Articles

Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures

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Summary

Background Previous studies have shown that alendronate can increase bone mineral density (BMD) and prevent radiographically defined (morphometric) vertebral fractures. The Fracture Intervention Trial aimed to investigate the effect of alendronate on the risk of morphometric as well as clinically evident fractures in postmenopausal women with low bone mass.

Methods Women aged 55–81 with low femoral-neck BMD were enrolled in two study groups based on presence or absence of an existing vertebral fracture. Results for women with at least one vertebral fracture at baseline are reported here. 2027 women were randomly assigned placebo (1005) or alendronate (1022) and followed up for 36 months. The dose of alendronate (initially 5 mg daily) was increased (to 10 mg daily) at 24 months, with maintenance of the double blind. Lateral spine radiography was done at baseline and at 24 and 36 months. New vertebral fractures, the primary endpoint, were defined by morphometry as a decrease of 20% (and at least 4 mm) in at least one vertebral height between the baseline and latest follow-up radiograph. Non-spine clinical fractures were confirmed by radiographic reports. New symptomatic vertebral fractures were based on self-report and confirmed by radiography.

Findings Follow-up radiographs were obtained for 1946 women (98% of surviving participants). 78 (8·0%) of women in the alendronate group had one or more new morphometric vertebral fractures compared with 145 (15·0%) in the placebo group (relative risk 0·53 [95% CI 0·41–0·68]). For clinically apparent vertebral fractures, the corresponding numbers were 23 (2·3%) alendronate and 50 (5·0%) placebo (relative hazard 0·45 [0·27–0·72]). The risk of any clinical fracture, the main secondary endpoint, was lower in the alendronate than in the placebo group (139 [13·6%] *vs* 183 [18·2%]; relative hazard 0·72 [0·58–0·90]). The relative hazards for hip fracture and wrist fracture for alendronate versus placebo were 0·49 (0·23–0·99) and 0·52 (0·31–0·87). There was no significant difference between the groups in numbers of adverse experiences, including upper-gastrointestinal disorders.

Interpretation We conclude that among women with low bone mass and existing vertebral fractures, alendronate is well tolerated and substantially reduces the frequency of morphometric and clinical vertebral fractures, as well as other clinical fractures.

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Introduction

Osteoporosis is a common disorder that is a contributing factor in about 1·5 million fractures per year among women in the USA alone, with an estimated treatment cost of more than US$10 billion.[1] On average, a 50-year-old white woman has a risk of hip fracture during her remaining lifetime of about 16%.[2] About 1·7 million hip fractures occurred world wide in 1990.[3]

Randomised trials have shown increases in bone mass with several treatments, including oestrogen,[4,5] calcitonin,[6] calcitriol,[7] sodium fluoride,[8,9] and bisphosphonates.[10–12] Trials of some of these drugs have also reported reductions in the incidence of vertebral fracture,[4,9,11,12] although some were small and of short duration, and in some the outcome was decrease in vertebral height. Only about a third of radiographically diagnosed vertebral fractures cause symptoms;[13] the effect of these agents on clinically evident fractures is uncertain. A combination of calcium and vitamin D reduced the incidence of hip and non-spine fracture in very elderly women in nursing homes,[14] and long-term use of oestrogen has been associated with reduced risk of hip fracture in observational studies.[15] No randomised trial has shown, however, a reduction in risk of hip fracture in community-dwelling women.

Liberman and colleagues[12] reported that the aminobisphosphonate alendronate sodium (alendronate) increases bone mineral density (BMD) at the spine and hip and in the whole body and reduces the risk of radiographically defined vertebral fracture in women with low BMD. Their study did not, however, have sufficient power to demonstrate a significant effect on non-vertebral fractures.

The Fracture Intervention Trial was designed to find out the effect of alendronate on the frequencies of vertebral and non-vertebral fractures in postmenopausal women with low bone mass.[16] The investigation was carried out as two separate studies in women with and without vertebral fractures at baseline. We report here the results among women with at least one vertebral fracture at recruitment.

