

## ALENDRONATE FOR THE TREATMENT OF OSTEOPOROSIS IN MEN

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### ABSTRACT

**Background** Despite its association with disability, death, and increased medical costs, osteoporosis in men has been relatively neglected as a subject of study. There have been no large, controlled trials of treatment in men.

**Methods** In a two-year double-blind trial, we studied the effect of 10 mg of alendronate or placebo, given daily, on bone mineral density in 241 men (age, 31 to 87 years; mean, 63) with osteoporosis. Approximately one third had low serum free testosterone concentrations at base line; the rest had normal concentrations. Men with other secondary causes of osteoporosis were excluded. All the men received calcium and vitamin D supplements. The main outcome measures were the percent changes in lumbar-spine, hip, and total-body bone mineral density.

**Results** The men who received alendronate had a mean ( $\pm$ SE) increase in bone mineral density of  $7.1 \pm 0.3$  percent at the lumbar spine,  $2.5 \pm 0.4$  percent at the femoral neck, and  $2.0 \pm 0.2$  percent for the total body ( $P < 0.001$  for all comparisons with base line). In contrast, men who received placebo had an increase in lumbar-spine bone mineral density of  $1.8 \pm 0.5$  percent ( $P < 0.001$  for the comparison with base line) and no significant changes in femoral-neck or total-body bone mineral density. The increase in bone mineral density in the alendronate group was greater than that in the placebo group at all measurement sites ( $P < 0.001$ ). The incidence of vertebral fractures was lower in the alendronate group than in the placebo group (0.8 percent vs. 7.1 percent,  $P = 0.02$ ). Men in the placebo group had a 2.4-mm decrease in height, as compared with a decrease of 0.6 mm in the alendronate group ( $P = 0.02$ ). Alendronate was generally well tolerated.

**Conclusions** In men with osteoporosis, alendronate significantly increases spine, hip, and total-body bone mineral density and helps prevent vertebral fractures and decreases in height. (N Engl J Med 2000; 343:604-10.)

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**O**STEOPOROTIC fractures are widely recognized as a common and important cause of disability and death among postmenopausal women.<sup>1,2</sup> Osteoporosis is less common in men,<sup>3</sup> but approximately 25 to 30 percent of all hip fractures occur in men,<sup>4</sup> and many men have vertebral deformities.<sup>5</sup> The number of hip fractures among men and women is rising, and by 2025, the number of hip fractures occurring annually in men is expected to exceed 1.1 million worldwide — a figure that is close to the incidence of 1.2 million hip fractures among women in 1990.<sup>4</sup> The causes of osteoporosis in men include an excess of glucocorticoids, hypogonadism, and a variety of other systemic conditions, medications, and lifestyle factors, but often there is no obvious cause. In the United States there are currently no approved therapies for men with osteoporosis. In men with hypogonadism, testosterone therapy has limited efficacy,<sup>6</sup> and the efficacy of other therapies for osteoporosis in men has not been evaluated.

Alendronate is a potent bisphosphonate that inhibits osteoclast-mediated bone resorption.<sup>7</sup> In postmenopausal women with osteoporosis and in patients with glucocorticoid-induced osteoporosis, alendronate significantly increases bone mineral density; it also reduces the incidence of major osteoporotic fractures, including those of the spine and hip, in postmenopausal women.<sup>8-11</sup> Therefore, we evaluated whether alendronate treatment prevents or reverses bone loss in men with osteoporosis.

### METHODS

#### Study Subjects

We studied 241 men (age, 31 to 87 years; mean, 63) at 20 centers in the United States and 10 other countries. The chief entry criteria were a bone mineral density at the femoral neck that was at least 2 SD below the mean value in normal young men and a bone mineral density at the lumbar spine that was at least 1 SD below the mean in normal young men or a bone mineral density at

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the femoral neck that was at least 1 SD below the mean in normal young men and at least one vertebral deformity or a history of an osteoporotic fracture. Men were identified primarily at osteoporosis clinics or during community assessments of bone mineral density.

