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REVIEW ARTICLE

A comprehensive review of treatments for postmenopausal osteoporosis

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Abstract The aim of this review is to assess the efficacy of treatments for postmenopausal osteoporosis in women with low bone mass or with an existing vertebral fracture. We searched the literature for studies (randomized, double-masked, placebo-controlled and prospective) that reported on drugs registered in Europe or North America. We included 41 reports on 12 agents. To assess the consistency among the studies for each drug, we plotted the percent change in bone mineral density (BMD) for the control group against the percent change in BMD for the treated group for lumbar spine and femoral neck. We used methods of cluster analysis to determine consistency among the studies. For each agent we summarized the relative risk for vertebral fracture (patients with new fracture) and for hip fractures. The duration of the studies ranged from 1 to 4.3 years. The proportion of patients who discontinued treatment ranged from 4% to 80%. Most of the studies reported on change in BMD. Twenty-six studies (10 drugs) provided data on new vertebral fractures and 12 (6 drugs) on hip fractures. Apart from fluoride effects on spine BMD, increases in BMD with bisphosphonates were greater than those seen with the remaining treatments. Generally, for each agent the changes in BMD (relative to placebo) were consistent among the studies. The exceptions were calcitriol and calcitonin for changes in BMD of the spine and of the femoral neck. Alendronate, calcitonin, risedronate and raloxifene caused significant reductions in the risk of vertebral fractures. Alendronate, risedronate or the combination of calcium plus vitamin D had a significant effect on the risk of hip fracture. Most therapies are effective in increasing BMD; some decrease the risk of vertebral fracture. For hip fracture, alendronate and risedronate reduce the risk in women with osteoporosis, and calcium and vitamin D reduce the risk in institutionalized patients.

Keywords Bone · Bone mineral density · Fracture · Prevention

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Introduction

The incidence of osteoporotic fractures in postmenopausal women increases exponentially with age. As a consequence of the progressive aging of the population, the related problems are becoming major issues in many countries [1]. By causing prolonged handicap, fractures markedly alter the quality of life, and represent a major source of health costs [2]. The fracture burden is expected to worsen because, for instance, the number of hip fractures is expected to quadruple over the next 30 years, exceeding 6 million cases per year by 2050 [3]. By increasing the demand for health care, the treatment and consequences of osteoporotic fractures could compromise the economy and social equilibrium in many countries. Under these conditions, there is an unavoidable necessity to select optimal and most efficacious treatments aimed at preventing and/or treating osteoporosis, and diminishing thereby the incidence of osteoporotic fractures. There is a need not only to provide patients with the best possible therapy, but also to spend the available resources on well-proven efficacious treatments, in order to achieve the highest benefits/costs ratio. To solve this clinical problem, evidence-based medicine offers an objective and analytical approach, using the available evidence to guide patient management. Evidence-based medicine is the conscientious search for the best evidence available [4]. It is based on the establishment of a hierarchy in the level of evidence. Consistent results from a well-conducted meta-analysis based on well-conducted randomized controlled trials is at the top of the hierarchy. Results from a well-conducted single randomized controlled trial are at the next highest level. However, the latter achieve a higher degree of certainty than observational studies. Finally, expert opinion represents the least convincing evidence [4].

An improved understanding of the pathophysiology of osteoporosis has led to the development of treatments with effects on bone mineral density (BMD), bone turnover and/or fracture [5,6]. The various agents available for the treatment of osteoporosis and the prevention of osteoporotic fractures do not equally meet the criteria of evidence-based medicine. The present review attempts a critical appraisal of the evidence and, in addition, an assessment of the levels of evidence attained by the studies of the various drugs or agents used in the treatment of osteoporosis and/or in the prevention of osteoporotic fractures. Thus, we searched the literature for randomized, double-masked, placebo-controlled studies on drugs with vertebral or hip fracture as a primary or secondary end-point.

Statistical methods

Data collection

We systematically searched the literature for randomized, double-masked, controlled and prospective trials, that reported on drugs for the treatment of osteoporosis in Europe or North America. To be eligible for analysis, the studies had to include patients with a low bone mass, as defined by a BMD *T*-score below or equal to −2.0, or with an existing morphometrically determined vertebral fracture. Based on these criteria, we included in the analysis 41 reports on 12 agents used in the treatment of osteoporosis: alendronate, alpha-calcidol, calcitonin, calcitriol, calcium alone, calcium and vitamin D, etidronate, fluoride, hormone replacement therapy, raloxifene, risedronate, and vitamin D alone. Only full articles published in peer-reviewed journals were analyzed. We excluded studies reported only in abstract form. A quality score (maximum 32) assessing various aspects of the presentation of the paper, such as a clear formulation of the hypothesis, the full description of statistical analysis and of dropouts, internal and external validity, was attributed to each report [7] (see Appendix).

Bone mineral density

For each study we plotted the percent change in BMD for the control group on the vertical axis and the percent change in BMD for the treated group on the horizontal axis. The size of the symbol used in the plot is proportional to the total number of patients who were evaluated at the end of the study. Symbols on the so-called line of equality indicate that the percent changes in BMD in the control group were the same as those in the treated group. Symbols below the line of equality indicate that percent changes in BMD in the treated group exceeded those in the controls. Symbols above the line indicate that the treated group had percent changes lower than those in the control group. If there was an increase in the treated group but a decrease in the controls, then the symbols are in the lower region on the right. Lastly, symbols in the lower left quadrant indicate a BMD decrease in both treated and control groups.

