

# Effect of Alendronate on Risk of Fracture in Women With Low Bone Density but Without Vertebral Fractures

## Results From the Fracture Intervention Trial

Steven R. Cummings, MD; Dennis M. Black, PhD; Desmond E. Thompson, PhD; William B. Applegate, MD; Elizabeth Barrett-Connor, MD; Thomas A. Musliner, MD; Lisa Palermo, MA; Ronald Prineas, MD; Susan M. Rubin, MA; Jean C. Scott, PhD; Thomas Vogt, MD, MPH; Robert Wallace, MD; A. John Yates, MD; Andrea Z. LaCroix, PhD; for the Fracture Intervention Trial Research Group

**Context.**—Alendronate sodium reduces fracture risk in postmenopausal women who have vertebral fractures, but its effects on fracture risk have not been studied for women without vertebral fractures.

**Objective.**—To test the hypothesis that 4 years of alendronate would decrease the risk of clinical and vertebral fractures in women who have low bone mineral density (BMD) but no vertebral fractures.

**Design.**—Randomized, blinded, placebo-controlled trial.

**Setting.**—Eleven community-based clinical research centers.

**Subjects.**—Women aged 54 to 81 years with a femoral neck BMD of 0.68 g/cm<sup>2</sup> or less (Hologic Inc, Waltham, Mass) but no vertebral fracture; 4432 were randomized to alendronate or placebo and 4272 (96%) completed outcome measurements at the final visit (an average of 4.2 years later).

**Intervention.**—All participants reporting calcium intakes of 1000 mg/d or less received a supplement containing 500 mg of calcium and 250 IU of cholecalciferol. Subjects were randomly assigned to either placebo or 5 mg/d of alendronate sodium for 2 years followed by 10 mg/d for the remainder of the trial.

**Main Outcome Measures.**—Clinical fractures confirmed by x-ray reports, new vertebral deformities detected by morphometric measurements on radiographs, and BMD measured by dual x-ray absorptiometry.

**Results.**—Alendronate increased BMD at all sites studied ( $P < .001$ ) and reduced clinical fractures from 312 in the placebo group to 272 in the intervention group, but not significantly so (14% reduction; relative hazard [RH], 0.86; 95% confidence interval [CI], 0.73-1.01). Alendronate reduced clinical fractures by 36% in women with baseline osteoporosis at the femoral neck ( $>2.5$  SDs below the normal young adult mean; RH, 0.64; 95% CI, 0.50-0.82; treatment-control difference, 6.5%; number needed to treat [NNT], 15), but there was no significant reduction among those with higher BMD (RH, 1.08; 95% CI, 0.87-1.35). Alendronate decreased the risk of radiographic vertebral fractures by 44% overall (relative risk, 0.56; 95% CI, 0.39-0.80; treatment-control difference, 1.7%; NNT, 60). Alendronate did not increase the risk of gastrointestinal or other adverse effects.

**Conclusions.**—In women with low BMD but without vertebral fractures, 4 years of alendronate safely increased BMD and decreased the risk of first vertebral deformity. Alendronate significantly reduced the risk of clinical fractures among women with osteoporosis but not among women with higher BMD.

*JAMA*. 1998;280:2077-2082

OSTEOPOROSIS results in millions of fractures,<sup>1</sup> more than 400 000 hospital admissions, more than 44 million patient-days in nursing homes, and \$13.8 billion in health care expenditures among women and men yearly in the United States alone.<sup>2</sup> Alendronate sodium increases the density of mineral in bone and reduces the risk of vertebral fractures

**For editorial comment see p 2119.**

in women with osteoporosis.<sup>3,4</sup> In the Fracture Intervention Trial (FIT), we showed that 3 years of alendronate also reduced the risk of hip and wrist fractures by about 50% among women who had low bone mineral density (BMD) and vertebral fractures.<sup>5</sup> However, only 10%

From the Departments of Epidemiology and Biostatistics (Drs Cummings and Black and Mss Palermo and Rubin) and Medicine (Dr Cummings), University of California, San Francisco; Merck Research Laboratories, Rahway, NJ (Drs Thompson, Musliner, and Yates); Department of Preventive Medicine, University of Tennessee, Memphis (Dr Applegate); University of California, San Diego (Dr Barrett-Connor); University of Miami, Miami, Fla (Dr Prineas); University of Maryland, Baltimore (Dr Scott); Cancer Research Center of Hawaii, Honolulu (Dr Vogt); Department of Preventive Medicine, University of Iowa, Iowa City (Dr Wallace); and the Center for Health Studies, Group Health Cooperative, Seattle, Wash (Dr LaCroix).

The authors have received grant support from Merck for an extension of the Fracture Intervention Trial. Dr Applegate also receives other grant support from Merck. Dr Cummings, Dr Black, and Dr Applegate have received honoraria as speakers for Merck.

Members of the Fracture Intervention Trial Research Group are listed in reference 11.

Reprints: Steven R. Cummings, MD, Prevention Sciences Group, Box 0886, University of California, San Francisco, CA 94105 (e-mail: scummings@psg.ucsf.edu).

