Osteoporosis Int (1997) 7:213–218

Osteoporosis International

Original Article

Effects of Cyclical Etidronate Therapy on Bone Loss in Early Postmenopausal Women Who Are Not Undergoing Hormonal Replacement Therapy

J. M. Pouilles[1], F. Tremollieres[1], C. Roux[2], J. L. Sebert[3], C. Alexandre[4], D. Goldberg[5], R. Treves[6], P. Khalifa[7], P. Duntze[8], S. Horlait[8], P. Delmas[9] and D. Kuntz[10]

[1]CHU Toulouse, Hôpital Purpan, Toulouse; [2]Hôpital Cochin, Paris; [3]CHU Amiens, Hôpital Nord, Amiens; [4]Hôpital Bellevue, Saint-Etienne; [5]Fondation Rotschild, Paris; [6]Hôpital Dupuytren, Limoges; [7]79 avenue de Breteuil, Paris; [8]Procter & Gamble Pharmaceuticals, Neuilly sur Seine; [9]Unité INSERM 403, Hôpital Edouard Herriot, Lyon; [10]Hôpital Lariboisière, Centre Viggo Petersen, Paris, France

Abstract. This study was carried out to investigate the effectiveness and tolerability of cyclical etidronate therapy in the prevention of bone loss occurring in early postmenopausal women who are not undergoing hormone replacement therapy (HRT). A total of 109 Caucasian women aged 45–60 years were treated with etidronate 400 mg/day or placebo for 14 days followed by calcium supplementation 500 mg/day for 77 days. Ninety-one women completed the 2 years of the study. After 2 years, the estimated difference between the two groups as regards lumbar spine bone mineral density (BMD) was 2.53% (SEM 1.07%; $p = 0.01$); BMD of the hip and wrist were not significantly different between treatment groups. A clear reduction in bone turnover was obtained as evidenced by a significant decrease in serum alkaline phosphatase level and in urinary N-telopeptide/creatinine ratio in the etidronate group; the difference between the two groups was $-12\% \pm 3.2\%$ for serum alkaline phosphatase level ($p = 0.019$) and $-22.9\% \pm 13.7\%$ for the urinary N-telopeptide/creatinine ratio ($p = 0.047$). There was no statistically significant difference between the two groups in terms of the serum osteocalcin levels and urinary hydroxyproline/creatinine and calcium/creatinine ratios. Etidronate was generally well tolerated and its adverse event profile was similar to that of placebo. The results of this study indicate that cyclic etidronate therapy can prevent trabecular bone loss, with no deleterious effect on cortical bone, in the first 5 years of menopause and that it has a very high safety margin.

Keywords: Bone mineral density; Dual-energy X-ray absorptiometry; Etidronate; Postmenopausal osteoporosis; Postmenopausal bone loss

Correspondence and offprint requests to: D. Kuntz, Hôpital Lariboisière, Centre Viggo Petersen, 6 rue Guy Patin, 75475 Paris Cedex 10, France.

Introduction

Osteoporosis is a major medical and socio-economic problem in Western society. Clinical manifestations of established osteoporosis include vertebral fractures, Colles' fracture and hip fractures. It is well established from prospective studies that a decrease in bone mass leads to an increased risk of fractures [1–4].

Hormone replacement therapy (HRT) is well known to reduce postmenopausal bone loss and to prevent osteoporotic fractures (vertebral crush fractures, femoral neck fractures), myocardial infarction and stroke [5–9]. However, acceptance of HRT remains controversial, mainly because of fears of breast cancer as discussed in one recent report [10]. In some women, HRT cannot be prescribed for one reason or another (contraindications, side effects, non-compliance) and a non-hormonal treatment is needed to prevent postmenopausal osteoporosis.

An alternative effective way of preventing postmenopausal bone loss is the use of bisphosphonates. Bispho-

sphonates are synthetic compounds that are taken up preferentially by bone, inhibiting osteoclastic resorption and consequently bone loss. They are being developed for the prevention and treatment of diseases characterized by increased bone resorption such as Paget's disease of bone, malignant hypercalcaemia and postmenopausal osteoporosis [11,12].