For each study we computed the distance of the symbol from the line of equality. This distance is proportional (by a factor equal to $1/\sqrt{2}$) to the difference between the change in BMD in the treated group and the change in BMD in the control group. To summarize the data from each agent we computed the mean distance of all the studies for a particular agent from the line of equality. The mean was weighted by the number of patients randomized into the study. To evaluate consistency of the data for each agent, we computed the weighted deviation from the line of equality and the weighted standard error of the mean.

Fracture risk

To summarize the relative risk for vertebral fractures and for hip fractures, we used the method of analysis for combining multiple contingency tables as proposed by Mantel and Haenszel [8]. For some agents there was only one study. In such cases we reported the published relative risk if the analysis was based on women with fracture as opposed to number of fractures. Indeed, to avoid deriving overestimates of the relative risk if the analysis was based on number of fractures, we computed the relative risk based on women with a new fracture (i.e., fracture incidence) rather than a risk based on events per person-year [9].

Results

With the exception of three studies [10–12], where the mean age was in the eighties, all studies having BMD, or vertebral fracture or hip fracture as an end-point, enrolled patients whose mean age was in the seventies (Table 1). Study duration ranged from 1 to 4.3 years. The number of patients included per study varied markedly from 34 (for calcitriol) [13] to more than 9000 (for risedronate) [14]. The dropout rate also varied markedly according to the study, from a low of 4% (for alendronate) [15] to a high of 80% (one study on fluoride) [16]. The mean age among studies in which morphometric vertebral fracture was an end-point ranged from 60 to 71 years (Table 2). The definition of a morphometric fracture differed among the trials. Most trials compared the heights (anterior, middle and posterior) of the vertebral bodies at baseline with the corresponding heights at selected time points during the study. The definition of an event (a fracture) among the different trials ranged from a reduction in vertebral body height of 15% to 20%. The total number of events (patients with at least one fracture) per study was as low as 10 (for alendronate, calcium or fluoride) [17–19] and as high as 358 (for raloxifene) [20] (Table 2). Among the studies on hip fracture incidence, only 2 [10,14] had hip fracture as a primary end-point. Specifically this means that sufficient patients, assuming a specific incidence rate in the placebo groups, were enrolled to detect a prespecified reduction in the risk of hip fracture. The remaining studies had hip fracture as a secondary end-point. This means that the number of patients enrolled could not guarantee the power needed to detect a prespecified difference. Four (for alendronate, calcium and vitamin D, raloxifene or risedronate) [10,14,20,21] had sufficient power to detect a difference (Table 3). The number of hip fracture events was 58 in the report on calcium and vitamin D in institutionalized elderly [10] and in the study with raloxifene [20]. It reached 232 in the study with risedronate [14]. The quality score ranged from 11 (for one study with fluoride) [22] to 28 (one study with alendronate) [15].