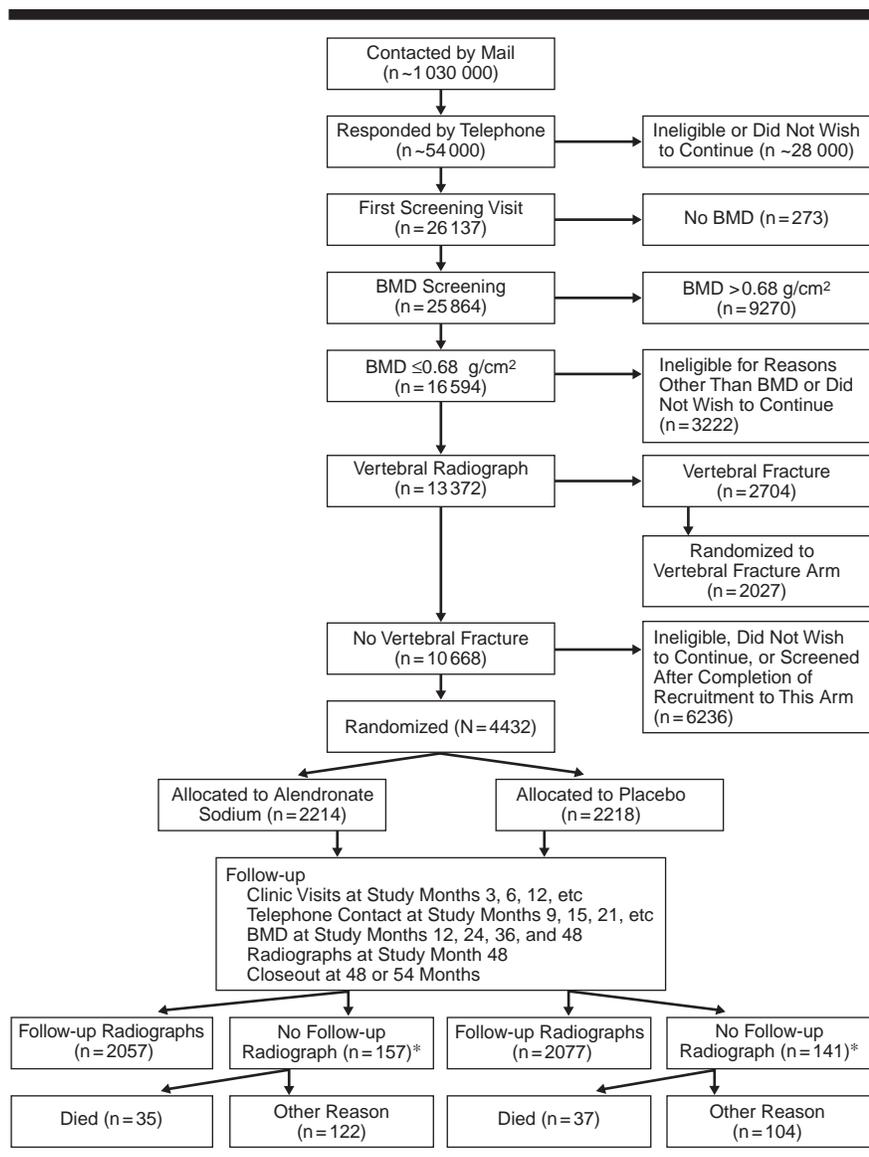


Figure 1.—Design and patient flow in the clinical fracture arm of the Fracture Intervention Trial. Asterisks indicate deaths included; BMD, bone mineral density.

to 15% of postmenopausal women have vertebral fractures,<sup>6,7</sup> and the effectiveness of treatments for the larger group of women who have low BMD but no prior vertebral fractures has not been specifically studied. The clinical fracture arm of FIT was designed to test the hypothesis that 4 years of treatment with alendronate would also reduce the risk of clinical fractures in postmenopausal women who have low BMD but no vertebral fracture. As planned, we analyzed the effect of alendronate in subgroups of women by tertile of initial levels of femoral neck BMD.

## METHODS

### Protocol

The trial was conducted at 11 clinical centers in the United States, with a co-

ordinating center at the University of California, San Francisco.<sup>8</sup> The FIT had 2 arms: the vertebral fracture arm,<sup>5</sup> which included women who had vertebral fractures, and the clinical fracture arm, which included women without vertebral fractures and is the subject of this article.

### Selection of Participants

We aimed to enroll 4000 women aged 55 through 80 years who had been postmenopausal for at least 2 years and had femoral neck BMD of 0.68 g/cm<sup>2</sup> (QDR-2000, Hologic Inc, Waltham, Mass) or less. At the time of enrollment, this was believed to correspond to a BMD value of at least 2 SDs below the mean of normal young adult white women, based on the manufacturer's reference values.

Subsequently, results from the Third National Health and Nutritional Examination Survey indicated that our inclusion criteria instead corresponded to 1.6 SD or more below the normal young adult mean.<sup>6</sup> Consequently, about one third of women in the trial actually had higher BMD than expected. Women were recruited principally by mass mailings (Figure 1).

We excluded women who had recent peptic ulcers or ulcers that required hospitalization, dyspepsia requiring daily treatment, significant renal or hepatic dysfunction, medical problems that precluded 3 years of participation, severe malabsorption, blood pressure exceeding 210 mm Hg systolic or 105 mm Hg diastolic, myocardial infarction within 6 months, unstable angina, hypothyroidism, hyperthyroidism, or hyperparathyroidism. We also excluded women who had taken estrogen or calcitonin within the preceding 6 months or bisphosphonates or sodium fluoride (>1 mg/d) at any time. Although women taking estrogen were excluded from entry into the trial, 246 (11.1%) in the placebo group and 204 (9.2%) in the alendronate group took estrogen at some time during the study. All women provided written informed consent and the protocol was approved by the appropriate institutional review boards.