Etidronate disodium, the disodium salt of (1-hydroxyethylidene) bisphosphonic acid, was first used for treatment of osteoporosis in 1971. Clinical studies involving postmenopausal women with established osteoporosis have indicated that oral etidronate in an intermittent cyclical therapy increases BMD of the spine and appears to reduce the incidence of vertebral fracture [13–15]. Other recently published studies involving postmenopausal women have suggested that etidronate could prevent bone loss in such women [16,17].

The purpose of this study was to investigate the effectiveness and tolerability of cyclical etidronate therapy in the prevention of bone loss occurring in early postmenopausal women who are not undergoing HRT.

Patients and Methods

Study Population

Included in the study were Caucasian women aged 45–60 years who were ambulatory and active, weighed between 45 and 80 kg and within 20% of the normal body mass index (BMI), had spontaneously or after bilateral oophorectomy ceased menstruating between 6 and 60 months prior to enrolment and had not been treated by HRT. For those who had ceased menstruating between 6 and 12 months prior to enrolment, biochemical evidence of menopause was required (FSH levels <30 UI/l or LH <30 UI/l and oestradiol >20 pg/l). For women who had undergone a hysterectomy without oophorectomy before menopause, the date of menopause was determined according to clinical (flushes) and biological criteria.

Women with a documented history of alcoholism or with evidence, from physical examination, laboratory tests or radiography of any bone metabolism disorder were also excluded. We also excluded women undergoing treatment which might interfere with bone metabolism.

All women provided informed consent to participate in the study, which was approved by the hospital ethics committee.

Treatment

This was a multi-centre (seven centres), double-masked, placebo-controlled, randomized study.

One cycle of treatment was defined as follows: etidronate 400 mg/day of placebo for 14 days continued by calcium supplementation 500 mg/day (Cacit tablets) for 77 days. Etidronate or placebo tablets were taken with water, coffee, tea or juice but not with milk, on an empty stomach, i.e. 2 h before meals. If Cacit was not well tolerated by the women, the investigator was allowed to prescribe either Sandocal, Orocal or Calcium Sandoz Forte (each containing 500 mg elemental calcium). Women were instructed to take the calcium supplement orally during a meal. A third year of calcium supplementation has been carried out for all patients who completed the 2-year treatment period. Etidronate or placebo were not administered during this year.

Compliance was assessed by pill count. Women were defined as compliant if they took at least 80% of etidronate or its placebo over the treatment period.

End Points

Bone Densitometry. The primary end point was a change in BMD of the lumbar spine (L2–4) measured by DXA (dual-energy X-ray absorptiometry) at baseline and at weeks 26, 52, 78 and 104. If a lumbar vertebra fractured during the study, that one was deleted from all previous measurements. Both Hologic and Lunar DEXA machines were used in this study and BMD was expressed as the mean percentage change from baseline. The percentage changes in lumbar spine BMD observed in the etidronate and placebo groups were compared at week 104. Similarly the changes in hip BMD (non-dominant side at the femoral neck, Ward's triangle, and trochanter regions) and changes in distal radial BMD (non-dominant side) measured by DXA were compared.

Bone Markers. Changes in serum and urine markers (morning fasting urine) of bone turnover (serum osteocalcin, alkaline phosphatase, urinary calcium/creatinine, hydroxyproline/creatinine and N-telopeptide/creatinine ratios) were recorded. Bone turnover markers were analyzed only if the samples were obtained outside the study drug intake period, and no more than 14 days before the next study drug cycle. Serum osteocalcin, urinary hdyroxyproline and N-telopeptide were measured at a central laboratory.

Adverse Events

All adverse events (AE), regardless of their severity or relationship to etidronate, were assessed at each visit. The investigator graded events as serious or not and the severity of each AE as mild, moderate or severe. A serious AE was defined as death, overdose, a diagnosis of cancer, or any event that was life-threatening, permanently disabling, required patient hospitalization, or extended hospitalization.