Table 1 Characteristics of studies and patients

Authors	Agent (alphabetical)	Duration (years)	Age of patients (mean ± SD)		Patients included[b] (n)		Drop out due to adverse events[c] (%)	
			Placebo	Treatment	Placebo	Treatment	Placebo	Treatment
Adami S et al. 1995[a] [38]	Alendronate	2	59 ± 6	59 ± 6	71	68	5.6	4.4
Chesnut CH et al. 1995[a] [39]		2	64 ± 7	63 ± 6	31	30	18.0	
Black DM et al. 1996 [15]		2.9	71 ± 6	71 ± 6	1005	1022	9.6	7.6
Devogelaer JP et al. 1996[a] [40]		3	63 ± 7	63 ± 7	205	102	5.4	2.9
Tucci JR et al. 1996[a] [41]		3	64 ± 7	64 ± 6	192	94	6.8	5.3
Bone HG et al.1997 [17]		2	71 ± 6	71 ± 6	91	93	9.9	14.0
Cummings SR et al. 1998 [21]		4.2	68 ± 6	68 ± 6	2218	2214	10.2	10.0
Pols HAP et al. 1999 [42]		1	63 ± 7	63 ± 8	958	950	5.6	6.4
Orimo H et al. 1994 [43]	Alpha-calcidol	1	72 ± 7	71 ± 7	42	38	10.5	4.8
Shiraki M et al. 1996 [44]		2	73 ± 8	72 ± 6	56	57	n.a.	n.a.
Overgaard K et al. 1989 [45]	Calcitonin	1	64 ± 9	65 ± 10	20	20	0	15
Overgaard K et al. 1992[d] [46]		2	70 ± 1	70 ± 1	52	156	15.4	15.4
Thamsborg G et al. 1996 [47]		2	65 ± 7	66 ± 7	31	31	0	0
Flicker L et al. 1997 [48]		2	70 ± 6	71 ± 7	30	32	10	18.8
Chesnut III CH et al. 2000[e] [27]		5	68 ± 8	69 ± 8	311	316	58.8	58.2
Falch JA et al. 1987[f] [49]	Calcitriol	3	59 ± 4	60 ± 4	39	47	5.1	17
Aloia JF et al. 1988 [13]		2	65 ± 2	64 ± 2	17	17	11.8	29.4
Gallagher JC et al. 1990 [50]		2	71 ± 8	69 ± 6	25	25	12	28
Ott SM et al. 1989 [51]		2	67 ± 8	68 ± 7	43	43	14	18.6
Chevalley T et al. 1994 [18]	Calcium (Ca)	1.5	72 ± 6	72 ± 8	31	62	14.0	
Recker RR et al. 1996 [26]		4.3	73 ± 7	74 ± 7	251		21.5	
Dawson Hughes B et al. 1997 [52]	Ca and Vit. D_3[g]	3	72 ± 5	71 ± 4	246		33.3	
Chapuy MC et al. 1997[10]		1.5	84 ± 6	84 ± 6	1636	1634	45.7	46.3
Storm T et al. 1990 [53]	Etidronate	3	69 ± 5	68 ± 5	33	33	39.4	39.4
Harris ST et al. 1993[h] [54]		3	66 ± 6[i]	65 ± 6[i]	105	105	31.4	30.5
Riggs BL et al. 1990 [33]	Fluoride, slow release	4	68 (57–74)	68 (58–74)	101	101	31.7	34.7
Kleerekoper M et al. 1991 [16]		4	68 ± 6	66 ± 6	38	46	68.4	80.4
Pak CYC et al. 1995 [22]		3.5	69 ± 9	67 ± 9	56	54	30.4	31.5
Meunier PJ et al. 1998 [55]		2	66 (47–76)	66 (47–75)	146	208	37.3	
Reginster JY et al. 1998 [19]		4	63 ± 9	64 ± 9	100	100	40	38
Steiniche T et al. 1989 [56]	Hormone replacement therapy (HRT)	1	66 (55–75)		17	20	17.6	30
Christiansen C et al. 1990 [57]		1	65 ± 6	64 ± 5	20	20	25	20
Lufkin EG et al. 1992 [58]		1	64 (55–70)	66 (55–72)	39	36	12.8	8.3
Gonnelli S et al.1997 [59]		2	56 ± 5	56 ± 5	45	45	8.9	11.1
Recker RR et al. 1999 [60]		3.5	74 ± 5	73 ± 5	64	64	15.6	17.2
Ettinger B et al. 1999 [20]	Raloxifene	3	67 ± 6	66 ± 7	2576	5129	25.3	22.5
Harris ST et al. 1999[j] [23]	Risedronate	3	68 ± 7	69 ± 8	820	821	45.1	40
Reginster JY et al. 2000[j] [24]		3	71 ± 7	71 ± 7	407	407	45.7	38.3
McClung MR et al 2001[k] [14]		3	74 ± 4	74 ± 4	1821	3624	43.0	43.5
Ooms ME et al. 1995 [11]	Vitamin D_3[g]	2	81 ± 6	80 ± 6	171	177	31.0	28.8
Lips P et al. 1996 [12]		3	80 ± 6	80 ± 6	958	958	38.5[l]	35.4[k]

[a] Only patients receiving 10 mg of alendronate are considered
[b] Number of patients included in study and randomized for treatment or placebo
[c] The percentage was calculated using the number of patients who permanently discontinued treatment due to any adverse event related or unrelated to the treatment regimen (cumulative drop-outs), divided by the number of randomized patients (where possible). If cumulative drop-outs are not specified in the text or tables, n.a.(not available) is mentioned
[d] Fifty-two of 156 patients received 200 IU of salmon calcitonin. Drop-out for these 52 patients was 13.5%
[e] Only patients receiving 200 IU of nasal salmon calcitonin are listed here. With respect to all treatment dosages (100, 200 and 400 IU) 944 patients were included; drop-out rate of these was 59.4%
[f] Placebo denotes (25)OH-cholecalciferol
[g] Vitamin D_3 denotes (25)OH-cholecalciferol
[h] Only patient groups receiving either etidronate alone or placebo alone are considered. Only data from the randomized double-masked 3-year study are considered here
[i] Standard error
[j] Only patients receiving 5 mg of risedronate are considered, because all patients receiving 2.5 mg were discontinued per protocol amendment
[k] Only patients with densitometrically confirmed osteoporosis, 70–79 years of age, receiving 2.5 or 5 mg of risedronate are considered here
[l] Drop-out rate accounts for women and men participating in the study

Bone mineral density

The effects on changes in BMD relative to placebo differed by agent and somewhat within the studies for a specific agent (Figs 1, 2). For most of the trials, the term "placebo" refers to calcium and vitamin supplements. The largest increases in spine BMD (relative to placebo) were observed with fluoride. Whereas the differences in