Men with secondary causes of osteoporosis other than low serum free testosterone concentrations were ineligible, including those who were taking medications or who had medical conditions associated with bone loss, as were those with other bone diseases, vitamin D deficiency (defined as a serum 25-hydroxyvitamin D concentration of less than 25 ng per milliliter [62.4 nmol per liter]), renal disease (indicated by a serum creatinine concentration of more than 1.6 mg per deciliter [144  $\mu$ mol per liter]), severe cardiac disease, a history of cancer other than basal-cell carcinoma of the skin, a recent history (within the previous year) of peptic ulcer or esophageal disease, or esophageal abnormalities that delayed esophageal emptying. We also excluded men who were unable to follow the instructions for taking the study drug and those with a history of treatment for osteoporosis. Men who were taking nonsteroidal antiinflammatory drugs and those with a history of upper gastrointestinal symptoms, other than those just described, were not excluded from the study.

Serum free testosterone was measured twice at base line, and men with low values (<9 ng per deciliter [312 pmol per liter]) were offered the opportunity to start testosterone therapy. Two men did so and were not included in the study. Ten men (seven in the placebo group and three in the alendronate group) who were receiving stable doses of testosterone were included in the study; the doses were not changed during the study. For the purpose of analysis, these men were considered to be eugonadal. The ethics committee or institutional review board at each center approved the study protocol, and all the men gave written informed consent.

### Treatment

The men were randomly assigned in a ratio of 3 to 2 to receive 10 mg of alendronate or placebo daily for up to two years in a double-blind manner. The men were classified on the basis of their initial serum free testosterone values as androgen-deficient (those with low serum free testosterone concentrations) or androgen-replete (those with normal serum free testosterone concentrations), and randomization was stratified to ensure that the distribution of these two subgroups was balanced between the treatment groups. Calcium supplements (500 mg daily in the form of calcium carbonate) and vitamin D supplements (400 IU daily in the United States and 400 to 450 IU daily in the other countries) were provided to all the men.

### Base-Line and Follow-up Studies

At base line, a complete history was obtained, and each subject underwent a physical examination, electrocardiography, and chest radiography. Men returned for visits at 3, 6, 12, 18, and 24 months. At each visit, height was measured in triplicate with a stadiometer (Harpenden, Holtain, Crymmych, Pembrookshire, United Kingdom). If any two of the measurements differed by 4 mm or more, two additional measurements were obtained. Posteroanterior and lateral radiographs of the lumbar and thoracic spine were obtained at base line and after two years of treatment. Bone mineral density was measured at base line and at 6, 12, 18, and 24 months. At each clinic visit, the men were questioned about symptoms, and standard clinical evaluations and laboratory analyses, including hematologic tests and tests of renal and liver function, were performed. The average of the two base-line serum free testosterone values was used in the analyses. Serum estradiol was measured at the end of the study in samples that had been obtained at base line and stored at  $-80^{\circ}\text{F}$ . All adverse or unexpected clinical events, including fractures, and laboratory abnormalities, were considered adverse effects.

### Measurements of Bone Mineral Density

The bone mineral density of the lumbar spine, hip, and total body was measured by dual-energy x-ray absorptiometry in the

anteroposterior view (Hologic, Waltham, Mass., or Lunar, Madison, Wis.). To determine subjects' eligibility on the basis of their bone mineral density T scores (standard deviations from the mean value in normal young men) at the proximal femur, we used values obtained from the National Health and Nutrition Examination Survey reference population,<sup>12</sup> with adjustments for values for the various brands of absorptiometers.<sup>13</sup> We derived T scores at the lumbar spine from manufacturers' reference populations. Quality assurance with respect to measurements of bone mineral density was carried out as described previously<sup>14</sup> by a central facility (at the University of California, San Francisco) by personnel who were unaware of the subjects' treatment assignments.