Methods

Participants were recruited from population-based listings in 11 metropolitan areas of the USA. All women in the Fracture Intervention Trial were aged between 55 and 81 years at baseline, had been postmenopausal for at least 2 years, and had femoral-neck BMD of 0·68 g/cm^2 or less (QDR-2000 Hologic, Waltham, MA, USA), about 2·1 SDs below peak bone mass based on the manufacturer's normative data. Details of the study design and methods have been published previously.[16] We excluded women with peptic-ulcer disease (a single hospital admission for upper-gastrointestinal bleeding or two or more documented ulcers within the preceding 5 years), dyspepsia requiring daily treatment, abnormal renal function (serum creatinine >144 µmol/L), major medical problems that would be likely to preclude participation for 3 years, severe malabsorption syndrome, uncontrolled hypertension (blood pressure >210 mm Hg systolic or >105 mm Hg diastolic), myocardial infarction during the previous 6 months, unstable angina, or evidence of disturbed thyroid or parathyroid function. We also excluded women who had taken oestrogen or calcitonin within the preceding 6 months or bisphosphonates or sodium fluoride (>1 mg daily for 2 weeks or longer) at any time. All women provided written informed consent, and the study protocol was approved by the institutional review board at each participating clinical centre.

The initial dose of alendronate was 5 mg daily; however, data that became available in November, 1993, from other studies of alendronate indicated that a 10 mg dose produced significantly greater increases in bone mass than 5 mg, with similar tolerability. Therefore, the dose was increased from 5 mg to 10 mg for each participant at her 24-month clinic visit; the double-blinding was maintained. The placebo pills were identical to the active treatment in appearance and all contents except alendronate.

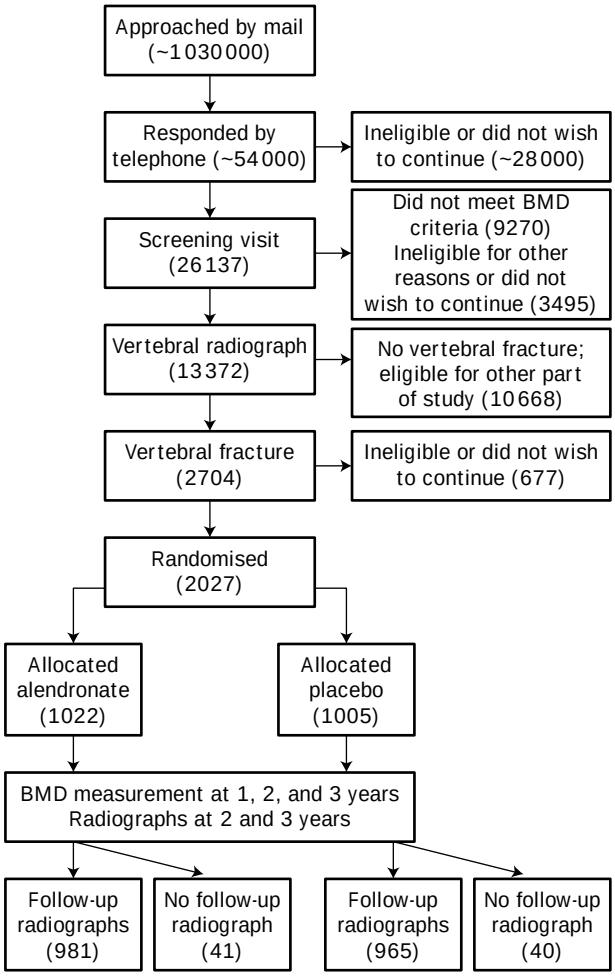


Figure 1: **Trial profile**

Participants were instructed to take one tablet of the study drug daily with at least 100 mL water, having fasted overnight, and at least 30 min before breakfast; they were told not to lie down within 30 min of taking the medication. Other medications prescribed to be taken in the fasting state could also be taken before breakfast, with the exception of calcium supplements, antacids, tetracyclines, sucralfate, or bile-acid-binding resins, which participants were asked to take after breakfast. Daily calcium intake was estimated by food-frequency questionnaire,[17] and participants in both groups who had calcium intakes less than 1000 mg were given a supplement providing 500 mg elemental calcium (as the carbonate salt) and 250 IU vitamin D. About 82% of participants received the supplement at the randomisation visit. The proportion of participants receiving supplements was similar at baseline (83·4% placebo, 81·2% alendronate) and throughout follow-up in the two treatment groups.