Table 2 Vertebral fractures: characteristics of studies and patients

Authors	Agent (alphabetical)	Duration (years)	Definition of new vertebral fracture	Patients with vertebral fractures at baseline (%)		Patients analyzed (*n*)		Patients with ⩾1 vertebral fracture (*n*)		Quality score
			Reduction of vertebral body height	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	
Liberman UA et al. 1995 [25]	Alendronate	3	⩾20% and ⩾4 mm	21	21	397	597	22	17	23
Black DM et al.1996 [15]		2.9	⩾20% and ⩾4 mm	100	100	1005	1022	145	78	28
Bone HG et al.1997 [17]		2	⩾20%	34	38	91	93	6	4	21
Cummings SR et al. 1998 [21]		4.2	⩾20% and ⩾4mm	0	0	2218	2214	78	43	26
Orimo H et al. 1994 [43]	Alpha-calcidol	1	⩾20%	55	55	42	38	7	2	19
Shiraki M et al. 1996 [44]		2	⩾20%	57	38	56	57	3	2	17
Overgaard K et al. 1992[a] [46]	Calcitonin (sCT)	2	⩾20%	No data	No data	52	52	13	9 (5)	18
Chesnut III CH et al. 2000[b] [27]		5	⩾20% or ⩾4mm and two sq readings[c]	79	78	311	316	70	51	15
Falch JA et al. 1987 [f] [49]	Calcitriol	3	⩾15%	21	19	39	47	6	10	14
Aloia JF et al. 1988 [13]		2	Not mentioned	100	100	17	17	5	6	13
Gallagher JC et al. 1990 [50]		2	⩾15%	100	100	25	25	9	8	15
Ott SM et al. 1989 [51]		2	⩾15%	No data	No data	43	43	6	9	18
Chevalley T et al. 1994 [18]	Calcium (Ca)	1.5	⩾20%	No data	No data	26	56	4	6	17
Recker RR et al. 1996 [26]		4.3	⩾20% plus review	0	0	61	42	13	12	15
				100	100	41	53	21	15	
Storm T et al. 1990 [53]	Etidronate	3	⩾20%	100	100	20	20	No data	No data	16
Harris ST et al. 1993[d] [54]		3	⩾20%	100	100	104	105	20	17	12
Riggs BL et al. 1990 [33]	Fluoride	4	⩾15%	100	100	101	101	No data	No data	18
Kleerekoper M et al. 1991 [16]		4	⩾15%	100	100	38	46	22	31	16
Pak CYC et al. 1995 [22]	Slow release	4	⩾20% and >10% of vertebral area	100	100	56	54	22	7	11
Meunier PJ et al. 1998 [55]	NaF	3	⩾20%	100	100	146	208	50	71	22
Reginster JY et al. 1998 [19]		4	⩾20% and ⩾4mm	No data	No data	100	100	8	2	19
Lufkin EG et al. 1992 [58]	HRT	1	⩾15%	100	100	39	36	12	7	18
Ettinger B et al. 1999[e] [20]	Raloxifene	3	⩾20% or ⩾4mm and	10	11	1522	1490	68	35	25
Ettinger B et al. 1999[e] [20]		3	two sq readings[c]	88	90	770	769	163	113	25
Harris ST et al. 1999 [23]	Risedronate[f]	3	⩾15% and one sq reading or	79	80	820	821	93	61	22
Reginster JY et al. 2000 [24]		3	⩾4mm[d]	98		407	407	89	53	18

[a] Only 5 patients receiving 200 IU of salmon calcitonin in the treatment arm demonstrated a vertebral fracture
[b] Only patients receiving 200 IU calcitonin are listed in the treatment group
[c] At least two out of three methods (one quantitative; two semiquantitative, sq) had to be positive to qualify for an incident fracture
[d] Only data from the randomized 3-year study were considered. A worsening vertebral fracture was recorded if ⩾4mm or a change by one grade in the semiquantitative (sq) method was registered
[e] Only patients receiving 60 mg raloxifene are considered here
[f] Only patients receiving 5mg of risedronate are considered here

Table 3 Hip fractures: characteristics of studies and patients

Authors	Agent (alphabetical)	Duration (years)	Age of patients (mean ± SD)		Patients randomized[a] (n)		Patients with hip fracture (n)		Quality score
			Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	
Liberman UA et al. 1995 [25]	Alendronate	3	64	64	397	597	3	1	23
Black DM et al. 1996 [15]		3	71 ± 6	71 ± 6	1005	1022	22	11	28
Cummings SR et al. 1998 [21]		4.2	68 ± 6	68 ± 6	2218[b]	2214[b]	24	19	26
Chesnut III CH et al. 2000[c] [27]	Salmon calcitonin	5	68 ± 8	69 ± 8	311	316	9	5	15
Chapuy MC et al. 1992 [10]	Calcium and vitamin D_3	1.5	84 ± 6	84 ± 6	1636	1634	37	21	20
Riggs BL et al. 1990 [33]	Fluoride	4	68 (57–74)	68 (58–74)	325 PY[d]	310 PY[d]	3	7	18
Meunier P et al. 1998 [55]		2	66 (47–76)	66 (47–75)	146	208	2	4	22
Reginster JY et al. 1998 [19]		4	63 ± 1	64 ± 1	100	100	1	1	19
Ettinger B et al. 1999[e] [20]	Raloxifene	3	67 ± 6	66 ± 7	2576	5129	18	40	25
Harris ST et al.1999[f] [23]	Risedronate	3	68 ± 7	69 ± 8	450	489	15	12	22
Reginster JY et al. 2000 [24]		3	71 ± 7	71 ± 7	406	406	11	9	18
McClung et al. 2001[g] [14]		3	74 ± 3	74 ± 3	1821	3624	49	55[h]	17