Statistics

Descriptive statistics were used to assess the baseline comparability of all effectiveness and demographic

variables between the treatment groups. All analyses were performed for the intent-to-treat (ITT) population comprising all women who were randomized to treatment and who had been given etidronate or placebo.

The primary hypothesis tested was that changes from baseline in the lumbar spine BMD were equivalent in each group of treatment. A two-way analysis of variance (ANOVA) was performed to test the hypothesis. The factors tested in the ANOVA model were treatment group, centre effect and their interaction. If no interaction was observed, then this term was dropped from the model and the treatment effect was assessed, keeping centre effect in the model. Normality assumption was checked for validity by the Shaprio–Wilk statistic and by visual inspection of the normal plot (Q–Q plot of the residuals). Homoscedasticity was tested using Levene's method. The *F*-test was replaced by the Wilcoxon rank-sum test if model assumptions were not tenable. Hypothesis testing was two-sided with a 5% significance level.

The same analyses were performed for BMD of femoral neck, trochanter, Ward's triangle and distal radius at week 104. These analyses were repeated for changes from baseline in serum alkaline phosphatase and osteocalcin levels, and in the ratios of urinary excretion of N-telopeptide and urinary hydroxyproline and calcium to urinary creatinine at week 104. Third year data on the calcium supplement follow-up period have not been analysed yet.

Results

One hundred and nine women were enrolled in the study. Fifty-four were randomly assigned to receive cyclical etidronate therapy and 55 were assigned to receive placebo. The duration of exposure to the study drug was on average 12.9 weeks in the placebo group and 12.8 weeks in the etidronate group. Nine (16.7%) of the women on etidronate and 9 (16.4%) on placebo withdrew from the study during the first 2 years on the drug. Hence, 91 women completed 2 years in the study. In addition, 1 in the etidronate group and 4 in the placebo group attended the week 104 visit but were either unwilling to participate in the third-year follow-up or were starting HRT. These 5 women withdrew just after the week 104 visit, but are included in the 91 women who completed 2 years in the study. One on etidronate withdrew from the study due to an adverse event. She experienced two episodes of stomatitis of mild severity. Eight women voluntarily withdrew from the study: 5 in the placebo group and 3 in the etidronate group. Seven were withdrawn from the study due to protocol violations: 3 in the placebo group and 4 in the etidronate group. Two were withdrawn from the study for poor compliance or non-compliance. All the women who completed the study were at least 80% compliant to the study drug.

The demographic data of the study population are summarized in Table 1. The treatment groups were comparable with respect to all demographic and baseline data. However, the etidronate group had a slightly lower mean lumbar spine BMD than the placebo group when Lunar DXA was used; the mean was less than half of the pooled standard deviation. This slight baseline difference, which was not clinically significant, did not affect the outcome of the study.

Table 1. Baseline demographic data

	Treatment group	
	Placebo (n=55)	Etidronate (n=54)
Age (years)	53.89 ± 2.92	53.63 ± 3.19
Height (cm)	159.78 ± 5.82	158.79 ± 6.23
Weight (kg)	58.12 ± 7.18	57.93 ± 7.95
Time since menopause (months)	30.16 ± 16.93	31.44 ± 17.22

n, number of patients randomized to the treatment group. Values are the mean ± SD.

Bone Mineral Density

Lumbar Spine. Eighteen patients withdrew from the study before the week 104 visit, 2 patients did not have an evaluable baseline DXA scan and 3 patients did not have a week 104 DXA scan. Therefore, 86 patients were evaluable at the week 104 visit. Percentage change from baseline in BMD of th spine (L2, L3, L4) is presented in Fig. 1. The mean BMD of the L2, L3 and L4 vertebrae was always used since no fractures for these three vertebrae were reported.