Women were randomly assigned treatment in blocks of ten, with stratification within clinical centre. Several measures were used to ensure maintenance of masking: all investigators involved with outcome and adverse-experience data were unaware of treatment assignment; participants and clinicians were not told the results of BMD measurements during follow-up; and, at the coordinating centre, the treatment assignments were available only to the statistician responsible for reports to the Data and Safety Monitoring Board. When bone loss (as monitored by the coordinating centre) exceeded predetermined values, the clinical centre investigators were informed of the bone loss (but not treatment assignment) and could, at their discretion, discuss these results with the participants or their personal physicians.

BMD was measured at the hip, posterior-anterior spine, and lateral spine and in the whole body on all participants. BMD of the forearm was measured in a random sample of 20% of participants. Follow-up measurements were made each year, except for whole-body BMD, which was measured only at the start and end of the study. We analysed percentage change in BMD from baseline to each visit. Quality control efforts included daily scanning with local phantoms, regular cross-clinic comparison of scans performed on a study-wide phantom, central review of a random sample of scans, and regular training and certification of each densitometry operator.[16]

Lateral radiographs were obtained at baseline and at 24 months and 36 months after randomisation.[18] Vertebral morphometry was done with a translucent digitiser and cursor.[19] Six points defining the anterior, middle, and posterior heights were marked on each vertebra.[16]

Baseline vertebral fractures were defined as previously described:[16] a woman was classified as having a fracture if any of the ratios of vertebral heights was more than 3 SDs below the mean population norm for that vertebral level.[20,21]

A new vertebral fracture was defined as a decrease of 20% and at least 4 mm in any vertebral height from the baseline radiograph to that taken at the end of the study. Each fracture was confirmed by a repeat digitisation of the involved vertebral body. In addition, vertebrae classified as having a new fracture by morphometry but not judged to be fractured by the morphometry technicians were reviewed by the study radiologist (HKG), who either confirmed or disqualified the fracture. Vertebrae judged to be fractured by the morphometry technicians, but which could not be digitised because of technical problems or other disease processes, were also reviewed by the study radiologist. If he identified a new fracture, the vertebra was classified as fractured. All evaluations by the technicians and the radiologist used a semiquantitative method.[22] Technicians were trained and certified by the radiologist before the study. The technicians and the study radiologist remained unaware of treatment allocation during their assessments.

Clinical fractures were initially reported by participants and confirmed by a required written report of a radiological procedure (radiograph, bone scan). As planned in the protocol, we excluded pathological fractures (eg, those due to malignant disease), those due to excessive trauma (sufficient to cause a fracture in young individuals with normal bone mass), and those involving the face and skull, because of the lack of association with osteoporosis.[23]

	Placebo (n=1005)	Alendronate (n=1022)
Age distribution		
<65 years	15·8%	16·7%
65–74 years	56·8%	57·4%
75–81 years	27·4%	25·8%
Mean (SD) age in years	71·0 (5·6)	70·7 (5·6)
Mean (SD) BMD in g/cm²		
Femoral neck	0·56 (0·07)	0·57 (0·07)
Posterior-anterior spine	0·79 (0·14)	0·79 (0·14)
Vertebral fractures at baseline		
1	68%	70%
2	17%	17%
⩾3	15%	13%
History of postmenopausal fracture*	58%	57%
Self-rated health status		
Very good/excellent	58%	59%
Good	35%	34%
Fair/poor	7%	8%
Mean (SD) anthropometry		
Baseline height (cm)	159 (6·3)	159 (6·1)
Body-mass index (kg/cm²)	25·6 (4·2)	25·5 (4·2)
Mean (SD) calcium intake in mg daily	619 (397)	652 (417)
Smoking status		
Current	12%	10%
Ever	33%	36%
Never	54%	53%

*After age 45 years.

Table 1: **Baseline characteristics of randomised groups**

Clinical vertebral fractures were defined as those that came to medical attention and were reported to the clinical centres by the participants. A copy of the radiograph obtained by the patient's physician was sent to the coordinating centre and compared with the baseline study radiograph. Because such clinical radiographs were not standardised for morphometry, an incident clinical vertebral fracture was defined by semiquantitative reading by the study radiologist.

Clinical fractures were grouped into six non-exclusive categories: all clinical fractures, non-spine clinical fractures, hip fractures, wrist fractures, and clinical vertebral fractures; and other clinical fractures (other than a wrist, spine, or hip fracture). Women were classified according to whether they had any fracture within each category. Since women could have more than one fracture and because the categories overlapped, women could be included in more than one category. The time to the first fracture was calculated as the time from randomisation to the event (non-spine clinical fractures) or to the onset of clinical symptoms (clinical vertebral fractures).