### Assessment of Vertebral Fractures

To detect both vertebral fractures that were present at base line and those that occurred during the study, x-ray films were assessed at a central site (University of California, San Francisco) by personnel who were unaware of the subjects' treatment assignment; both semiquantitative and quantitative morphometric methods were used.<sup>15,16</sup> Radiographs of the spine obtained at base line and those obtained at two years were available for analyses by semiquantitative methods in the case of 216 men. Because of overexposure of the film, radiographs of 209 men were available for quantitative analyses. Painful vertebral fractures were identified when the men sought medical attention for back pain and spinal radiographs demonstrated a new vertebral deformity. Nonvertebral frac-

TABLE 1. BASE-LINE CHARACTERISTICS OF THE MEN.\*

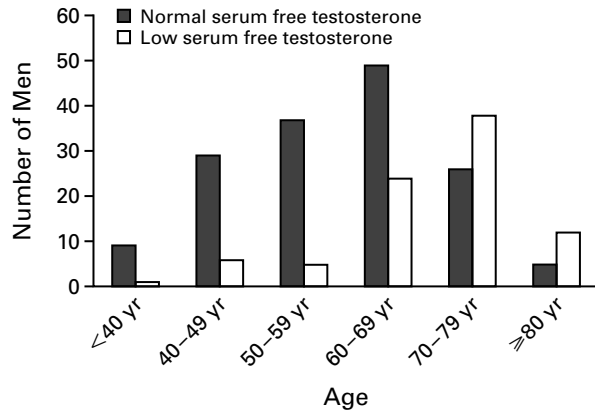
CHARACTERISTIC	PLACEBO GROUP (N=95)	ALENDRONATE GROUP (N=146)
Age (yr)	63 $\pm$ 12	63 $\pm$ 13
Race (%)		
White	99	97
Other	1	3
Serum free testosterone (%)†		
Normal	64	64
Low	36	36
Smoking history (%)		
Nonsmoker	77	72
Smoker	23	28
Consumption of $\geq$ 1 alcoholic drinks/day (%)	31	25
Body-mass index‡	25 $\pm$ 3	25 $\pm$ 3
Bone mineral density T score§		
Lumbar spine	2.1	2.0
Femoral neck	2.3	2.2
Hip	2.1	2.1
Vertebral fractures (%)	52	49
Biochemical markers of bone turnover		
Urinary excretion of type I collagen N-telopeptides (pmol of bone collagen equivalents/ $\mu$ mol of creatinine)	40 $\pm$ 22	35 $\pm$ 17
Serum bone-specific alkaline phosphatase (ng/ml)	13 $\pm$ 5	13 $\pm$ 5

\*Plus-minus values are means  $\pm$ SD.

†Values were considered normal or low in comparison with values obtained in normal men who were 20 to 60 years of age. Ten men (seven in the placebo group and three in the alendronate group) who were receiving testosterone-replacement therapy were considered to have normal concentrations of serum free testosterone.

‡The body-mass index was calculated as the weight in kilograms divided by the square of the height in meters.

§The T score is the mean number of standard deviations below the mean value in normal young men.



**Figure 1.** Number of Men with Normal or Low Serum Free Testosterone Concentrations at Base Line, According to Age.

tures involving any skeletal site were reported by the subjects themselves and were confirmed by a review of radiographic records.

**Biochemical Measurements**

Serum estradiol was measured by an ultrasensitive radioimmunoassay (Endocrine Sciences, Calabasas Hills, Calif.) for which the normal range is 0.8 to 3.5 ng per deciliter (29 to 129 pmol per liter). Serum free testosterone was measured by equilibrium dialysis; with the use of this method, the normal range in men who are 20 to 60 years of age is 9 to 30 ng per deciliter (312 to 1040 pmol per liter). Serum samples and urine samples obtained in the morning at the time of the second voiding were obtained for measurements of biochemical markers of bone turnover (serum bone-specific alkaline phosphatase and urinary excretion of the N-telopeptide of type I collagen, corrected for the creatinine concentration, respectively) and serum calcium and phosphate. All samples were analyzed at a central reference laboratory (Mayo Medical Laboratories, Rochester, Minn.).