### Assignment

Women were randomized in blocks of 10 that were stratified within clinical center. Treatment was assigned by computer-generated codes. Each bottle of medication was labeled with a nonrepeating allocation number that could be revealed only for safety concerns. Those who generated the allocation schedule were not allowed to communicate with anyone who assigned the study drugs.

### Treatment

The dosage of alendronate sodium was 5 mg/d for 2 years but was increased to 10 mg/d at the second annual visit because other trials suggested that 10 mg/d had greater effects on BMD. Participants were instructed to take the study drug with at least 120 mL (4 oz) of water in a fasting state and not lie down or eat or drink any other food or liquid for at least a half hour. Prescription medications that had to be taken in the fasting state could be taken before breakfast. Participants were instructed to take calcium supplements, antacids, tetracycline, sucralfate, or bile acid-binding resins after breakfast. Eighty-two percent of participants in each treatment group had dietary calcium intakes of less than 1000 mg/d; they were asked to take a

Table 1.—Baseline Characteristics of the Randomized Participants

	Placebo (n = 2218)	Alendronate Sodium (n = 2214)
Age, %, y		
<65	33.3	34.5
65-74	53.7	52.6
75-80	13.0	12.9
Mean (SD)	67.7 (6.1)	67.6 (6.2)
Bone mineral density, %, g/cm <sup>2</sup>		
Femoral neck, SDs below peak*		
>2.5	36.6	37.0
2.0-2.5	32.0	32.8
1.5-2.0	31.4	30.2
Mean (SD)	0.593 (0.06)	0.592 (0.06)
Posterior-anterior spine, mean (SD)	0.842 (0.13)	0.841 (0.13)
History of fractures since age 45 y, %	35	36
Self-rated health status, %		
Very good/excellent	67	69
Good	29	27
Fair/poor	5	4
Baseline height, mean (SD), cm	160 (6.0)	161 (6.0)
Body mass index, mean (SD), kg/m <sup>2</sup>	25.0 (4.0)	24.9 (3.9)
Dietary calcium intake, mean (SD), mg/d	638 (395)	634 (405)
Smoking, %†		
Current	10	10
Ever	35	37
Never	54	52

\*Peak bone density based on National Health and Nutrition Examination Survey reference data.

†Numbers may not add up to 100% because of rounding.

daily supplement containing 500 mg of elemental calcium (OsCal) and 250 IU of cholecalciferol (vitamin D). Women had study visits semiannually and all information regarding clinical fractures was forwarded to the coordinating center.

### Assessment of Outcomes

**Clinical Fractures.**—A clinical fracture was defined as one diagnosed by a physician. Self-reports of fractures were confirmed by written reports of radiographs or other tests. We excluded pathologic fractures or fractures due to trauma sufficient to fracture a normal bone in most young adults. Facial and skull fractures were excluded because they are not associated with low BMD.<sup>9</sup>

Before study unblinding, subgroups of clinical fractures were defined as non-spine fractures, hip fractures, wrist fractures, clinical vertebral fractures and clinical fractures other than a wrist, spine, or hip fracture. Participants could have more than 1 type of fracture and so could appear in more than 1 category.

**Radiographic Evidence of Vertebral Fractures.**—Lateral spine radiographs were obtained according to published guidelines<sup>10</sup> at baseline and 4 years after randomization. Women with vertebral fractures assessed by morphometry<sup>5,10-12</sup> were excluded from this arm of the study.

A new deformity, or radiographic vertebral fracture, was defined as a decrease of 20% and 4 mm or more in any vertebral height from baseline to the end of the study<sup>5,12</sup> and confirmed by a repeat

measurement of the involved vertebral body. All assessments were blinded to treatment allocation.

**Bone Mineral Density.**—Bone mineral density was measured at the hip, posterior-anterior spine, and in the whole body on all participants using Hologic QDR 2000 densitometers. Forearm BMD was measured (one third of the way up from the wrist to the elbow) in a 20% random sample of participants and lateral spine BMD was measured on 82% of participants. All BMD measurements were repeated annually except total body BMD, which was obtained at the start and end of the study. Quality control measures have been detailed elsewhere.<sup>8</sup>

**Stature.**—Height was calculated as the mean of 2 repeat measurements using Harpenden stadiometers (Holtain Ltd, Crymmych, Pembrookshire, England).

**Adverse Experiences.**—Patients were questioned at each contact regarding adverse events, defined as any untoward condition, including minor illnesses such as common colds. We analyzed all adverse experiences, including those requiring hospitalization or discontinuation of study medication. Because of reports about bisphosphonates and upper gastrointestinal tract disorders,<sup>13</sup> we analyzed upper gastrointestinal tract events by specific symptoms and diagnoses.