There was a continuous loss of bone density over the 2-year treatment period in the placebo group. Patients receiving etidronate had an increase in BMD over the first 6 months of treatment, then experienced a slight decrease in BMD over the remaining period. There were no significant changes in spinal BMD in the etidronate group except at the week 26 visit ($p > 0.036$). At 2 years

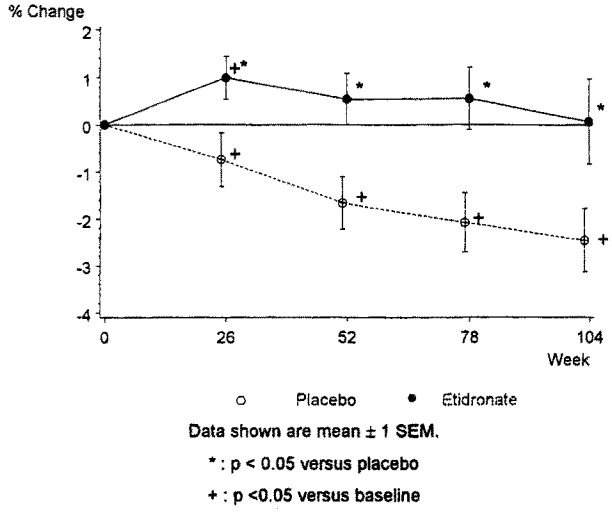

Fig. 1. Lumbar spine BMD: mean percentage change from baseline.

there was a significant difference between the two groups (p = 0.017, Wilcoxon two-sample test). The estimated difference between the two groups was 2.53% (SEM 1.07%; 95% CI 0.394 to 4.664). An analysis of the first time point (week 26) showed a significant difference at the 5% levels, indicating that the treatment groups diverge from very early in the trial. The regression analysis found a statistically significant difference between the slopes for the two treatments ($p = 0.004$).

Femoral Neck. There were no significant changes in the BMD from baseline in the placebo or the etidronate group (Fig. 2). At 2 years there was no significant difference between the two groups (p = 0.314). The estimated difference was 0.97% (SEM 1.17%).

Trochanter. BMD of the trochanter remained constant over the 2-year period in the placebo group. There was a significant increase in the BMD of the etidronate group (Fig. 3) at week 26 and at week 78 ($p > 0.030$), and a nearly significant increase at week 104 (p = 0.055). At 2 years there was no significant difference between the two groups (p = 0.132). The estimated difference was 1.64% (SEM 1.08%).

Ward's Triangle. There was a significant decrease from baseline in the placebo group at week 104 ($p > 0.050$). There was no significant decrease in the etidronate group at any point. At 2 years there was no significant difference between the two groups (p = 0.213). The estimated difference was 1.41% (SEM 1.56%).

Distal Radius. In both groups there was no significant change from baseline, with a plateau in the BMD of the distal radius over the first year and then a slight progressive bone loss from baseline over the second year. At 2 years there was no significant difference between the two groups (p = 0.714).

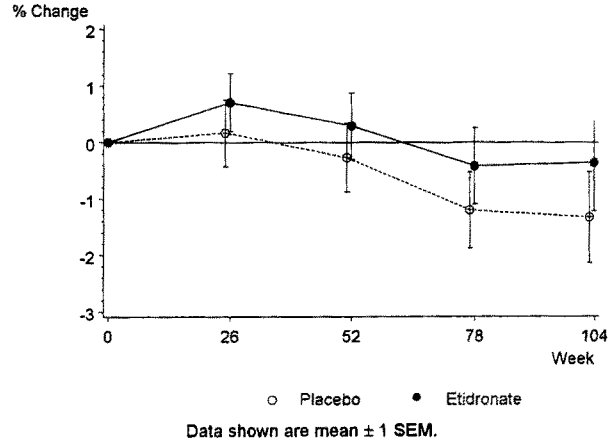

Fig. 2. Femoral neck BMD: mean percentage change from baseline.

