Responsiveness of Endpoints in Osteoporosis Clinical Trials — An Update

ANN CRANNEY, VIVIAN WELCH, PETER TUGWELL, GEORGE WELLS, JONATHAN D. ADACHI, JESSIE McGOWAN, and BEVERLEY SHEA

ABSTRACT. As an update of our earlier paper, published as part of the Outcome Measures in Rheumatology Clinical Trials (OMERACT 3) proceedings in 1996, we surveyed the types of outcomes incorporated in recent clinical trials. A literature search was conducted on MEDLINE and Current Contents, from January 1996 to March 1998, using the search strategy recommended by the Cochrane Collaboration for the identification of randomized controlled trials (RCT). Two independent reviewers selected trials according to inclusion criteria. The same reviewers extracted data on clinical and radiographic fractures, pain, quality of life, and bone mineral density (BMD). Seventy-four RCT conducted on bone loss in postmenopausal women were identified. Most trials incorporated biochemical markers and BMD as outcome measures. Fewer trials included vertebral fractures, pain, height, and quality of life. The responsiveness is presented in terms of the sample size needed per group to show a statistically significant difference. The most responsive outcomes were pain, BMD, and biochemical markers. The number needed to treat to prevent one vertebral fracture ranged from 13 to 54, depending on the intervention and population. Investigators should examine the characteristics of the patient population and the nature of the intervention in determining the sample size required to demonstrate a significant effect. The selection of endpoints should be based on their responsiveness, feasibility, and the importance of using standardized outcomes. Standardized outcomes greatly facilitate the synthesis of available information into systematic reviews by groups such as the Cochrane Collaboration. (J Rheumatol 1999;26:222–8)

Key Indexing Terms:
OSTEOPOROSIS CLINICAL TRIALS OUTCOME MEASURES RESPONSIVENESS

In our previous article[1], we reviewed the use of the 6 main clinical and non-clinical endpoints recommended at the third Outcome Measures in Rheumatology Clinical Trials (OMERACT 3) conference for use in osteoporosis clinical trials, namely: clinical and radiographic fractures, bone density, biochemical markers, pain, health status, and height. In this update, we present new information on the responsiveness of total body bone mineral density (BMD) and N-telopeptide, a biochemical marker. The selection of endpoints for clinical trials depends on truth, discrimination, and feasibility according to the OMERACT Filter[2]. The usefulness of an endpoint depends on its ability to detect meaningful change, which is often termed "responsiveness"[3]and is captured by the OMERACT filter of discrimination. We present responsiveness as the sample size per group needed to show a statistically significant difference in postmenopausal women.

This article presents a survey of the literature on the endpoints used in randomized controlled trials (RCT) between 1996 and 1998, in the context of the scope of interventions adopted by the Cochrane Collaboration Osteoporosis Subgroup, the responsiveness of these endpoints, and their clinical relevance in terms of the number needed to treat and the minimal clinically important difference.

MATERIALS AND METHODS

A literature search of MEDLINE and Current Contents was conducted from 1996 to March 1998, using the search strategy of the Cochrane Musculoskeletal Review Group, adapted from the Cochrane Collaboration search strategy for RCT[4]. We hand searched recent conference proceedings and contacted experts in the field of osteoporosis to identify other potential trials, including abstracts. Two independent reviewers (AC, VW) identified RCT, based on the abstracts, keywords, and titles.

This list of 74 RCT was surveyed for their use of the 6 core outcomes defined at OMERACT 3: BMD, vertebral and nonvertebral fractures, biochemical markers, pain, quality of life, and height. The trials were classified according to the framework of the Cochrane Collaboration Osteoporosis Subgroup scope, listed on the Cochrane Library[5].

For the analysis of responsiveness, the analysis was limited to the 52 trials published between 1997 and 1998. We selected trials according to 4 criteria: (1) randomized controlled trial, (2) availability of 2 year data on one of the 6 core OMERACT 3 outcomes, (3) pharmacological agent used for the treatment or prevention of osteoporosis, and (4) a comparator of calcium or placebo. Two independent reviewers extracted the necessary

From the Department of Medicine, University of Ottawa, Ottawa and McMaster University, Hamilton, Canada.

A. Cranney, MD, FRCPC, MSc, Department of Medicine, Ottawa Hospital; V. Welch, MSc, Clinical Epidemiology Unit; P. Tugwell, MD, FRCPC, MSc, Department of Medicine; G. Wells, MSc, PhD, Clinical Epidemiology Unit, University of Ottawa; J.D. Adachi, MD, FRCPC, Department of Medicine, McMaster University; J. McGowan, MSc, Canadian Medical Association, Ottawa; B. Shea, BSc, RN, Clinical Epidemiology Unit, University of Ottawa.