Height was calculated as the mean of two measurements with Harpenden stadiometers (Holtain Ltd, Pembrokeshire, UK).

Patients were questioned at each visit about any adverse event (including minor illnesses such as colds, heartburn, and constipation, as well as more serious events), irrespective of association with study therapy. Two general categories of adverse experiences were included in the analysis: those necessitating hospital admission and those resulting in discontinuation of study medication. Because of reports about a relation between bisphosphonates and upper-gastrointestinal disorders, we also analysed all such events as a group and within subcategories including abdominal pain, oesophagitis, oesophageal ulcers, oesophageal reflux/regurgitation, other oesophageal disorders, gastritis, gastric ulcer, other gastric disorders, and duodenal ulcers.

The study had a power of 99% to detect a 40% reduction in risk of vertebral fractures and a power of 90% to detect a 32% reduction, assuming a 6·5% annual incidence.[16] For the primary endpoint (morphometric vertebral fracture), for which time to event is unknown, we analysed the proportion of women with one or more fractures and calculated the relative risk as the ratio of the proportion of women with fractures in the alendronate and in the placebo group. Treatment-group differences were assessed by Mantel-Haenszel χ^2 statistics. For clinical fractures and adverse

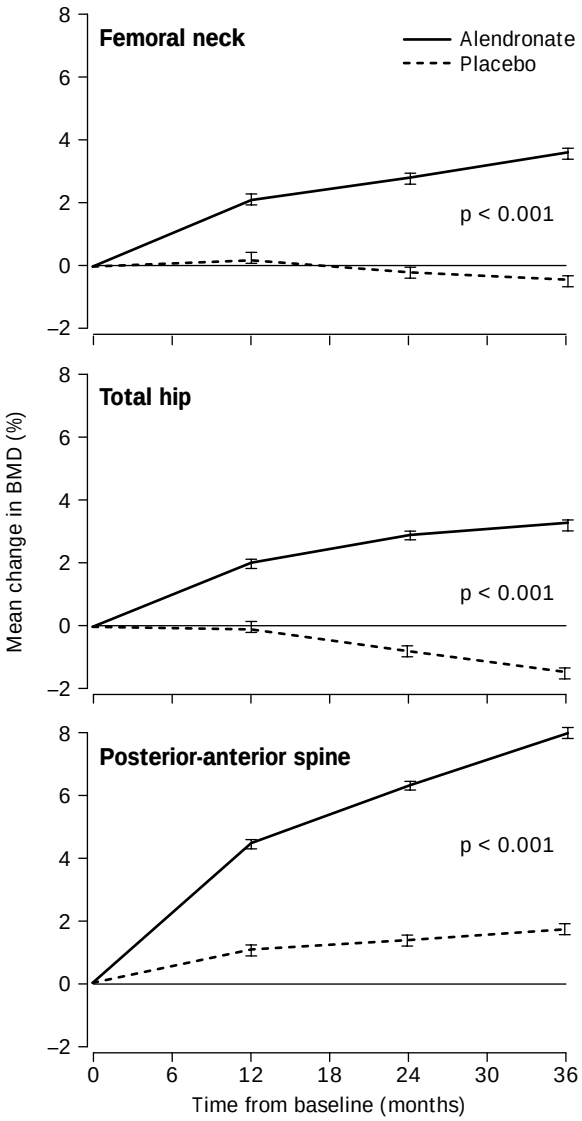


Figure 2: **Mean percentage changes in BMD from baseline in women receiving alendronate or placebo for 36 months**
Error bars=SE.

experiences, we report the proportion of women with at least one event. We analysed these events by survival analysis techniques and present relative hazard as the measure of association. We assessed significance of treatment-group differences by the log-rank test, and the estimate of the relative hazard was derived from a proportional hazards model by the likelihood ratio method.[24] We calculated significance of differences between the treatment groups for change in BMD and change in height by *t* tests. Statistical significance was defined as $p<0{\cdot}05$, two-sided.