### Blinding

We maintained blinding in several ways. Collection and review of data were blinded to treatment assignment. Re-

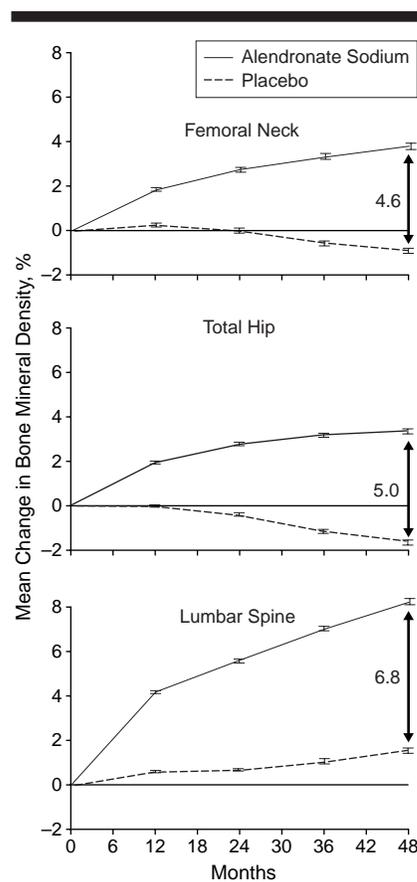


Figure 2.—Mean (SD) percentage changes in bone mineral density from baseline to 48 months in the alendronate and placebo groups.

sults of bone densitometry during follow-up were not available to participants or clinicians except when bone loss (monitored by the coordinating center) exceeded predetermined rates (8% over 1 year, 10% over 2 years, 12% over 3 years, etc, at the total hip or posterior-anterior spine). The appropriate clinical center investigator was informed of the bone loss but not the treatment assignment, and he/she, in turn, informed the participants or their primary care physicians. Finally, treatment assignments were kept in a locked file by 1 statistician at the coordinating center who was responsible for preparing reports to the data safety and monitoring board.

### Statistical Analysis

Assuming a 4% annual incidence of clinical fracture in placebo-treated women, the trial required 4000 women to detect a 25% decrease in risk with 90% power and an  $\alpha$  level of .05.<sup>8</sup> We recruited 4432 women and observed a 3.5% annual incidence of fracture in the placebo group, which provided 88% power to detect a 25% reduction in risk.

Clinical fractures and adverse experiences are reported as the proportion of

Table 2.—Participants With Clinical Fractures by Study Group

	Women With $\geq 1$ Fracture of Each Type			P Value
	Placebo, No. (%)	Alendronate Sodium, No. (%)	Relative Hazard (95% Confidence Interval)*	
Type of fracture				
Any clinical†	312 (14.1)	272 (12.3)	0.86 (0.73-1.01)	.07
Any nonvertebral	294 (13.3)	261 (11.8)	0.88 (0.74-1.04)	.13
Hip	24 (1.1)	19 (0.9)	0.79 (0.43-1.44)	.44
Wrist	70 (3.2)	83 (3.7)	1.19 (0.87-1.64)	.28
Other clinical‡	227 (10.2)	182 (8.2)	0.79 (0.65-0.96)	.02
Vertebral fractures§				
$\geq 1$	78 (3.8)	43 (2.1)	0.56 (0.39-0.80)	.002
$\geq 2$	10 (0.5)	4 (0.2)	0.40 (0.13-1.24)	.11

\*Data are relative risk for vertebral fractures.

†Data include clinical vertebral fractures.

‡Data include fractures other than hip, wrist, or spine.

§Among the 2218 women in the placebo group, there were 89 new vertebral fractures among 2077 women. Among the 2214 women in the alendronate group, there were 47 fractures among 2057 women. Vertebral fractures were based on x-ray findings alone.

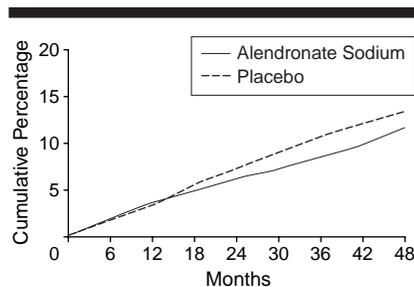


Figure 3.—Life-table graph of the cumulative proportion of women with any clinical fracture. Survival data are grouped in 6-month intervals.

women with 1 or more events. We used survival analysis with the log-rank test to analyze and test the statistical significance of differences between treatment groups. We present the results as the number and percentage of women with fractures along with relative hazards (RHs) and 95% confidence intervals (CIs) calculated by the likelihood ratio method.<sup>14</sup>

We analyzed the proportion of women with 1 or more radiographically detected vertebral fracture and present the rates in each group along with the relative risk (RR), calculated as the ratio of the proportion of women with fractures in the alendronate group compared with the placebo group. We used the Mantel-Haenszel  $\chi^2$  statistic to test the significance of differences between treatment groups. We used *t* tests to compute the statistical significance of differences between the treatment groups for changes in BMD and height. All *P* values are 2-sided. We also estimated the number needed to treat (NNT) for 4.25 years to prevent 1 fracture. All analyses followed an intention-to-treat design.

Before unblinding, we planned to analyze the effects of alendronate on the risk of clinical fractures, vertebral fractures, and bone densities in subgroups stratified by tertile of baseline BMD; in this analysis we use femoral neck BMD. The cutoff for the bottom tertile (femoral neck

BMD  $< 0.571$  g/cm<sup>2</sup>) represented a T score of  $-2.55$  or less, which is similar to the World Health Organization definition of osteoporosis as a T score of less than  $-2.5$ .<sup>12</sup> The middle tertile was 2.06 (0.631 g/cm<sup>2</sup>) to 2.56 SD, and the highest tertile was 1.6 (0.681 g/cm<sup>2</sup>) to 2.05 SDs below the normal young adult mean. Thus, for simplicity of presentation, we report the results in 3 ranges of T scores:  $-2.5$  or less,  $-2.0$  to  $-2.5$ , and  $-1.6$  to  $-2.0$  or more.