Address reprint requests to Dr. A. Cranney, 1053 Carling Avenue, Parkdale Clinic, Ottawa Hospital — Civic Site, Ottawa, Ontario, Canada K1N 5R2.

data, using predetermined forms, for the endpoints after 2 or more years of treatment (AC, VW).

Twenty-seven trials were excluded. Four were excluded since they were nonpharmacological interventions[6–9]. Nine were excluded since they were combination trials with no placebo condition[10–18]. Six were excluded since they measured only one year data[19–24]. Two were excluded since they were followup trials to an earlier RCT that included open label phases[25,26]. Two were excluded since they did not include any of the 6 core OMERACT 3 outcomes[27,28]. One trial was excluded since it was a low dose of risedronate, which revealed nonsignificant effects[29]. Another was excluded since it considered only men[30]. Two trials were not obtained in time for this update[31,32]. The responsiveness results are based on the remaining 26 publications from 24 placebo controlled RCT. For each endpoint, an effect size was calculated. For continuous endpoints (e.g., bone densitometry, biochemical markers, pain, and health status), effect size was calculated as the difference of the means of the treatment and placebo groups divided by the standard deviation (SD) of the placebo. For dichotomous endpoints (e.g., fracture), effect size was taken as twice the difference between the treatment and placebo groups of the inverse arc sine of the square root of the rates[33]. A large effect size indicates a high sensitivity to change. Effect sizes were classified according to Cohen[33] as small (0.2), medium (0.5), or large (0.8). Sample size was calculated based on the effect size derived for each endpoint, and for the probability of Type I and II errors of 0.05 and 0.20, respectively. Sample sizes were classified as small (< 50 evaluable patients per group), fair (51–150), large (150–900), or very large (> 900). The sites considered for bone densitometry were the lumbar spine, femoral neck, trochanter, distal forearm, and total body. Due to inconsistency in reporting of the SD and the mean change in bone mineral density (BMD), percentage change from baseline was used.

For vertebral and nonvertebral fractures, the results are also presented as the number needed to treat (NNT), calculated as the inverse of the absolute risk reduction[34].

RESULTS

Endpoints used in RCT. The OMERACT outcomes that were used in the 74 eligible RCT published between January 1996 and March 1998, classified according to the Cochrane topic list, are shown in Table 1. Thirty trials evaluated women with established osteoporosis (defined as BMD ≥ 2.5 SD below normal or one or more vertebral fracture) and 44 investigated postmenopausal women with low or normal BMD. Sixty-two of 74 trials included BMD as a measurement. Only half of the trials included the measurement of biochemical markers. Vertebral fractures were measured in 11 of 30 RCT in women with established osteoporosis, but in only one of the RCT in women with normal or low BMD. Similarly, pain was measured in 5 RCT of women with established osteoporosis, but in only 2 RCT in women with normal or low BMD. Quality of life was used as an outcome in 7 RCT and height in 2 RCT.

Responsiveness of endpoints. The included studies measured the effects of alendronate[35–40], etidronate[41–44], calcitonin[45,46], ipriflavone[47–49], fluoride[50,51], hormone replacement therapy (HRT)[52–56], risedronate[57], vitamin D/calcium in combination[58], and calcium alone[59]. Five of these were abstracts[16,37,40,46,52]. The responsiveness, described by both effect size and sample size, of all 6 outcomes considered are summarized in Figure 1 and presented in detail below.

The only RCT to evaluate clinical fractures is the Fracture Intervention Trial (FIT)[39,60], which we reported in our original article. The most recent paper by FIT presents the results of subgroup analyses. These results indicate that clinical fractures are a more responsive endpoint in people at the highest risk of fracture. In particular, those with femoral neck BMD < 0.59 g/cm^2 or more than one vertebral fracture at baseline had medium effect sizes of 0.16 and 0.24, respectively, compared to 0.06 and 0.07 for people with BMD ≥ 0.59 g/cm^2, and only one vertebral fracture at baseline, respectively. The sample size needed was large for these high risk groups and very large for the overall group (Table 2). The subgroups of women older than 75 years or with a history of postmenopausal fracture also had very poor responsiveness and are not reported separately in Table 2

Table 1. Distribution of randomized controlled trials published between January 1996 and March 1998[†].

Intervention	Total RCT	Vertebral Fractures	BMD	Biochem Markers	Pain	Quality of Life	Height
Bisphosphonates*	19	5	16	11	0	1	1
Calcitonin*	6	1	5	5	2	0	0
Calcium*	6	0	5	5	0	0	0
Exercise*	9	1	9	0	2	2	0
Fluoride*	3	2	2	1	1	1	0
Growth hormone	2	0	2	2	0	0	0
HRT*	13	0	12	2	0	2	0
Ipriflavone	4	0	4	3	2	0	0
Nandrolone decanoate	1	0	1	0	0	0	0
Parathyroid hormone	3	2	2	2	0	1	1
Tibolone	2	0	2	1	0	0	0
Vitamin D*	6	1	4	5	0	0	0
Total	74	12	62	37	7	7	2

[†]Combination trials are counted only once.
*Indicates that a Cochrane systematic review is underway or completed.