Randomised patients who did not withdraw informed consent received full follow-up for all endpoints irrespective of compliance, to the extent possible. Analyses were by intention to treat. For calculation of follow-up time for those participants who were still alive but did not have closeout visits (n=33), we assumed that they had 36 months of follow-up irrespective of the date of their last contact with the clinical centre. In the analysis of morphometric vertebral fractures, the 24-month radiograph was used for participants for whom a 36-month radiograph was not available.

The independent Data and Safety Monitoring Board examined endpoints and adverse experiences by treatment group twice a year, with predefined operating guidelines. On Oct 29, 1995, the Board recommended that the remaining closeout visits be accelerated for completion in February, rather than May, 1996, because of the positive results. Since most of the visits had been

	Women with vertebral fractures*		Relative risk (95% CI)
	Placebo	Alendronate	
Morphometric fractures			
One or more	145 (15·0%)	78 (8·0%)	0·53 (0·41–0·68)
Two or more	47 (4·9%)	5 (0·5%)	0·10 (0·05–0·22)
Clinical vertebral fractures	50 (5·0%)	23 (2·3%)	0·45† (0·27–0·72)

*Among 965 women in placebo group, there were 240 morphometric fractures in 145 women. Among 981 women in alendronate group, there were 86 morphometric fractures in 78 women. †Relative hazard.

Table 2: **Participants with new vertebral fractures**

completed or scheduled before this recommendation, its effect was to reduce the average follow-up by only 0·1 years.

Results

2027 women were recruited into the vertebral fracture arm of the Fracture Intervention Trial, 1022 to alendronate and 1005 to placebo (figure 1). Potential confounding variables were similarly distributed between the treatment groups (table 1). 97% of participants identified themselves as Caucasian, 1% as Asian, and 1% as African-American.

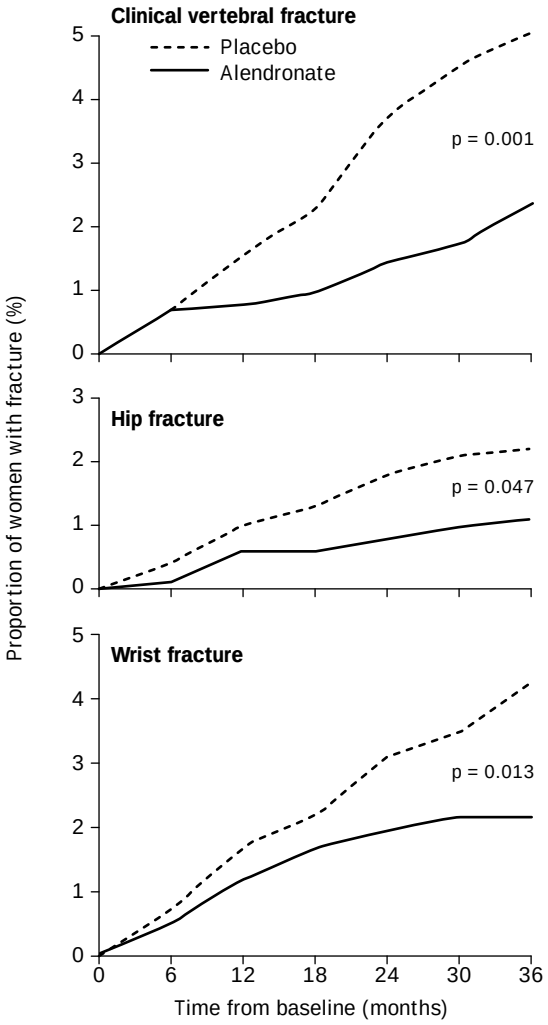
The average follow-up time was 2·9 years in both groups (range 0·7–3·5 alendronate, 0·3–3·5 placebo). Closeout information was obtained either in clinic or by telephone from 1949 participants; 68% occurred during the 3-year period of clinic visits (±2 months). At the time of the closeout visit, 87% of surviving placebo participants and 89% of surviving alendronate participants were still taking the study medication. Adherence to the treatment regimen as assessed by pill count was high throughout the trial; for example, at the closeout visit, of the participants still taking medication, 96% in each treatment group had taken at least 75% of their pills since the last clinic visit.

Treatment with alendronate significantly increased average bone mass compared with placebo at the femoral neck (4·1% difference, p<0·001), at the total hip (4·7%, p<0·001), and in the posterior-anterior lumbar spine (6·2%, p<0·001; figure 2). There were also significant differences in BMD between the alendronate and placebo groups at other measured sites, including the trochanter (6·1%, p<0·001), whole-body (1·8%, p<0·001), the lateral spine (6·8%, p<0·001), and the proximal forearm (1·6%, p<0·001).