We tested the statistical significance of any interactions between BMD and the effect of treatment on the risk of clinical fractures by performing a proportional hazards analysis, which included terms for treatment, BMD (continuous), and treatment-by-BMD interaction.

#### Data Monitoring

An independent data and safety monitoring board examined end points and adverse events by treatment group semi-annually. Adjustments for repeated tests of significance required *P* = .046 for statistical significance of the main result.

#### RESULTS

A total of 4432 women were randomized, 2214 to alendronate and 2218 to placebo (Figure 1). Participants had a mean age of 68 years, 97% were white, and potential confounding variables were equally distributed between the 2 treatment groups (Table 1). Subjects were followed up for an average of 4.2 years; close-out contacts were completed by 4272 (96%) of the participants. At closeout, 82.5% of surviving participants randomized to placebo and 81.3% of those assigned to alendronate were still taking study medication. Of those taking study medication, 96% in each of the 2 treatment groups had taken at least 75% of their pills. Thirty-four participants (22 in the placebo group and 12 in the alendronate group) had stopped taking their study medication because their rate of bone loss exceeded predetermined limits.

#### Bone Mineral Density

Compared with placebo, treatment with alendronate increased average BMD at all measured sites (Figure 2). After 4 years, women in the placebo group lost an average of 0.8% of femoral neck BMD, while women in the alendronate group gained 3.8% (difference, 4.6%; *P* < .001). The placebo group lost an average of 1.6% of BMD in the total hip, while the alendronate group gained 3.4% (difference, 5.0%; *P* < .001). In the lumbar spine, the placebo group gained 1.5% vs an 8.3% gain in the alendronate group (difference, 6.6%; *P* < .001). Women who received alendronate also gained significantly more BMD than the placebo group in the trochanter (difference, 6.8%), total body (difference, 2.0%), lateral spine (difference, 7.1%), and ultradistal forearm (difference, 3.1%).

Alendronate increased BMD similarly in all subgroups of initial BMD. For example, it increased femoral neck BMD by 4.6% (95% CI, 4.0%-5.1%) in those with baseline femoral neck T scores of  $-2.5$  or less, 4.8% (95% CI, 4.2%-5.3%) in those with T scores of  $-2.0$  to  $-2.5$ , and 4.8% (95% CI, 4.2%-5.4%) in those with T scores of  $-1.6$  to  $-2.0$  or more.

#### Clinical Fractures

Clinical fractures, the primary end point, occurred in 312 women (14.1%) in the placebo and 272 women (12.3%) in the alendronate group (RH, 0.86; 95% CI, 0.73-1.01) (Table 2 and Figure 3). Twenty-four women (1.1%) in the placebo group and 19 women (0.9%) in the alendronate group had hip fractures (14% reduction; RH, 0.79; 95% CI, 0.43-1.44), while 70 (3.2%) in the placebo group and 83 (3.7%) in the alendronate group fractured a wrist (RH, 1.19; 95% CI, 0.87-1.64). Fewer women assigned to alendronate (*n* = 182, 8.2%) than to placebo (*n* = 227, 10.2%) had fractures at sites other than spine, hip, or wrist (RH, 0.79; 95% CI, 0.65-0.96; placebo-treatment difference, 2.0%; NNT, 50).

The effect of treatment on the risk of clinical fractures depended on initial femoral neck BMD (*P* = .01 for the interaction) (Table 3 and Figure 4). Alendronate significantly reduced the risk of clinical fractures by 36% (RH, 0.64; 95% CI, 0.50-0.82; placebo-treatment difference, 6.5%; NNT, 15) in women whose initial femoral neck T score was  $-2.5$  or less. However, 4 years of alendronate did not significantly affect risk of clinical fracture in those with higher BMD. We observed a 22% lower risk of clinical fracture in those whose T scores were more than 2.0 SDs below the normal mean (RH, 0.78; 95% CI, 0.65-0.94; placebo-treatment difference, 3.3%; NNT, 30) (Figure 4). Alendronate did not decrease the risk of fracture among sub-

jects whose initial T scores were greater than  $-2.5$  (RH, 1.08; 95% CI, 0.87-1.35).

In post hoc analyses, alendronate reduced the risk of hip fractures by 56% among women with a femoral neck T score of  $-2.5$  or less: 18 (2.2%) in the placebo group vs 8 (1.0%) in the alendronate group (RH, 0.44; 95% CI, 0.18-0.97; placebo-treatment difference, 1.2%; NNT, 81). There was no reduction in risk among those whose femoral neck T scores were more than  $-2.5$ : 6 (0.4%) in the placebo group vs 11 (0.8%) in the alendronate group (RH, 1.84; 95% CI, 0.70-5.36).