**Statistical Analysis**

The primary end point of the study was the lumbar-spine bone mineral density. The primary analysis of the efficacy data was

based on the intention-to-treat principle. All men in whom bone mineral density was measured at base line and at least once after randomization were included in the evaluation. The analysis of the bone-mineral-density variables was based on the percent changes from base line. For the analysis of biochemical markers, we used the log-transformed fraction of the base-line value after two years of treatment. We assessed the effect of treatment using an analysis of variance that included factors for treatment, study site, and gonadal status. We also examined interactions between variables. We used Fisher's exact test to compare the incidence of adverse effects in the two treatment groups. All statistical tests were two-sided.

**RESULTS**

**Characteristics of the Subjects**

The base-line characteristics of the 146 men in the alendronate group and the 95 men in the placebo group were similar (Table 1). In each group, 36 percent of the men had low serum free testosterone concentrations, and the proportion with low concentrations increased with age (Fig. 1). The mean bone mineral density at the lumbar spine, femoral neck, and hip was approximately 2.0, 2.2, and 2.1 SD below the respective mean values for young men. Approximately half the men had vertebral fractures at base line, and 29 percent had multiple vertebral fractures. Eighty-three percent of the men in the placebo group and 86 percent of the men in the alendronate group completed the study.

**Bone Mineral Density**

The lumbar-spine bone mineral density increased by a mean ( $\pm$ SE) of  $1.8 \pm 0.5$  percent in the placebo group ( $P < 0.001$  for the comparison with base line), but femoral-neck or total-body bone mineral density did not change significantly (Table 2 and Fig. 2). In the alendronate group, lumbar-spine bone mineral density increased by a mean of  $7.1 \pm 0.3$  percent, femoral-neck bone mineral density increased by a mean of  $2.5 \pm 0.4$  percent, and total-body bone min-

**TABLE 2.** CHANGES IN BONE MINERAL DENSITY FROM BASE LINE TO YEAR 2.\*

SITE	PLACEBO GROUP		ALENDRONATE GROUP		P VALUE	ABSOLUTE DIFFERENCE BETWEEN GROUPS (95% CI)
	NO. OF SUBJECTS	PERCENT CHANGE	NO. OF SUBJECTS	PERCENT CHANGE		
Lumbar spine	79	$1.8 \pm 0.5$	123	$7.1 \pm 0.3$	<0.001	5.3 (4.3-6.3)
Femoral neck	81	$-0.1 \pm 0.5$	128	$2.5 \pm 0.4$	<0.001	2.6 (1.6-3.7)
Trochanter	81	$1.3 \pm 0.5$	128	$4.3 \pm 0.4$	<0.001	3.1 (1.9-4.4)
Hip	81	$0.6 \pm 0.5$	128	$3.1 \pm 0.3$	<0.001	2.6 (1.5-3.7)
Total body	83	$0.4 \pm 0.3$	132	$2.0 \pm 0.2$	<0.001	1.6 (1.0-2.1)

\*Plus-minus values are means  $\pm$ SE. The data were analyzed on an intention-to-treat basis. CI denotes confidence interval.