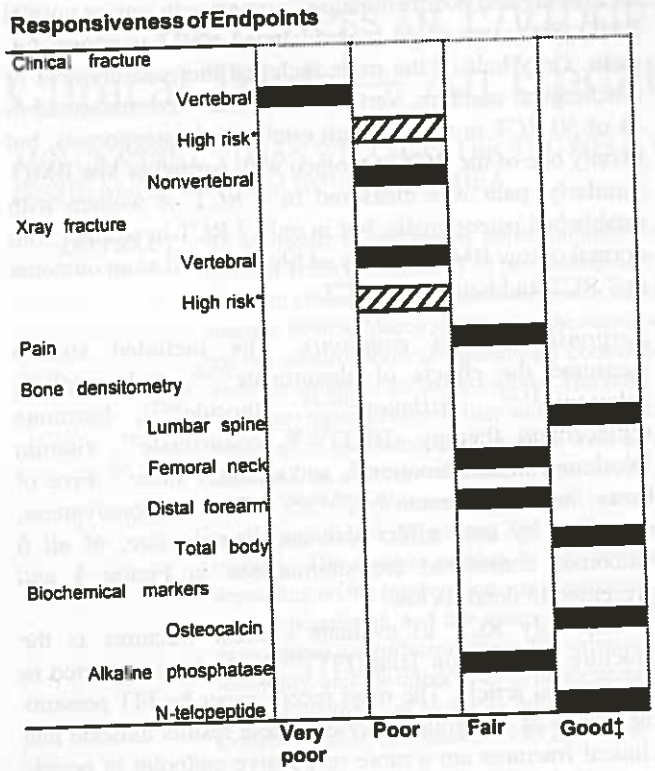

Figure 1. Responsiveness of osteoporosis endpoints for 2 year trials, published between 1997 and 1998. *High risk in the Fracture Intervention Trial (FIT) corresponds to femoral neck BMD < 0.59 g/cm^2 or > 1 before vertebral fracture. ‡The responsiveness is classified based on sample sizes of > 900, 151–900, 51–150, and < 51 for responsiveness of very poor, poor, fair, and good, respectively.

(effect sizes 0.06 and 0.11, respectively). Clinical nonvertebral and hip fractures from the FIT trial have extremely poor responsiveness[60].

Radiographic evidence of fractures has better responsiveness than clinical fracture, with effect sizes ranging from 0.17 to 0.56, corresponding to small to medium effect sizes. The sample sizes needed were large for alendronate and calcitonin and small for etidronate and ipriflavone. Importantly, the small sample size required for ipriflavone[47] and etidronate[44] are based on sample sizes of 40 and 78, respectively. In contrast, the calcitonin and alendronate trials are based on trials with more than 300 patients enrolled. Contrary to our previous report, fluoride was found to increase vertebral fracture rate in the recent FAVOS (Fluoride Against Vertebral Osteoporosis Study) trial[50]. Therefore, the calculated sample size of 620 is of questionable use for designing a trial to detect a meaningful difference among treatment groups. Radiographic nonvertebral

Table 2. Responsiveness of fractures.

	Treatment	Effect Size	Sample Size	NNT
Clinical vertebral fracture	Alendronate[39]	0.13	939	22
	< 0.59 fem neck BMD	0.16	620	
	≥ 0.59 fem neck BMD	0.06	4406	
	Baseline > 1 fracture	0.24	276	
	Baseline 1 fracture	0.07	3237	
Radiographic vertebral fracture	Alendronate[39]	0.22	328	15–44
	< 0.59 fem neck BMD	0.25	254	
	≥ 0.59 fem neck BMD	0.17	549	
	Calcitonin[46]	0.21**	360	14
	Etidronate[44]	0.56	51	14–54
	Fluoride[50]	–0.16*	620	
	Ipriflavone[47]	0.44**	42–82	5
		0.62		
Clinical nonvertebral fracture	Alendronate[60]	0.08	2350	36
Radiographic nonvertebral fracture	Vit D + calcium[58]	0.24	276	17
	HRT[52]	0.37	117	10
	Ipriflavone[47]	0.45	78	20
	Vit D[52]	0.18	482	17
Radiographic nonvertebral and vertebral fracture	Etidronate[41]	0.12	1102	29
Clinical hip fracture	Alendronate[60]	0.09	1997	90
Radiographic hip fracture	Vit D + calcium[58]	0.14	810	202

NNT: number needed to treat.
*The effect size is negative since the rate of fractures was higher in the fluoride group than the placebo group. Because of this, number needed to treat was not calculated.
**The results for ipriflavone and etidronate are based on small sample size trials.

fractures were rated as having fair responsiveness[58]. However, the best responsiveness was found for the longest treatment period of about 5 years[33]. One trial used a combined endpoint of nonvertebral and vertebral fractures[41], and this had very poor responsiveness.