Follow-up radiographs were obtained for 1946 participants, 98% of those surviving at study closeout. 1916 of these were obtained as part of the closeout visit, and for 30 other participants radiographs taken at 24 months were the latest available. The risk of new radiographic vertebral fractures was 47% lower (p<0·001) in the alendronate than in the placebo group; 145 women (15·0%) experienced new vertebral fractures in the placebo group compared with 78 women (8·0%) in the alendronate group (table 2). Treatment also substantially reduced the risk of multiple new vertebral fractures; 47 women in the placebo group and only five in the alendronate group had two or more new vertebral fractures (table 2); the corresponding numbers for four or more new vertebral fractures were 13 and none. The proportion of women with fractures between the baseline and 24-month radiographs was lower in the alendronate group than in the placebo group (42 [4·4%] *vs* 109 [11·6%]).

Significantly fewer women in the alendronate group than in the placebo group had clinical vertebral fractures (hazard reduction 55%, p<0·001; table 2, figure 3).

The cumulative proportion of women with any clinical fracture, the main secondary endpoint, was significantly



Number of women							
Placebo	1005	1004	1000	999	998	993	742
Alendronate	1022	1022	1021	1020	1015	1010	753

Figure 3: **Cumulative proportions of women with clinical vertebral fracture, hip fracture, or wrist fracture**

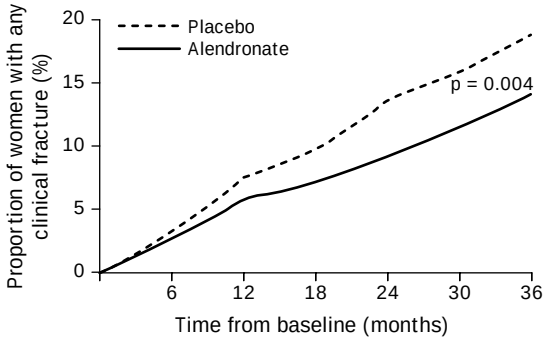
lower in the alendronate group than in the placebo group (table 3, figure 4). 148 women (14·7%) allocated placebo experienced at least one clinical non-vertebral fracture compared with 122 women (11·9%) allocated alendronate; this difference did not achieve statistical significance (p=0·063). There were significant differences between the groups in the cumulative proportions of women with hip fractures and wrist fractures (figure 3,

	Women with at least one fracture		Relative hazard (95% CI)
	Placebo	Alendronate	
Any clinical fracture*	183 (18·2%)	139 (13·6%)	0·72 (0·58–0·90)
Type of fracture			
Any non-vertebral	148 (14·7%)	122 (11·9%)	0·80 (0·63–1·01)
Hip	22 (2·2%)	11 (1·1%)	0·49 (0·23–0·99)
Wrist	41 (4·1%)	22 (2·2%)	0·52 (0·31–0·87)
Other†	99 (9·9%)	100 (9·8%)	0·99 (0·75–1·31)

*Including clinical vertebral fracture.

†Placebo *vs* alendronate: shoulder 3 *vs* 2, arm 22 *vs* 21, hand 7*vs* 5, fingers 6 *vs* 7, other small wrist bones 0 *vs* 3, ribs 12 *vs* 15, chest / sternum 1 *vs* 3, pelvis 9 *vs* 6, coccyx / sacrum 0 *vs* 2, leg 12 *vs* 9, ankle 10 *vs* 15, foot / metatarsal 17 *vs* 14, toes 9 *vs* 10, peri-prosthetic 1 *vs* 0.

Table 3: **Participants with clinical fractures**



Number of women							
Placebo	1005	1004	1000	999	998	993	742
Alendronate	1022	1022	1021	1020	1015	1010	753

Figure 4: **Cumulative proportion of women with any clinical fracture**

table 3). The numbers of women with clinical fractures at sites other than spine, hip, or wrist were similar in the two treatment groups.

The average height loss over 36 months of follow-up was 6·1 mm in the alendronate group compared with 9·3 mm in the placebo group (p<0·001).