The effect of alendronate on the risk of wrist fractures also varied by baseline femoral neck BMD. There was no significant reduction among women with a T score of  $-2.5$  or less: 38 (4.7%) in the placebo and 34 (4.2%) in the alendronate group (RH, 0.88; 95% CI, 0.55-1.40). Similarly, we observed no reduction in risk among women with T scores of  $-2.0$  to  $-2.5$ : 20 (2.8%) in the placebo group vs 27 (3.7%) in the alendronate group (RH, 1.33; 95% CI, 0.75-2.4). Among those whose femoral neck T scores were more than  $-2.0$ , more fractures occurred in the treatment group ( $n = 22$ , 3.3%) than in the placebo group ( $n = 12$ , 1.7%; RH, 1.9; 95% CI, 1.0-4.0; placebo-treatment difference, 1.6%).

Stratification of the results by BMD of the total hip, spine, or other sites indicated that alendronate consistently decreased the risk of nonspine fractures among women with BMD T scores of  $-2.5$  or less but not among women with BMD T scores of more than  $-2.0$ . The apparent threshold for a significant effect of treatment on risk of clinical fractures varied by BMD measurement site from a T score of  $-2.5$  or less at the femoral neck and spine to less than  $-2.0$  at the total hip.

### Radiographic Vertebral Fractures

We obtained final follow-up radiographs for 4134 participants (95% of those surviving at that time). Alendronate reduced the overall risk of new radiographic vertebral fractures by 44%: 78 women (3.8%) in the placebo group developed at least 1 new fracture compared with 43 (2.1%) in the alendronate group (44% reduction; RR, 0.56; 95% CI, 0.39-0.80;  $P = .001$ ; placebo-treatment difference, 1.7%; NNT, 60) (Table 2). The risk of radiographic vertebral fractures was highest among women with the lowest BMD. Consequently, estimated NNTs increased from 35 among women with a femoral neck BMD T score of less than  $-2.5$  to 59 for those with T scores of  $-2.5$  to  $-2.0$ , and to approximately 363 for those with T scores of  $-2.0$  to  $-1.6$ .

Alendronate also reduced the mean loss of height by 1.5 mm over 4 years: 8.5 mm in the placebo group vs 7.0 mm in the alendronate group ( $P < .001$ ).

Table 3.—Effect of Alendronate Sodium on Risk of Clinical and Vertebral Fracture in T Scores of Femoral Neck Bone Mineral Density

T Score of Bone Marrow Density*	Clinical Fractures			Vertebral Fractures		
	Placebo, No. (%)	Alendronate, No. (%)	RH (95% CI)†	Placebo, No. (%)	Alendronate, No. (%)	RH (95% CI)†
$< -2.5$	159 (19.6)	107 (13.1)	0.64 (0.50-0.82)	44 (5.8)	22 (2.9)	0.50 (0.31-0.82)
$-2.5$ to $-2.0$	87 (12.3)	92 (12.7)	1.03 (0.77-1.39)	24 (3.6)	13 (1.9)	0.54 (0.28-1.04)
$-2.0$ to $-1.6$	66 (9.5)	73 (10.9)	1.14 (0.82-1.60)	10 (1.5)	8 (1.3)	0.82 (0.33-2.07)

\*T scores correspond to femoral neck bone mineral density in SDs below the bone density of young white women using data from the Third National Health and Nutrition Examination Survey.<sup>12</sup>  
†RH indicates relative hazard; CI, confidence interval.

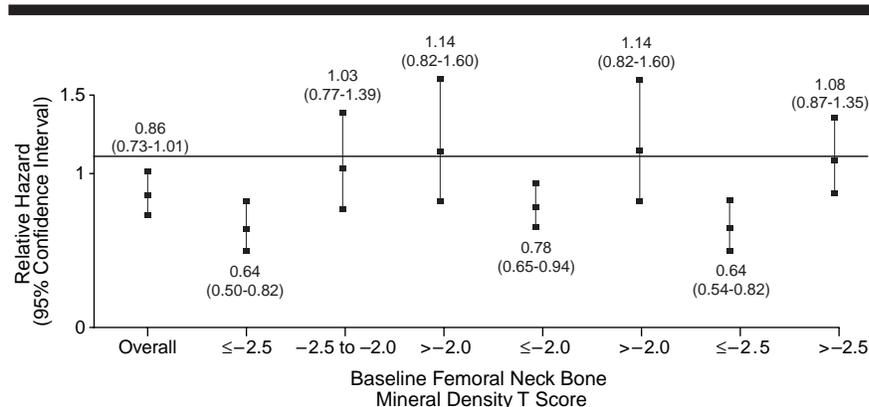


Figure 4.—Risk of a clinical fracture of any type grouped by stratum of femoral neck bone mineral density measured at baseline and by combinations of those strata.

Table 4.—Participants With Adverse Experiences by Treatment Group

Type of Adverse Experience	Placebo, No. (%)	Alendronate Sodium, No. (%)	Relative Hazard (95% Confidence Interval)
Any leading to permanent discontinuation	227 (10.2)	221 (9.9)	0.96 (0.80-1.16)
Any resulting in hospitalization	596 (26.9)	644 (29.1)	1.09 (0.98-1.22)
Deaths	40 (1.8)	37 (1.7)	0.92 (0.59-1.45)
Upper gastrointestinal tract events			
Any	1047 (47.2)	1052 (47.5)	1.00 (0.92-1.09)
Abdominal pain	325 (14.7)	322 (14.5)	0.99 (0.85-1.16)
Esophagitis	10 (0.5)	19 (0.9)	1.90 (0.90-4.26)
Esophageal ulcer	4 (0.2)	4 (0.2)	1.00 (0.24-4.23)
Other esophageal	41 (1.8)	44 (2.0)	1.07 (0.70-1.65)
Acid regurgitation/reflux	194 (8.7)	204 (9.2)	1.06 (0.87-1.29)

### Safety

Permanent discontinuations of study medication due to adverse experiences were similar in the 2 groups (Table 4). Similarly, there were no significant differences in rates of death or adverse experiences resulting in hospitalization. There were no significant differences between the groups in rates of abdominal pain, esophagitis, esophageal ulcer, gastric ulcer, duodenal ulcer, or other adverse upper gastrointestinal tract effects.