Another way to consider the effectiveness of treatments for the prevention of vertebral and nonvertebral fractures is to calculate the number needed to treat to prevent one fracture. Table 2 illustrates that alendronate, etidronate, and calcitonin appear to have similar effectiveness in preventing radiographic fractures. Ipriflavone seems extremely effective but is based on a sample size of only 20 subjects in each group. For nonvertebral fractures, HRT is more effective than vitamin D alone or in combination with calcium. Table 2 highlights the difference in effectiveness at preventing clinical events compared to radiographically defined fractures.

Responsiveness of bone densitometry at 5 sites and with several treatments is summarized in Table 3. Effect sizes were largest for lumbar spine and total body BMD. Responsiveness was rated as good and was consistent across treatments. The calcium/vitamin D effect size was small. Although not shown in this table, trials conducted in women with normal BMD at baseline required larger sample sizes for the same intervention and were less responsive. Total body BMD effect sizes were consistently large, but were measured in only 13 of the 74 RCT published between 1996 and 1998. For alendronate, etidronate, HRT, vitamin D and calcium, and parathyroid hormone, all sample sizes fell between 9 and 67. For the femoral neck, the effect sizes were less consistent than for lumbar BMD. Five of the 14 trials that reported femoral neck BMD found a small effect size, corresponding to sample sizes of greater than 150. However, the other trials found fair to good responsiveness. The sample sizes needed were small for alendronate, large for calcium-vitamin D, fair for etidronate, fair for HRT, large for fluoride, and fair for risedronate. The distal forearm was used as an endpoint for only 21 of 71 RCT published between 1996 and 1998. In the 4 trials that used this endpoint and were evaluated for this update, the distal forearm had fair responsiveness.

When using a surrogate endpoint such as BMD, a clinician may seek to determine the minimal clinically important difference (MCID). Eastell[61] suggested a MCID of 5% for lumbar spine and 8% for femoral neck, based on the amount of measurement error and SD inherent in densitometry. Applying this MCID of 5% for lumbar BMD suggests that alendronate[35–38], fluoride[50], HRT[53,55], risedronate[57], and etidronate[44] are effective at reducing bone loss.

Height was evaluated as having fair responsiveness in our previous paper, but none of the trials examined for this update included height as an endpoint.

We assessed the responsiveness of several biochemical markers, including serum osteocalcin, serum bone-specific alkaline phosphatase, N-telopeptide, C-telopeptide, and N-telopeptide corrected for creatinine. All had fair to good responsiveness for all treatments.

Pain was measured by 3 trials assessed in this paper and

Table 3. Responsiveness of bone densitometry.

	Treatment	Effect Size	Sample Size
Total body	Alendronate[35–38]	0.56–1.39	9–51
	Calcium citrate[59]	0.38	42
	Etidronate[43]	0.49–0.63	40–67
	HRT[35,54]	0.82–1.02	16–24
	Vit D + calcium[58]	0.67	36
Lumbar spine	Alendronate[35–38]	1.36–2.86	< 11
	Calcium citrate[59]	0.08	204
	Etidronate[41–44]	0.55–1.57	7–53
	Fluoride[50]	0.46	73
	HRT[53–56]	0.16–2.17	4–101
	Ipriflavone[47]	0.32	50
	Risedronate[57]	1.82	5
	Vit D + calcium[58]	0.14	810
	Vit D[56]	0.01	1577
Femoral neck	Alendronate[35,36,38]	0.68–0.94	18–39
	Calcium citrate[59]	0.58	28
	Etidronate[41,42,44]	0.17–0.88	21–549
	Fluoride[50]	0.12	1075
	HRT[35,53,54,56]	0.12–1.25	11–1137
	Risedronate[57]	0.87	21
	Vit D + calcium[58]	0.24	276
Distal forearm	Alendronate[35,38]	0.21–0.56	51–360
	HRT[35]	1.26	10
	Ipriflavone[48]	0.28	58

was rated with good responsiveness for calcitonin. Menopausal symptoms were measured using a visual analog scale by Heikkinen[53], but the results were not reported in sufficient detail to estimate an effect size.

Quality of life was assessed only by 5 trials and 2 abstracts published between 1996 and 1998. The FIT trial measured days of bed rest and limited activity due to back pain. They found alendronate significantly reduced bed rest days (2.9 and 6.0 in the alendronate and placebo groups, respectively) and limited activity days (68.2 in alendronate and 78.6 in the placebo group)[40]. However, variance was not reported, hence an effect size could not be calculated.