Similar proportions of women in the two groups permanently discontinued study medication because of adverse experiences (96 [9·6%] placebo *vs* 78 [7·6%] alendronate; p=0·123). Adverse experiences resulting in hospital admission were significantly more common in the placebo than the alendronate group (300 [29·9%] *vs* 250 [24·5%], p=0·009). When hospital admissions for women with fractures were excluded, this difference was smaller (208 [20·7%] *vs* 186 [18·2%], p=0·17). Similar proportions of women died in the two treatment groups (21 [2·1%] *vs* 24 [2·3%], p=0·687).

402 women (40·0%) in the placebo group reported any upper-gastrointestinal problems compared with 422 (41·3%) in the alendronate group (p=0·67, table 4). There was no significant difference between the groups for any subcategory of upper-gastrointestinal events. During the 3rd year of follow-up (after the dose was increased to 10 mg daily), there was no increase in the rate of events within the alendronate group or in the number of events in the alendronate group compared with the placebo group for any category of upper-gastrointestinal adverse event (data not shown). When we limited the analysis to upper-gastrointestinal events resulting in hospital admission, there was no significant difference between the treatment groups (2·2% placebo *vs* 1·6% alendronate). About 75% of women in both groups took non-steroidal anti-inflammatory drugs for a month or longer during the study. The rates of all adverse events and gastrointestinal adverse events in women taking these drugs did not differ by study treatment.

	Placebo	Alendronate	p
Any upper-gastrointestinal event	402 (40·0%)	422 (41·3)	0·67
Type of event			
Dyspepsia	158 (15·7%)	155 (15·2%)	0·76
Abdominal pain	98 (9·8%)	121 (11·8%)	0·14
Nausea	97 (9·7%)	96 (9·4%)	0·88
Acid regurgitation/reflux	71 (7·1%)	71 (6·9%)	0·90
Gastritis	20 (2·0%)	24 (2·3%)	0·58
Gastric ulcer	16 (1·6%)	7 (0·7%)	0·05
Other gastric	2 (0·2%)	4 (0·4%)	0·43
Oesophagitis	4 (0·4%)	7 (0·7%)	0·38
Oesophageal ulcer	2 (0·2%)	3 (0·3%)	0·67
Other oesophageal	11 (1·1%)	16 (1·6%)	0·36
Duodenal ulcer	6 (0·6%)	2 (0·2%)	0·15
Peptic ulcer	7 (0·7%)	3 (0·3%)	0·22

Table 4: **Participants with upper-gastrointestinal adverse experiences**

Discussion

We found that postmenopausal women with low bone mass and pre-existing vertebral fractures who received alendronate had a lower incidence of several types of fractures than women who received placebo. Our findings confirm those of Liberman and colleagues,[12] and show in addition to the effect on radiographically defined vertebral fractures, effects on symptomatic vertebral fractures, hip fractures, and wrist fractures.

This randomised trial found a significant reduction in the risk of hip fractures among community-dwelling postmenopausal women. Chapuy and colleagues[14] showed (with their intention-to-treat analysis) that daily supplementation with both calcium and vitamin D reduced the risk of hip and other non-spine fractures by about 30% among elderly women in nursing homes, many of whom had deficiency of vitamin D and low calcium intake. Observational studies have consistently found that women who are currently taking oestrogen and who have been taking it for 5–10 years or longer have a lower risk of hip fracture than non-users;[15,25] however, there have been no randomised trials of the effect of oestrogen on hip or other clinical fractures. Hip fractures have the most serious consequences and account for most of the costs of osteoporosis; our findings suggest that use of alendronate for women at increased risk of hip fracture might reduce the disability and the costs of osteoporotic fractures. However, a formal analysis of the costs and effects is required to find out how alendronate can be used most cost-effectively.

Most vertebral fractures are symptomless and escape clinical recognition; only a third of the radiographically defined vertebral fractures that occurred during our trial were recognised clinically. However, alendronate therapy reduced the risk of clinically recognised and radiographically defined vertebral fractures to a similar extent. Alendronate treatment had an even stronger effect on multiple vertebral fractures.