[a] Number of patients randomized into the study
[b] Patients with BMD $\leqslant$–2.5 SD T-score at the femoral neck with DXA measurement are in parentheses
[c] Only patients receiving 200 IU of calcitonin are listed in the treatment group
[d] PY denotes patient-years
[e] For raloxifene only pooled results of the 60 mg and 120 mg treatment arms are provided
[f] Hip and pelvis fractures combined; separate hip fractures are not mentioned
[g] Only patients receiving 5 mg of risedronate and having a densitometrically confirmed osteoporosis (70–79 years of age) are considered here
[h] Numbers of patients having a new hip fracture were only provided for the combined group of risedronate 2.5 and 5 mg in this study

BMD changes presented in Figs 1 and 2 are those recorded at the end of the trials, the data for fluoride are expressed per year. Other agents with large increases included alendronate and risedronate. The estimates for alendronate were based on several studies. In the largest of these studies [15,21], the dose was 5 mg during the first 2 years and 10 mg thereafter. For risedronate, the estimate was based on two studies [23,24]. The dose used in the risedronate studies was 5 mg/day for 3 years. The largest increases seen in femoral neck BMD were observed in the alendronate studies [15,21] (Fig. 2), followed by changes in the raloxifene study [20]. The estimates in the raloxifene studies were based on the 60 mg/day dose, which is the registered dose.

In general, for each agent the estimates for percent change in BMD were rather consistent among the studies. The magnitude of the mean effect (relative to placebo) is expressed by the mean weighted distance from the line of equality (Figs 3, 4). The standard error is the reflection of the consistency of the effects on BMD. The less consistent data are those for calcitriol on the spine and those for calcitonin on femoral neck, with standard errors which are larger than for the other agents.

Morphometric vertebral fracture

The effects on the risk of vertebral fracture varied among the different agents (Fig. 5). Of the reports on the 12 agents analyzed, data on vertebral fracture were available for 10 of them. Alendronate, raloxifene and risedronate [15,20,21,23–25] showed a significant reduction, relative to placebo, in the risk of vertebral fractures in prespecified analyses. The reduction in the risk of vertebral fracture seen with calcium alone is based on a subgroup analysis of the patients with fracture at baseline and with a low dietary calcium (< 500 mg/day) [26]. The reduction for calcitonin was also based on a subgroup analysis [27]. The overall estimate (mean, 95% confidence interval) of the risk reduction for alendronate was based on four studies [15,17,21,25], for risedronate on two studies [23,24], for raloxifene (60 mg) on one study with two subgroups [20], and for calcitonin (200 IU) on a subgroup of one study [27]. One of the alendronate studies enrolled only patients with existing vertebral fracture, two of them enrolled patients with and without vertebral fracture and one enrolled only patients without prevalent vertebral fracture. Both the risedronate studies enrolled patients with prevalent vertebral fractures. The majority of the patients in the raloxifene study did not have a prevalent vertebral fracture.

Hip fracture

Significant reductions in the risk of hip fracture were observed with alendronate, the combination of calcium and vitamin D and risedronate, but only when the 2.5 and 5.0 mg dose results were pooled for the latter agent (Fig. 6). In our survey, neither fluoride, raloxifene nor calcitonin had any significant influence on the risk of hip fracture. The overall estimate of the reduction in the risk of hip fracture for alendronate was based on

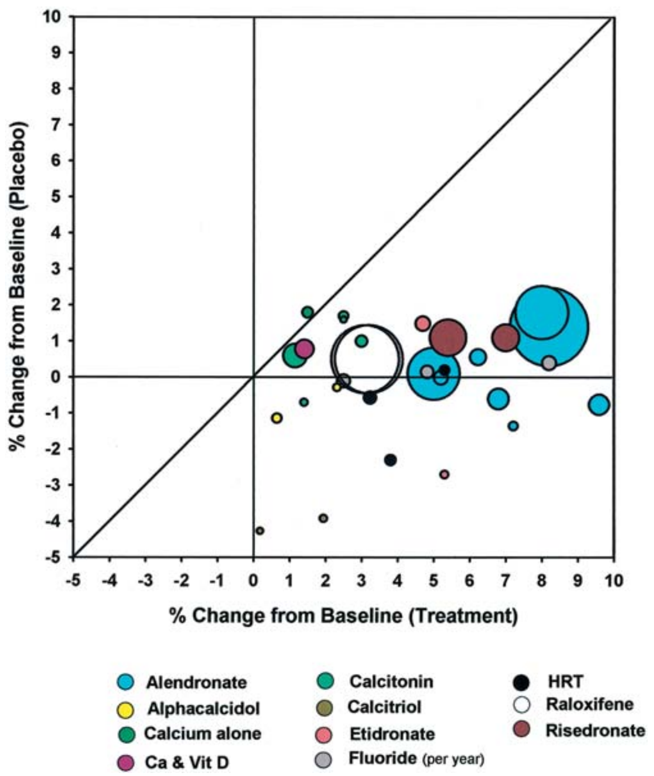


Fig. 1 Changes in spine BMD relative to placebo. Except for fluoride, for which annual changes are shown, the results are those recorded at the end of the study. The size of the symbols is proportional to the number of patients evaluated at the end. Displacement of the dot on the right and below the line f equality is a reflection of the magnitude of treatment effects. Raloxifene is represented by two symbols, one for 60 mg/day and one for 120 mg/day. For a calcitonin trial [27], only the dose of 200 IU/day is presented