DISCUSSION

This report addresses the ability of different endpoints to discriminate between placebo and various interventions in postmenopausal osteoporosis. Responsiveness is estimated based on effect and sample sizes of intervention compared to placebo (or calcium). Since the placebo group probably worsens, rather than staying the same, the effect sizes that we present could be viewed as an index of discrimination between placebo and interventions rather than a measure of sensitivity to change.

Radiographic fractures are more feasible to measure and more responsive than clinical fractures, being rated as fair to poor compared to very poor for clinical fractures. However, radiographic fractures do not reflect the associated pain, distress, disability, and costs that accompany a clinical fracture. Nonvertebral fractures were rarely used as a primary endpoint and had poor responsiveness, except in the 5 year HRT trials[52]. The results for numbers needed to treat show that newer treatments including alendronate, etidronate, and calcitonin appear more effective than calcium and vitamin D alone or in combination.

Bone densitometry information was available in 62 of 74 RCT of interventions for postmenopausal bone loss identified between 1996 and 1998. However, bone densitometry does not reflect the quality of the bone and may have different relationships to fractures depending on the intervention. For example, the recent trial on fluoride by Meunier[50] reveals a 10% increase in lumbar BMD, with no accompanying decrease in risk of fracture incidence, contrary to results for other interventions such as calcium-vitamin D[58] and alendronate[44]. The feasibility of this surrogate endpoint is high for absorptiometry. The results of this update concur with our previous report, showing good responsiveness for lumbar BMD and fair responsiveness for trochanter, femoral neck, and distal forearm BMD. Total body BMD was examined for the first time, and its responsiveness was classified as good.

Despite the importance of health status to quantify the effect of osteoporosis on health related quality of life, only 5 RCT and 2 abstracts used this outcome. Utility was reported in one abstract; the utility for current health was not different between HRT and raloxifene[16] and resulted in an effect size of 0.0. This endpoint may prove more useful when comparing interventions to placebo. Currently, the Osteoporosis Assessment Questionnaire[62] and the European Quality of Life as Outcome in the Treatment of Osteoporosis[63] are being cross-validated[64] and are incorporated in several osteoporosis clinical trials. Some other osteoporosis-specific health status questionnaires are also under evaluation[65–67].

Biochemical markers were reassessed in this update, providing evidence that biochemical markers have good responsiveness, although their clinical relevance is questioned by some[68]. Furthermore, they may be particularly useful in populations where measurement of lumbar BMD is impossible due to the presence of vertebral fracture[61].

Pain is an important component of a clinical event. Only a few trials measured pain in osteoporosis[45,50,53]. The results indicated good responsiveness. This endpoint is highly feasible. It deserves further investigation.

Height was not used by any trial selected for evaluation. In our previous report, height was rated to be a feasible endpoint with fair responsiveness.

This update confirms that responsiveness is poorer for patient populations with normal or low BMD than those with established osteoporosis. Similarly, the results of the FIT trial show that clinical fracture is a more responsive endpoint in high risk subgroups with lower BMD and more than one vertebral fracture at baseline. These results emphasize that investigators should consider the characteristics of the patient population and the nature of the intervention in determining the sample size required to confirm a significant effect.

Conclusion. The clinician needs the best available information to make a reasoned choice of therapy in patients with osteoporosis. It is hoped that all future trials will include the 6 measures recommended by OMERACT 3 so that each of these important domains can be accurately assessed. This is also crucial for the synthesis of results into the systematic overviews of all available data from clinical controlled trials being undertaken through the Cochrane Collaboration. Currently, the Cochrane Collaboration Osteoporosis Subgroup has systematic reviews including metaanalyses for bisphosphonates, calcitonin, calcium, exercise, fluoride, HRT, vitamin D, and combination approaches with these therapies, for both postmenopausal bone loss and corticosteroid induced osteoporosis.

REFERENCES

1. Wells G, Cranney A, Shea B, Tugwell P. Responsiveness of endpoints in osteoporosis clinical trials. J Rheumatol 1997;24:1230–3.
2. Boers M, Brooks P, Strand V, Tugwell P. The OMERACT Filter for outcome measures in rheumatology. J Rheumatol 1998;25:198–9.
3. Kazis LE, Andersen JJ, Meenan RF. Effect sizes for interpreting changes in health status. Med Care 1989;27:S178–S189.
4. Haynes R, Wilczynski N, McKibbon KA, Walker CJ, Sinclair JC.