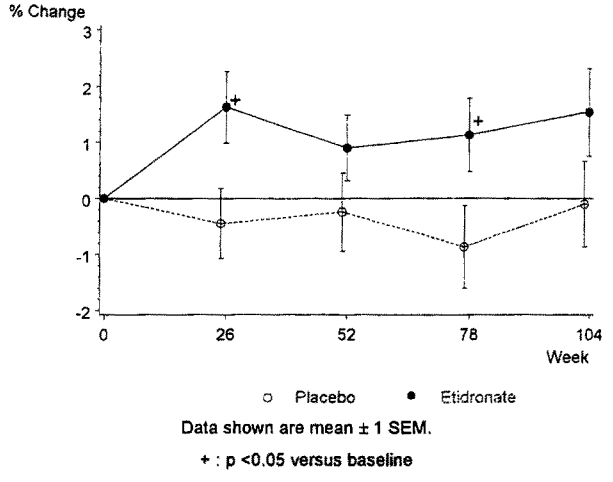

Fig. 3. Trochanter BMD: mean percentage change from baseline.

Biochemical Parameters

Serum Alkaline Phosphatase Levels. There were no significant changes in serum alkaline phosphatase level in the placebo group at any time point over the 2-year period. There was a significant decrease from baseline in the etidronate group at all timepoints ($p > 0.001$) (Fig. 4). An analysis of the first time point (week 26) showed a significant difference between the two groups at the 5% level (p = 0.01), indicating that the two treatments diverge, with respect to serum alkaline phosphatase level, from very early in the trial. At 2 years there was a significant difference between the two groups (p = 0.019). The estimated treatment difference was −12.0% (SEM 3.2%; 95% CI −18.2 to −5.7).

Serum Osteocalcin Level. There was no change in serum osteocalcin levels in the placebo group over the first year and an increase over the second year. There was a significant decrease in serum osteocalcin from baseline in the etidronate group at all timepoints ($p > 0.001$),

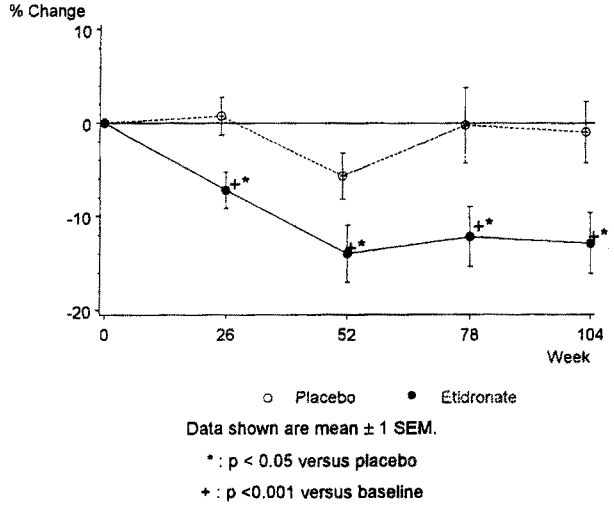

Fig. 4. Serum alkaline phosphatase: mean percentage change from baseline.

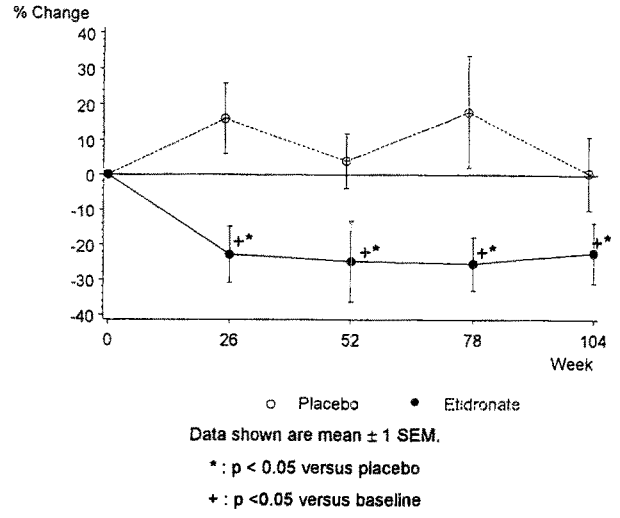

Fig. 5. Urinary N-telopeptide/creatinine ratio: mean percentage change from baseline.

except week 104. The absence of a significant change in the etidronate group at week 104 was unexpected. However, one patient in the etidronate group had a 499% change from baseline at week 104; if this outlying values was omitted, the mean treatment difference from baseline would have been −14.1% ± 7.8%. The estimated difference between treatment groups was −1.4% (SEM 14.3%; $p = 0.116$).