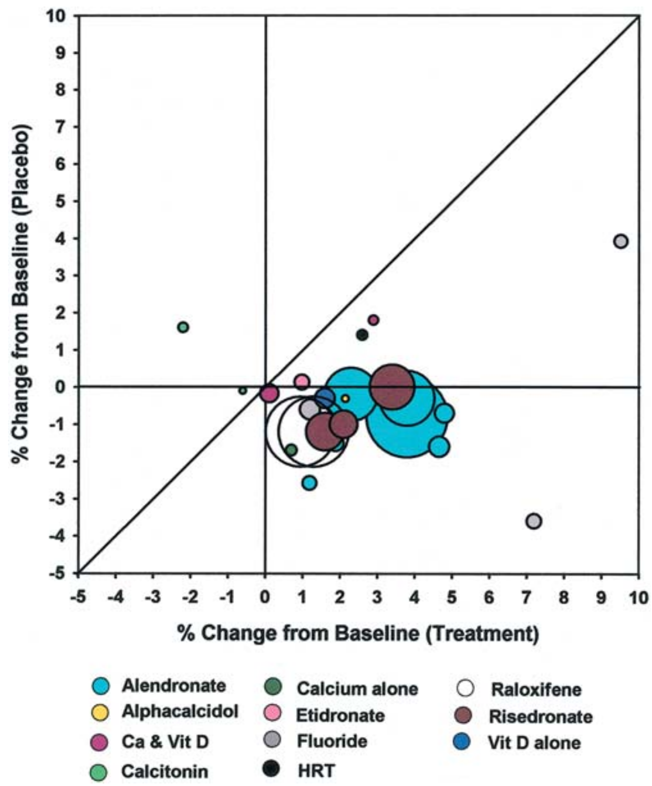


Fig. 2 Changes in femoral neck BMD relative to placebo. See legend to Fig. 1 for explanations

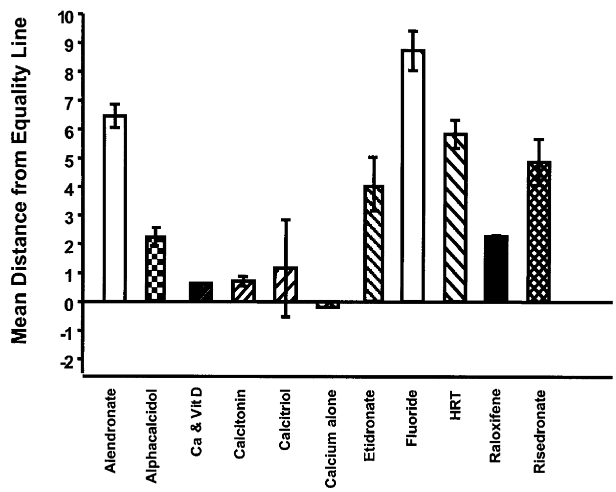


Fig. 3 Mean distance from the line of equality for the changes in spine BMD relative to placebo. The height of the column represents the magnitude of the effect and the error bar (SEM) is a reflection of the consistency among the studies for a given agent

two studies [15,21], for risedronate on three studies [14,23,24], and for raloxifene on one study [20]. The effects of 5 mg/day risedronate were not significant in the 70- to 79-year-old group with low BMD and prevalent vertebral fracture. Alendronate, raloxifene, risedronate and fluoride were tested in community-dwelling women. The combination of calcium and vitamin D was studied in calcium- and vitamin D-deficient women who were living in nursing homes [10] and showed a 43% reduction in levels.

Discussion

We searched the literature for studies on drugs used in the treatment of postmenopausal osteoporosis in which vertebral and/or hip fracture was a primary or secondary end-point. Only randomized, double-masked and placebo-controlled trials conducted in female patients with primary osteoporosis were analyzed. Osteoporosis was defined as a lumbar spine and/or femoral neck BMD below –2.0 *T*-score, or as the presence of vertebral fracture. Using these inclusion criteria, observational or prevention studies, as well as trials performed in men or in patients with secondary osteoporosis, were not included in the analysis. This selection does not infer that observational studies are of no value. Similarly, only published full papers were taken into consideration, in order to specifically appreciate the inclusion criteria and outcome definition, thereby excluding trials reported only in abstract form. We furthermore applied to each selected article a

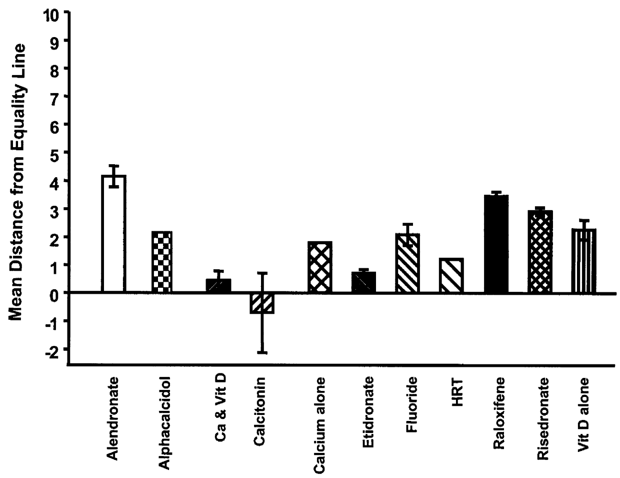


Fig. 4 Mean distance from the line of equality for the changes in femoral neck BMD. See legend to Fig. 3 for explanations

check-list of 31 items assessing the methodologic quality in terms of reporting methods and the results of external and internal validity, and of power [7] (see Appendix), which helped us in specifying the strengths and weaknesses of the studies. The r^2 correlation coefficient of the quality scores obtained by two independent examiners was 0.80, indicating a good inter-rater reliability. The highest scores were obtained with the most recent studies which included a large number of patients.