### COMMENT

We previously showed that alendronate decreased the risk of vertebral, hip, and wrist fractures by about 50% and all clinical fractures by 28% among women with vertebral fractures.<sup>5</sup> We have now found that 4 years of alendronate also de-

creased the risk of all clinical fractures, hip fractures, and vertebral deformity in women with hip BMD T scores below  $-2.5$  who did not have a vertebral fracture. An analysis by the National Osteoporosis Foundation concluded that estrogen or alendronate should be offered to postmenopausal women who have either vertebral fractures or osteoporosis confirmed by bone densitometry.<sup>15</sup> Our findings support those recommendations for the use of alendronate.

Although alendronate increased BMD to a similar degree regardless of initial density, we did not observe a significant decrease in the risk of clinical fractures in non-osteoporotic women. It is important to note that our study was not designed to pinpoint a threshold for this effect; it varied between T scores of  $-2.5$  or less at the femoral neck and spine to  $-2.0$  or less at the

total hip measurement sites. Why alendronate reduced clinical fractures more effectively in those with the lowest BMD is not clear. Alendronate may increase bone strength at least in part by decreasing the number of resorption pits on bone surfaces<sup>16-18</sup>; this might make a critical difference for the most fragile bones.

Alendronate reduced the risk of radiographically detected vertebral fractures by about half. Although most vertebral deformities elude clinical diagnosis, many cause pain and disability.<sup>19,20</sup> Women with radiographic vertebral fractures have an increased risk of vertebral, hip, or other fractures.<sup>21,22</sup> Thus, prevention of the first radiographic evidence of vertebral fracture may prevent disability and herald a decreased risk of other types of fractures. One needs to treat relatively few patients with osteoporosis, who have a high risk of fractures, to prevent a radiographic vertebral fracture, clinical fracture, or hip fracture. Although NNT estimates are not precise, it may be necessary to treat a few hundred women to prevent 1 radiographic vertebral fracture among women with a femoral neck T score of  $-2.0$  or more.

In 2 previous studies, alendronate reduced the risk of wrist fractures by 50% in women with vertebral fractures or osteoporosis.<sup>4,5</sup> In contrast, we found no overall reduction in risk of wrist fracture; alendronate appeared to increase the risk of wrist fractures in women with a femoral neck T score of more than  $-2.0$ .

It is not clear how long alendronate should be continued. To our knowledge, there are no data and no prospective study is under way to estimate the effect of more than 4 years of alendronate on risk of fractures. Treatment beyond 4 years may continue to improve or preserve BMD and maintain reduced bone turnover; this is being studied. Much of the antifracture effect of alendronate may be caused by reduction in bone resorption that occurs early and is sustained but does not increase over time.<sup>16,23-25</sup> Turnover repairs naturally accumulating microscopic damage.<sup>26</sup> There is no evidence that alendronate has detrimental effects on bone strength, microscopic bone structure, or fracture healing<sup>27</sup>; the effects of more than 4 years of treatment deserve study. Additionally, alendronate accumulates in bone and recirculates when bone containing alendronate is remodeled.<sup>27</sup> Thus, many years of treatment may produce self-sustaining concentrations of alendronate in bone such that the skeletal benefits of alendronate may continue after treatment is stopped.<sup>28</sup> On the other hand, if alendronate were to cause an adverse effect that has not yet been recognized, endogenous exposure to alendronate would also continue after stopping treatment.

Our results indicate that it would take more than 4 years of treatment to produce a substantial reduction in risk of clinical fractures in women who do not have osteoporosis. Some physicians may recommend long-term treatment with alendronate to preserve the density and structural integrity of bone in women without osteoporosis. Others may decide that it would be more prudent and cost-effective to limit alendronate treatment to women with osteoporosis, for whom there is clear evidence of reduction in risk of clinical fractures.

Four years of alendronate therapy did not significantly increase the risk of abdominal symptoms or gastrointestinal diagnoses. The risk of esophagitis, which has been occasionally reported with alendronate therapy,<sup>13</sup> was very low and not significantly different from placebo. We carefully instructed our participants to take their medication with at least 120 mL (4 oz) of water and not to lie down for a half hour. With the exception of some cases of esophagitis, our results indicate that when patients take alendronate correctly, upper gastrointestinal tract problems should not be attributed to alendronate and usually do not necessitate stopping treatment.

We conclude that 4 years of treatment with alendronate safely increases bone density and decreases the risk of radiographic vertebral fractures among women with low BMD. Alendronate treatment reduces the risk of clinical fractures among women with osteoporosis but not among those with hip or spine T scores of  $-2.0$  or more. The antifracture effectiveness of more than 4 years of treatment, especially among women without osteoporosis, is unknown.

This study was supported by funding from Merck Research Laboratories, Rahway, NJ.