Developing optimal search strategies for detecting clinically sound studies in MEDLINE. J Am Med Info Assoc 1994;1:447–58.
5. Cochrane Musculoskeletal Review Group. Musculoskeletal review module. In: Tugwell P, Wells G, Gillespie WJ, et al, editors. The Cochrane Library. Oxford: Update Software; 1998 Issue 2. Updated quarterly on CD-ROM.
6. Brooke-Wavell K, Jones PR, Hardman AE. Brisk walking reduces calcaneal bone loss in post-menopausal women. Clin Sci 1997;92:75–80.
7. Ebrahim S, Thompson PW, Baskaran V, Evans K. Randomized placebo-controlled trial of brisk walking in the prevention of postmenopausal osteoporosis. Age Ageing 1997;26:253–60.
8. Kohrt WM, Ehsani AA, Birge SJ. Effects of exercise involving predominantly either joint-reaction or ground-reaction forces on bone mineral density in older women. J Bone Miner Res 1997;12:1253–61.
9. Mayoux-Benhamou MA, Bagheri F, Roux C, Auleley GR, Rabourdin JP, Revel M. Effect of psoas training on postmenopausal lumbar bone loss: a 3-year follow-up study. Calcif Tissue Int 1997;60:348–53.
10. Crespo R, Revilla M, Crespo E, Villa LF, Rico H. Complementary medical treatment for Colles' fracture: a comparative, randomized, longitudinal study. Calcif Tissue Int 1997;60:567–70.
11. Flicker L, Hopper JL, Larkins RG, Lichtenstein M, Buirski G, Wark JD. Nandrolone decanoate and intranasal calcitonin as therapy in established osteoporosis. Osteoporosis Int 1997;7:29–35.
12. Hodsman AB, Fraher LJ, Watson PH, et al. A randomized controlled trial to compare the efficacy of cyclical parathyroid hormone versus cyclical parathyroid hormone and sequential calcitonin to improve bone mass in postmenopausal women with osteoporosis. J Rheumatol 1997;82:620–8.
13. Lindsay R, Nieves J, Formica C, et al. Randomised controlled study of effect of parathyroid hormone on vertebral-bone mass and fracture incidence among postmenopausal women on estrogen with osteoporosis. Lancet 1997;350:550–5.
14. Adachi JD, Sargeant EJ, Sagle MA, et al. A double-blind randomised controlled trial of the effects of medroxyprogesterone acetate on bone density of women taking oestrogen replacement therapy. Br J Obstet Gynecol 1997;104:64–70.
15. Chestnut CH, Bell NH, Clark GS, et al. Hormone replacement therapy in postmenopausal women: urinary N-telopeptide of type I collagen monitors therapeutic effect and predicts response of bone mineral density. Am J Med 1997;102:29–37.
16. Tosteson ANA, Houpt LS, Kneeland TS, et al. Impact of side effects on quality of life in a raloxifene osteoporosis prevention trial. J Bone Miner Res 1997;12 Suppl 1:501.
17. Gurlek A, Bayraktar M, Gedik O. Comparison of calcitriol treatment with etidronate-calcitriol and calcitonin-calcitriol combinations in Turkish women with postmenopausal osteoporosis: a prospective study. Calcif Tissue Int 1997;61:39–43.
18. Gonnelli S, Cepollaro C, Montomoli M, et al. Treatment of post-menopausal osteoporosis with recombinant human growth hormone and salmon calcitonin: a placebo controlled study. Clin Endocrinol 1997;46:55–61.
19. Heikkinen AM, Parviainen M, Niskanen L, et al. Biochemical bone markers and bone mineral density during postmenopausal hormone replacement therapy with and without vitamin D3: a prospective, controlled, randomized study. J Clin Endocrinol Metab 1997;82:2476–82.
20. Kapetanos G, Symeonides PP, Dimitriou C, Karakatsanis K, Potoupnis M. A double blind study of intranasal calcitonin for established postmenopausal osteoporosis. Acta Orthopaedica Scand 1997;275:108–11.
21. Heikkinen JE, Selander KS, Laitinen K, Arnala I, Vaananen HK. Short-term intravenous bisphosphonates in prevention of postmenopausal bone loss. J Bone Miner Res 1997;12:103–10.