BMD is the most important determinant of bone strength, accounting for more than 60% of the variance in breaking strength [28,29]. BMD is currently the best predictor available for fracture risk [1,30,31]. A BMD lower than –2.0 *T*-score was one of the criteria for inclusion in this survey, and BMD change was one of the end-points considered. Changes in BMD are also predictive of modification in fracture risk during treatment, though the relationship with fracture occurrence may be different when BMD decreases or increases [32]. For some treatments with

Fig. 5 Mean and 95% confidence interval for the relative risk of morphometric vertebral fracture. The details of the studies analyzed are in Table 2

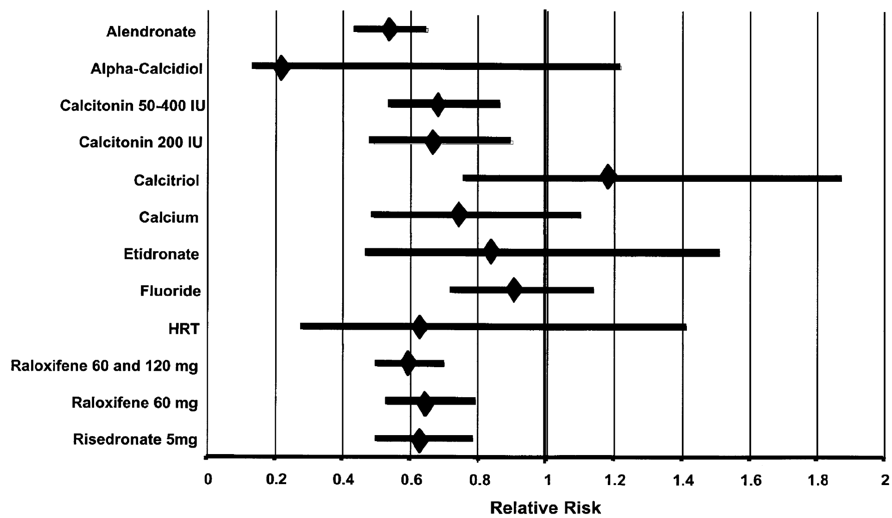
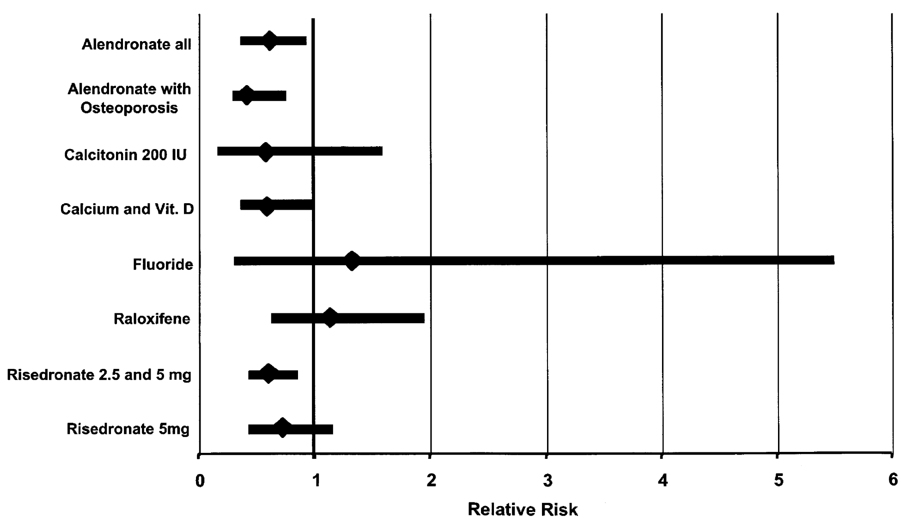


Fig. 6 Mean and 95% confidence interval for the relative risk of hip fracture. The details of the studies analyzed are in Table 3



bone resorption inhibitors, the decrease in fracture incidence is commensurate to the increase in BMD [32]. This contention is, however, not valid for fluoride, since treatment with this agent is associated with a marked increase in BMD but without any significant modification of fracture incidence [33,34]. BMD is used to monitor the response to treatment in individual patients. We analyzed changes in BMD in the treated group compared with the placebo-treated controls. The graphical representation used allowed us to appreciate the relative efficacy of the different treatments. Indeed, the more distant from the line of equality, the higher the magnitude of the effect of the agent considered compared with placebo. Furthermore, we used symbols of different sizes, the size being proportional to the number of patients evaluated at the end of the trial. The consistency of the effects of a substance on BMD, i.e., the direction and the magnitude of BMD changes with respect to controls for both spine and hip, was assessed in two ways. First, close spacing of the symbols referring to single trials was taken as a reflection of a consistent efficacy. Second, we computed the mean distance from the line of equality for each agent. The mean was weighted by the number of patients enrolled in the study (Figs 3, 4). The intertrial consistency was evaluated by the error bar. Consistent effects were thus represented by a small standard error of the mean. Under these conditions, the most consistent results were found with alendronate, hormone replacement therapy or risedronate at the lumbar spine, and with alendronate or etidronate at the femoral neck.