Drafts of the manuscript were reviewed and changes were recommended by coauthors and other staff at Merck. The final version of the manuscript was reviewed by all coauthors and the Fracture Intervention Trial Steering Committee; Merck investigators constituted a minority of the Steering Committee. The authors acknowledge the help and guidance of the data and safety monitoring board: David L. DeMets, PhD (chair); Robert J. Levine, MD; Lawrence Raisz, MD; Elizabeth Shane, MD; Lynn Rosenberg, PhD; Siu L. Hui, PhD; and Brian L. Strom, MD, MPH.

#### References

1. Riggs BL, Melton LJ III. The prevention and treatment of osteoporosis. *N Engl J Med*. 1992;327:620-627.
2. Ray N, Chan JK, Thamer M, Melton LJ III. Medical expenditures for the treatment of osteoporotic fractures in the United States in 1995. *J Bone Miner Res*. 1997;12:24-35.
3. Liberman UA, Weiss SR, Broll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. *N Engl J Med*. 1995;333:1437-1443.
4. Karpf DB, Shapiro DR, Seeman E, et al. Preven-

tion of nonvertebral fractures by alendronate: a meta-analysis. *JAMA*. 1997;277:1159-1164.

5. Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. *Lancet*. 1996;348:1535-1541.
6. Looker AC, Johnston CC Jr, Wahner HW, et al. Prevalence of low femoral bone density in older U.S. women from NHANES III. *J Bone Miner Res*. 1995;10:796-802.
7. Cooper C, Melton LJ. Vertebral fractures: how large is the silent epidemic? *BMJ*. 1992;304:793-794.
8. Black DM, Reiss TF, Nevitt MC, Cauley J, Karpf D, Cummings SR. Design of the Fracture Intervention Trial. *Osteoporos Int*. 1993;3(suppl 3):S29-S39.
9. Seeley DG, Browner WS, Nevitt MC, Genant HK, Scott JC, Cummings SR. Which fractures are associated with low appendicular bone mass in elderly women? *Ann Intern Med*. 1991;115:837-842.
10. National Osteoporosis Foundation Working Group on Vertebral Fractures. Assessing vertebral fractures. *J Bone Miner Res*. 1995;10:518-523.
11. Genant HK, Jergas M, van Kuijk C, eds. *Vertebral Fracture in Osteoporosis*. San Francisco, Calif: Radiology Research and Educational Foundation; 1995.
12. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. *J Bone Miner Res*. 1993;8:1137-1148.
13. de Groen PC, Lubbe DF, Hirsch LJ, et al. Esophagitis associated with the use of alendronate. *N Engl J Med*. 1996;335:1016-1021.
14. Cox DR, Oakes D. *Analysis of Survival Data*. New York, NY: Chapman & Hall; 1984.
15. Eddy DM, Johnston CC, Cummings SR, et al. Osteoporosis: review of the evidence for prevention, diagnosis, and treatment and cost-effectiveness analysis. *Osteoporos Int*. 1998;8:1-85.
16. Riggs BL, Melton LJ, O'Fallon WM. Drug therapy for vertebral fractures in osteoporosis. *Bone*. 1996;18(suppl):197S-201S.
17. Heaney RP. Is there a role for bone quality in fragility fractures? *Calcif Tissue Int*. 1993;53(suppl 1):S3-S5.
18. Garnero P, Hausherr E, Chapuy MC, et al. Markers of bone resorption predict hip fracture in elderly women: the EPIDOS prospective study. *J Bone Miner Res*. 1996;11:1531-1538.
19. Ross PD, Davis JW, Epstein RS, Wasnich RD. Pain and disability associated with new vertebral fractures and other spinal conditions. *J Clin Epidemiol*. 1994;47:231-239.
20. Nevitt M, Ettinger B, Black D, et al. Association of radiographically vertebral fractures with back pain and function: a prospective study. *Ann Intern Med*. 1998;128:793-780.
21. Black DM, Arden NK, Palermo L, Pearson J, Cummings SR. Prevalent vertebral deformities predict hip fractures and new vertebral deformities but not wrist fractures. *J Bone Miner Res*. In press.
22. Kotowicz MA, Melton LJ, Cooper C, et al. Risk of hip fracture in women with vertebral fracture. *J Bone Miner Res*. 1994;9:599-605.
23. McClung M, Clemmensen B, Daifotis A, et al. Alendronate prevents postmenopausal bone loss in women without osteoporosis. *Ann Intern Med*. 1998;128:253-261.
24. Hosking D, Chilvers CED, Christiansen C, et al. Prevention of bone loss with alendronate in postmenopausal women under age 60 years of age. *N Engl J Med*. 1998;338:485-492.
25. Eastell R. Treatment of postmenopausal osteoporosis. *N Engl J Med*. 1998;338:736-746.
26. Parfitt AM, Mundy GR, Rodman GD, et al. A new model for the regulation of bone resorption, with particular reference to the effects of bisphosphonates. *J Bone Miner Res*. 1996;11:150-159.
27. Fleisch H. Bisphosphonates: mechanisms of action and clinical use in osteoporosis: an update. *Horm Metab Res*. 1997;29:145-150.
28. Stock JL, Bell NH, Chestnut CH, et al. Increments in bone mineral density of the lumbar spine and hip and suppression of bone turnover are maintained after discontinuation of alendronate in postmenopausal women. *Am J Med*. 1997;103:291-297.