospital, Woolloongabba, Australia; M. d'Emden, Royal Brisbane Hospital, Brisbane, Australia; P. Ebeling, Royal Melbourne Hospital, Parkville, Australia; M. Hooper, Repatriation General Hospital, Concord, Australia; G. Nicholson, The Geelong Hospital, Geelong, Australia; A. Roberts, Ashford International Research Centre, Ashford, Australia; M. Yeates, Central Coast Radiology, Gosford, Australia; B. Fraser, Royal Liverpool University Hospital, Liverpool, UK.

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