Randomised trials have found that several other medications reduce the risk of radiographically defined vertebral fractures among women who already have a vertebral fracture. Lufkin and colleagues[4] found that 1 year of treatment with transdermal oestradiol decreased the risk of radiographically defined vertebral fractures. Two 3-year studies of cyclical administration of etidronate also showed a reduction in the rate of vertebral fractures during 2 of the 3 follow-up years;[10,11] however, neither showed a significant reduction in risk when the whole 3-year follow-up period was included in the analysis.[10,26] A small trial also suggested that calcitonin decreased the rate of new vertebral fractures, despite the negligible effect on bone density.[6] In a comparison of calcitriol and calcium in postmenopausal women, rates of vertebral and non-vertebral fractures were lower among those assigned calcitriol, but interpretation of that study is limited by the differences in treatment with calcium and the design (single-blind).[7] A low dose of a slow-release preparation of sodium fluoride, given with calcium citrate, may reduce the risk of new vertebral fractures;[9] however, there is

concern about the potential adverse effects of fluoride on the risk of stress fractures and hip fractures.

We carried out a full intention-to-treat analysis and attempted to obtain maximum follow-up, irrespective of whether participants continued to take study medication. We were able to obtain follow-up for the full study period for more than 98% of the surviving participants. In addition, we analysed the numbers of women with fractures and thus avoided the statistical problems encountered when the total number of fractures (with the possibility of multiple fractures per woman) is used as the primary endpoint. Furthermore, to keep to a minimum false-positive diagnoses of vertebral fractures, we chose a stringent cut-off point (20% vertebral height decrease rather than 15%) to define a new fracture, and required a radiological semiquantitative confirmation of each fracture.

This arm of the Fracture Intervention Trial included only women who had vertebral fractures at recruitment. These women are at substantially higher risk of subsequent vertebral and non-vertebral (including hip) fractures than women free of fractures.[27,28] A previous analysis of results from two trials of alendronate in women with low bone mass showed a reduction in radiographically defined vertebral fractures.[12] The reduction in vertebral fracture frequency among those without prevalent fractures (80% of the cohort) in that study was similar to the decrease observed in our study, but few such patients had vertebral fractures, and the reduction in this subgroup was not statistically significant. The effect of alendronate on fracture risk in women without existing vertebral fractures will be investigated in the other part of the Fracture Intervention Trial.

We observed no differences in the rates of adverse experiences between the alendronate or placebo groups. The lower rate of hospital admission in women treated with alendronate was attributable partly to the lower rate of fractures in that group. Clinical use of alendronate has occasionally been associated with oesophagitis and upper-gastrointestinal symptoms; however, we found no significant differences in the frequencies of such disorders between the alendronate and placebo groups. Although women with a history of gastrointestinal disease and those taking medication for dyspepsia less frequently than every day were eligible for this study, we should emphasise that women with a recent history of active peptic ulcer disease or complications (such as bleeding) and those using medication for dyspepsia daily were excluded. Also, participants were carefully instructed to take the medication with at least 100 mL water and not to lie down during the next 30 min. Careful use of alendronate and careful attention to dosing instructions may reduce the risk of oesophageal irritation.

The dose of alendronate was increased after 24 months because of evidence from other trials that 10 mg is more effective than 5 mg in increasing bone mass, and has a similar safety profile.[12] We found an effect of treatment on the vertebral fracture endpoint after 24 months of therapy, although this study cannot compare the efficacy of the two doses.

We found no significant reduction in the risk of fractures other than of the spine, hip, and wrist; such fractures constitute a heterogeneous group with variable relations to low bone mass.[23] In addition, they were not a primary endpoint of the study, so the power to detect an effect was limited.

Spinal bone density increased slightly in the placebo group, as has been seen previously.[29] This increase may be due to progression of degenerative osteoarthritic changes in the spine, the effect of higher calcium and vitamin D intake, or the increased density that accompanies new vertebral fractures.[30]

Our trial has several limitations. We included only postmenopausal women with low bone density and vertebral fractures. Although the protocol encouraged recruitment of non-Caucasian women, 97% of those enrolled were Caucasian. The effect of alendronate on osteoporosis in African-American women is currently being investigated. Other trials are investigating the efficacy of alendronate in men with osteoporosis. Our trial continued for about 3 years; it could not address the important questions of the effect of longer-term treatment on the risk of fractures, how long treatment should be continued, and what happens to the fracture risk when treatment stops. These questions must be answered by longer-term studies. Lastly, our results may not be applicable to women living in institutions or those in poor health.

Since alendronate substantially reduces the risk of fractures, including hip fractures, this treatment may reduce the costly and disabling consequences of osteoporosis in women at high risk of fracture.

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