22. Nordborg E, Schaufelberger C, Andersson R, Bosaeus I, Bengtsson BA. The ineffectiveness of cyclical oral clodronate on bone mineral density in glucocorticoid-treated patients with giant-cell arteritis. J Intern Med 1997;242:367–71.
23. Rosen CJ, Chestnut CH, Mallinak NJS. The predictive value of biochemical markers of bone turnover for bone mineral density in early postmenopausal women treated with hormone replacement or calcium supplementation. J Rheumatol 1997;82:1904–10.
24. Thiebaud D, Burckhardt P, Kriegbaum H, et al. Three monthly intravenous injections of ibandronate in the treatment of postmenopausal osteoporosis. Am J Med 1997;103:298–307.
25. Devine A, Dick IM, Heal SJ, Criddle RA, Prince RL. A 4-year follow-up study of the effects of calcium supplementation on bone density in elderly postmenopausal women. Osteoporosis Int 1997;7:23–8.
26. Miller PD, Watts NB, Licata AA, et al. Cyclical etidronate in the treatment of postmenopausal osteoporosis: efficacy and safety after seven years of treatment. Am J Med 1997;103:468–76.
27. Chavassieux PM, Arlot ME, Reda C, Wei L, Yates AJ, Meunier PJ. Histomorphometric assessment of the long-term effects of alendronate on bone quality and remodeling in patients with osteoporosis. J Clin Invest 1997;100:1475–80.
28. Heikkinen AM, Tuppurainen MT, Niskanen L, Komulainen M, Penttila I, Saarikoski S. Long-term vitamin D3 supplementation may have adverse effects on serum lipids during postmenopausal hormone replacement therapy. Eur J Endocrinol 1997;137:495–502.
29. Clemmesen B, Ravn P, Zegels B, Taquet AN, Christiansen C, Reginster JY. A 2-year phase II study with 1-year of follow-up of risedronate (NE-58095) in postmenopausal osteoporosis. Osteoporosis Int 1997;7:488–95.
30. Ringe JD, Dorst A, Kipshoven C, Rovati LC, Setnkar I. Avoidance of vertebral fractures in men with idiopathic osteoporosis by a three year therapy with calcium and low-dose intermittent monofluorophosphate. Osteoporosis Int 1998;8:47–52.
31. Nakatsuka K, Inaba M, Aratani H, et al. Effects of long-term administration of alfacalcidol on bone mass and bone metabolism in patients with primary osteoporosis — comparison with calcium preparations [in Japanese]. Jap J Geriatrics 1997;34:569–76.
32. Zarcone R, Carfora E, Sergio F, et al. Estrogen therapy in women with postmenopausal osteoporosis [in Italian]. Minerva Ginecologica 1997;49:355–9.
33. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale: Laurence Erlbaum; 1988.
34. Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. N Engl J Med 1988;38:1728–33.
35. Hosking D, Chilvers CED, Christiansen C, et al. Prevention of bone loss with alendronate in postmenopausal women under 60 years of age. N Engl J Med 1998;338:485–92.
36. McClung M, Clemmesen B, Daifotis A, et al. Alendronate prevents postmenopausal bone loss in women without osteoporosis — a double-blind, randomized, controlled trial. Ann Intern Med 1998;128:253–61.
37. Weiss S, McClung M, Gilchrist N, et al. Five-year efficacy and safety of oral alendronate for prevention of osteoporosis in early postmenopausal women. J Bone Min Res 1997;12 Suppl 1:S144.
38. Bone HG, Downs RJ, Tucci JR, et al. Dose-response relationships for alendronate treatment in osteoporotic elderly women. Alendronate Elderly Osteoporosis Study Centers. J Clin Endocrinol Metab 1997;82:265–74.
39. Ensrud KE, Black DM, Palermo L, et al. Treatment with alendronate prevents fractures in women at highest risk — results from the Fracture Intervention Trial. Arch Intern Med 1997;157:2617–24.
40. Nevitt MC, Thompson DE, Black DM, et al. The effect of