Another outcome which was analyzed in our survey was fracture of the spine or the hip, excluding thereby all other peripheral fractures. In the trials examined, fractures constituted either a primary or a secondary end-point. For hip fracture, the clinical expression and thus the diagnosis are evident. Concerning vertebral fracture, all deformities demonstrated on sequential radiographic examinations were included in the analysis, and not only the symptomatic ones, though the morphometric definition could vary according to the trial. The definition could be based on a semiquantitative assessment, or on a 15% decrease in one vertebral body height, up to a 20% and 4 mm decrease. The fracture events specifically defined in each study were included in the analysis. Moreover, instead of considering the number of fractures per observation time, which can violate a basic rule of statistics, we computed the number of patients with fracture [9]. Indeed, events must be independent of each other to be reliably analyzed. The occurrence of one vertebral fracture markedly increases the risk of experiencing another one [35]. Summarizing the relative risk of a vertebral fracture, alendronate, calcitonin, raloxifene or risedronate were associated with a significant reduction in this risk. The reduction varied from 35% for the 60 mg/day dose of raloxifene, which is the registered dose, up to 47% for alendronate [15,20,21,23,24]. The consistency of the results is illustrated by the narrow 95% confidence interval. Calcium supplements in vitamin D-replete osteoporotic patients led to a significant reduction in vertebral fracture only in the group with vertebral fracture at baseline and with a low calcium intake [26].

At the time of the survey, alendronate or risedronate treatment in community-dwelling elderly [14,15,21] and the combination of calcium plus vitamin D in institutionalized elderly [10] were associated with a significant reduction in hip fracture incidence. Hip fracture was the primary end-point in two studies [10,14] which enrolled patients whose age was in the eighties. In a study it was included in clinical fracture primary end-point [21]. All the other studies had vertebral fracture and/or changes in BMD as the primary end-point. Under these conditions, younger age groups were randomized, implying fewer hip fracture events and a lower power to detect a reduction in incidence.

Our analysis has several limitations. One is publication bias. Only results from published full papers were included in our survey, excluding thereby results reported in abstract form, or unpublished trials that had not demonstrated any significant result. It should be emphasized that our work is not a classical meta-analysis, but an analysis of the evidence collected in randomized controlled studies directly accessible to practitioners, aimed at helping them to take a therapeutic decision. Many of the trials were grossly underpowered and performed in age groups in which, for instance, hip fractures are relatively rare. The inclusion criteria differed among the trials, such as mean age, prevalent fracture at baseline, or BMD levels. Among the trials, there are different confounding variables likely to have a significant impact on the outcome and modify the reproducibility of the results. Finally, there is the possibility of having missed some studies, although, to our knowledge, it is unlikely that we have missed major trials that would have a significant influence on the conclusions. Lower vertebral fracture rate has been reported with bone anabolic agents such as PTH or strontium ranelate; but they are not yet registered for the treatment of osteoporosis [36,37].

In conclusion, our survey indicates that overall changes in BMD relative to controls were consistent with fracture risk reduction. Vertebral fracture incidence was decreased by treatments with alendronate, calcitonin, risedronate or raloxifene. For hip fracture, a favorable effect was found with alendronate or risedronate in women with osteoporosis, and with calcium plus vitamin D in institutionalized patients.

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Appendix
Checklist for quality according Downs and Black [7]

Questions 1–10: Reporting	Total points given
1) Aim	1
2) Are the main outcomes to be measured clearly described in introduction or methods?	1
3) Are the characteristics of the patients included in the study clearly described?	1
4) Are the interventions of interest clearly described?	1
5) Are the distributions of principal confounders in each group of subjects to be compared clearly described?	2
6) Are the main findings of the study clearly described?	1
7) Does the study provide estimates of the random variability in the data for the main outcomes?	1
8) Have all important adverse events that may be a consequence of the intervention been reported?	1
9) Have the characteristics of patients lost to follow-up been described?	1
10) Have actual probability values been reported (e.g., 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	1
Questions 11–13: External validity	
11) Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	1
12) Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	1
13) Were the staff, places and facilities where the patients were treated representative of the the treatment the majority of patients received?	1
Questions 14–20: Internal validity – bias	
14) Was an attempt made to mask study subjects to the intervention they received?	1
15) Was an attempt made to mask those measuring the main outcomes of the intervention?	1
16) If any of the results of the study were based on 'data dredging', was this made clear? (Analyses not preplanned have to be clearly indicated)	1
17) In trials and cohort studies, do the analyses adjust for different length of follow-up of patients, or in case–control studies, is the time period between the intervention and outcome the same for cases and controls?	1
18) Were the statistical tests used to asses the main outcomes appropriate?	1
19) Was compliance with the intervention/s reliable?	1
20) Were the main outcome measures used accurate (valid and reliable)?	1
Questions 21–26: Internal validity – confounding (selection bias)	
21) Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case–control study) recruited from the same population?	1
22) Were study subjects in different intervention groups (trials or cohort studies) or were the cases and controls (case–control study) recruited over the same peroid of time?	1
23) Were study subjects randomized to intervention groups?	1
24) Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	1
25) Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	1
26) Was loss of patients to follow-up taken into account?	1
Question 27: Power	
27) Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	5
Total points	**32**

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