Urinary N-Telopeptide/Creatinine Rato. There were no significant changes from baseline in urinary N-telopeptide/creatinine ratios in the placebo group at any timepoints (Fig. 5). There was a significant decrease from baseline in the etidronate group at all timepoints ($p > 0.036$). At 2 years there was a significant difference between the two groups ($p = 0.047$). The estimated difference was −22.9% (SEM 13.7%; 95% CI −50.2 to 4.5).

Urinary Hydroxyproline/Creatinine and Calcium/Creatinine Ratios. There was no change from baseline in either the placebo or etidronate group. The differences between the groups were small relative to the precision of the treatment means.

Adverse Events

Of the 109 women in the study, 92 (84%) experienced one or more AE (46 in each group). Etidronate was generally well tolerated and its AE profile was similar to that of placebo. Sixteen women (14.7%) experienced one or more serious AE during the study. There were 13 reports in 9 women in the placebo group and 11 reports in 7 women in the etidronate group. Abdominal pain was reported in 15 (13.8%): 7 reports in 6 women in the placebo group and 8 reports in 7 women in the etidronate group. There were 37 other digestive AE reported in 19 women in the placebo group (34.6%) and 17 in 10 women in the etidronate group (18.6%). There were 3 moderate-to-severe upper gastrointestinal AE during the study. One woman on etidronate with a history of duodenal ulcer experienced a haemorrhagic relapse of the ulcer, recovered and continued in the study; 2 women receiving placebo had moderate oesophagitis and gastritis; both recovered. These events were not considered by the investigators to be related to the study drug.

Non-vertebral and Vertebral Fractures

In 10 women (9.2%) a fracture occurred during the study: 6 (10.9%) in the placebo group and 4 (7.4%) in the etidronate group. There were 9 non-vertebral fractures (ribs in 3, leg in 2, wrist, metacarpal phalange and nose, 1 each) and 1 vertebral fracture. Fractures were the result of trauma, except in 1 woman on placebo who had a rib fracture following a strain when gardening. One woman on etidronate had a traumatic vertebral fracture (a compression of the upper plateau of L1) reported at week 26 after a fall on her buttocks.

Discussion

The data from this study show that cyclical etidronate therapy prevents lumbar spine bone loss at 2 years in early postmenopausal women. At 2 years there was a significant difference between the etidronate group and the placebo group. There was a continuous progressive decline in lumbar spine BMD in the placebo group over the 2-year treatment period; in contrast, lumbar spine BMD was maintained in the etidronate group. A gain in lumbar spine BMD was documented after the first 6 months. At 2 years BMD of the hip and wrist were not significantly different between treatment groups. This may be due to the lower rate of bone turnover at cortical sites or the effect of the calcium treatment or the power of the study, as femoral neck BMD was consistently higher in the etidronate group compared with the placebo group. The study population, at high risk of bone loss in the early postmenopausal period, or a low compliance with the treatment drug not reflected by tablet counting, could explain the moderate increment in bone density in the etidronate-treated group. The supplementation with calcium in the placebo group may explain why the difference between the two groups was less than expected. Similar results have been reported with etidronate [16,17] and other bisphosphonates [18–20].

A clear reduction in bone turnover was obtained as evidenced by a significant decrease in serum alkaline phosphatase level and in urinary N-telopeptide/creatinine ratio in the etidronate group. This difference was observed as early as the first time point (week 26). Similarly a significant decrease in the serum osteocalcin level was also observed in the etidronate group over the first year of treatment which plateaued over the first 6 months of the second year. The minimal changes in

urinary hydroxyproline/creatinine or urinary calcium/creatinine ratios may be related to the greater variability observed with these biochemical parameters of bone. These results are similar to those recently reported in similar populations by Herd et al. [16] and Meunier et al. [17].

Etidronate was well tolerated and the incidence of adverse events was comparable to that observed in the placebo group.