osteoporosis treatment on limitation of activity due to back pain. J Bone Miner Res 1997;12 Suppl 1:S144.
41. Pouilles JM, Tremollieres F, Roux C, et al. Effects of cyclical endronate therapy on bone loss in early postmenopausal women who are not undergoing hormonal replacement therapy. Osteoporosis Int 1997;7:213–8.
42. Meunier PJ, Confavreux E, Tupinon I, Hardouin C, Delmas PD, Balena R. Prevention of early postmenopausal bone loss with cyclical etidronate therapy (a double-blind, placebo-controlled study and 1-year follow-up). J Clin Endocrinol Metab 1997;82:2784–91.
43. Herd RJ, Balena R, Blake GM, Ryan PJ, Fogelman I. The prevention of early postmenopausal bone loss by cyclical etidronate therapy: a 2-year, double-blind, placebo-controlled study. Am J Med 1997;103:92–9.
44. Montessori ML, Scheele WH, Netelenbos JC, Kerkhoff JF, Bakker K. The use of etidronate and calcium versus calcium alone in the treatment of postmenopausal osteopenia: results of three years of treatment. Osteoporosis Int 1997;7:52–8.
45. Lyritis GP, Paspati I, Karachalios T, Ioakimidis D, Skarantavos G, Lyritis PG. Pain relief from nasal salmon calcitonin in osteoporotic vertebral crush fractures. A double blind, placebo-controlled clinical study. Acta Orthopaedica Scand 1997;275 Suppl:112–4.
46. Stock JL, Avioli LV, Baylink DJ, et al. Calcitonin-salmon nasal spray reduces the incidence of new vertebral fractures in postmenopausal women: three year interim results of the PROOF Study. J Bone Miner Res 1997;12 Suppl 1:S149.
47. Agnusdei D, Bufalino L. Efficacy of ipriflavone in established osteoporosis and long-term safety. Calcif Tissue Int 1997;61 Suppl 1:S23–S27.
48. Adami S, Bufalino L, Cervetti R, et al. Ipriflavone prevents radial bone loss in postmenopausal women with low bone mass over 2 years. Osteoporosis Int 1997;7:119–25.
49. Agnusdei D, Crepaldi G, Isaia G, et al. A double blind, placebo-controlled trial of ipriflavone for prevention of postmenopausal spinal bone loss. Calcif Tissue Int 1997;61:142–7.
50. Meunier PJ, Sebert JL, Reginster JY, et al. Fluoride salts are no better at preventing new vertebral fractures than calcium vitamin D in postmenopausal osteoporosis: the FAVOS study. Osteoporosis Int 1998;8:4–12.
51. Zerwekh JE, Padalino P, Pak CY. The effect of intermittent slow-release sodium fluoride and continuous calcium citrate therapy on calcitropic hormones, biochemical markers of bone metabolism, and blood chemistry in postmenopausal osteoporosis. Calcif Tissue Int 1997;61:272–8.
52. Komulainen MH, Kroger H, Tuppurainen MT, et al. Fracture incidence during HRT and vitamin D supplementation in postmenopausal women. Acta Obstet Gynecol 1997;76 Suppl 167;63.
53. Heikkinen J, Kyllonen E, Kurttila-Matero E, et al. HRT and exercise: effects on bone density, muscle strength and lipid metabolism. A placebo controlled 2-year prospective trial on two estrogen-progestin regimens in healthy postmenopausal women. Maturitas 1997;26:139–49.
54. Delmas PD, Bjarnason NH, Mitlak BH, et al. Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. N Engl J Med 1997;337:1641–7.
55. Gonnelli S, Cepollaro C, Pondrelli C, Martini S, Monaco R, Gennari C. The usefulness of bone turnover in predicting the response to transdermal estrogen therapy in postmenopausal osteoporosis. J Bone Miner Res 1997;12:624–31.
56. Komulainen M, Tuppurainen MT, Kroger H, et al. Vitamin D and HRT: no benefit additional to that of HRT alone in prevention of bone loss in early postmenopausal women. A 2.5-year randomized placebo-controlled study. Osteoporosis Int 1997;7:126–32.
57. Mortensen L, Charles P, Bekker PJ, Digennaro J, Johnston CC. Risedronate increases bone mass in an early postmenopausal population — two years of treatment plus one year of follow-up. J Rheumatol 1998;83:396–402.
58. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med 1997;337:670–6.
59. Riggs BL, Ofallon WM, Muhs J, O'Connor MK, Kumar R, Melton LJ. Long-term effects of calcium supplementation on serum parathyroid hormone level, bone turnover, and bone loss in elderly women. J Bone Miner Res 1998;13:168–74.
60. Black DM, Cummings S, Karpf D, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet 1996;348:1535–41.
61. Eastell R. Treatment of postmenopausal osteoporosis. N Engl J Med 1998;338:736–46.
62. Silverman SL, Mason J, Greenwald M. The Osteoporosis Assessment Questionnaire (OPAQ): a reliable and valid self-assessment measure of quality of life in osteoporosis. J Bone Miner Res 1993;8:S343.
63. Lips P, Cooper C, Agnusdei D, et al. Quality of life as outcome in the treatment of osteoporosis: the development of a questionnaire for quality of life by the European Foundation for Osteoporosis. Osteoporosis Int 1997;7:36–8.
64. Silverman S, Lips P, Minshall M. Cross calibration of OPAQ and QUALEffO: two disease targeted instruments in osteoporosis. J Bone Miner Res 1997;12 Suppl 1:504.
65. Lydick E, Zimmerman SI, Yawn B, et al. Development and validation of a discriminative quality of life questionnaire for osteoporosis (the OPTQoL). J Bone Miner Res 1997;12:456–63.
66. Cook DJ, Guyatt GH, Adachi JE, et al Quality of life issues in women with vertebral fractures due to osteoporosis. Arthritis Rheum 1993;36:750–6.
67. Helmes E, Hodsman A, Lazowski D, et al. A questionnaire to evaluate disability in osteoporotic patients with vertebral compression fractures. J Gerontol 1995;50A:M91–M98.
68. Blumsohn A, Eastell R. The performance and utility of biochemical markers of bone turnover: do we know enough to use them in clinical practice? Ann Clin Biochem 1997;84:449–59.