In conclusion, the results of this study indicate that cyclical etidronate therapy can prevent trabecular bone loss, with no deleterious effect on cortical bone, in the first 5 years of menopause and that the therapy has a very high safety margin. This safety margin is important for a "preventive" treatment in healthy individuals. The demonstrated effects of cyclical therapy with etidronate and calcium permit this regimen to be considered as a therapeutic option for the prevention of postmenopausal osteoporosis.

References

1. Hui SL, Slemenda CW, Johnston CC. Baseline measurement of bone mass predicts fracture in white women. Ann Intern Med 1989;111:355–61.
2. Melton LJ, Atkinson EJ, O'Fallon WM, et al. Long-term fracture prediction by bone mineral assessed at different skeletal sites. J Bone Miner Res 1993;8:1227–33.
3. Cummings SR, Nevitt MC, Browner WS, et al. Risk factors for hip fractures in white women. Study of Osteoporotic Fractures Group. N Engl J Med 1995;332:767–73.
4. Black DM, Cummings SR, Gennant HK, et al. Axial and appendicular bone density predict fractures in older women. J Bone Miner Res 1992;7:733–8.
5. Christiansen C. The different routes of administration and the effect of hormone replacement therapy on osteoporosis. Fertil Steril 1994;62:152S–6S.
6. Ettinger B, Genant HK, Cann CE. Long-term estrogen replacement therapy prevents bone loss and fractures. Ann Intern Med 1985;102:319–24.
7. Felson DT, Zhang Y, Hannan MT, et al. The effect of postmenopausal estrogen therapy on bone density in elderly women. N Engl J Med 1993;329:1141–6.
8. Sagraves R. Estrogen therapy for postmenopausal symptoms and prevention of osteoporosis. J Clin Pharmacol 1995;35:S2–10.
9. Griffing GT, Allen SH. Estrogen replacement therapy at menopause. How benefits outweigh risks. Postgrad Med 1994;96(5):131–40.
10. Colditz GA, Hankinson SE, Hunter DJ, et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women (see comments). N Engl J Med 1995;332:1589–93. Note: comment in N Engl J Med 1995;332:1638.
11. Papapoulos SE. The role of bisphosphonates in the prevention and treatment of osteoporosis. Am J Med 1995;10:315–24.
12. Fleisch H. The use of bisphosphonates in osteoporosis. Br J Clin Pract 1994;48:323–6.
13. Storm T, Thamsborg G, Steiniche T, et al. Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. N Engl J Med 1990;322:1265–71.
14. Watts NB, Harris ST, Genant HK, et al. Intermittent cyclical etidronate treatment of postmenopausal osteoporosis. N Engl J Med 1990;323:73–9.
15. Harris ST, Watts NB, Jackson RD, et al. Four-year study of intermittent cyclic etidronate treatment of postmenopausal osteoporosis: three years of blinded therapy followed by one year of open therapy. Am J Med 1993;95:557–67.
16. Herd RJM, Blake GM, Ryan PJ, et al. A 152 patient double blind placebo controlled study of cyclical etidronate therapy for the prevention of early postmenopausal bone loss. J Bone Miner Res 1995;10:S153.
17. Meunier PJ, Confavreux C, Tupinon I, et al. Cyclical etidronate therapy prevents bone loss in the early postmenopausal period. J Bone Miner Res 1995;10:S357.
18. Reginster JY Deroisy R, Denis D, Colette J, Lecart MP, Sarlet N, Ethgen D, Franchimont P. Prevention of postmenopausal bone loss by tiludronate. Lancet 1989; 2:1469–71.
19. Filliponi P, Pedetti M, Fedeli L, et al. Cyclical clodronate is effective in preventing postmenopausal bone loss: a comparative study with transcutaneous hormone replacement therapy. J Bone Miner Res 1995;10:697–703.
20. Eisman JA, Christiansen C, McClung M, et al. Alendronate prevents bone loss at the spine and hip in recently postmenopausal women. J Bone Miner Res 1995;10:S176.

Received for publication 26 June 1996
Accepted in revised form 22 November 1996