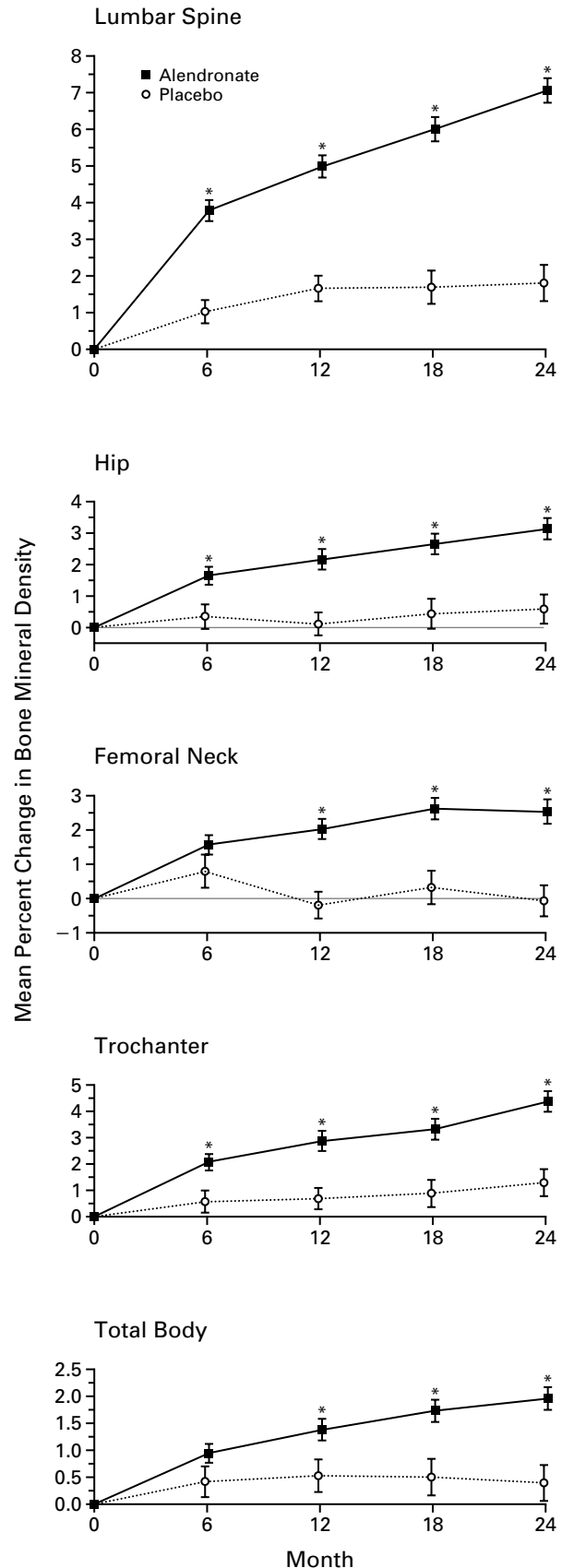
eral density increased by a mean of  $2.0 \pm 0.2$  percent ( $P < 0.001$  for all comparisons with base line). The changes in bone mineral density at the femoral trochanter and total hip were similar to those at the femoral neck. At each site, the increase in the alendronate group was significantly greater than that in the placebo group. The increases in the alendronate group were significant after six months at the lumbar spine and continued throughout the two years of the study without reaching a plateau, although the increase was greatest during the first year. The increase in lumbar-spine bone mineral density exceeded 3.0 percent in 87 percent of the men in the alendronate group, as compared with 29 percent of those in the placebo group.

**Changes in Bone Mineral Density in Subgroups of Men**

The effects of alendronate on lumbar-spine bone mineral density were similar in men who had normal serum free testosterone concentrations at base line and in those who had low concentrations at base line (Fig. 3), but there was a slightly greater effect on total-body bone mineral density in the latter group (data not shown). In addition, the response to alendronate was independent of base-line serum estradiol concentrations (Fig. 3). The effect of alendronate on bone mineral density was independent of age. In men younger than 65 years of age, lumbar-spine bone mineral density increased by a mean of  $1.4 \pm 0.8$  percent in the placebo group and  $7.3 \pm 0.5$  percent in the alendronate group, and it increased by a mean of  $2.2 \pm 0.6$  percent and  $6.8 \pm 0.4$  percent, respectively, in men who were 65 years of age or older. Smoking status did not affect the response of bone mineral density to alendronate (data not shown).

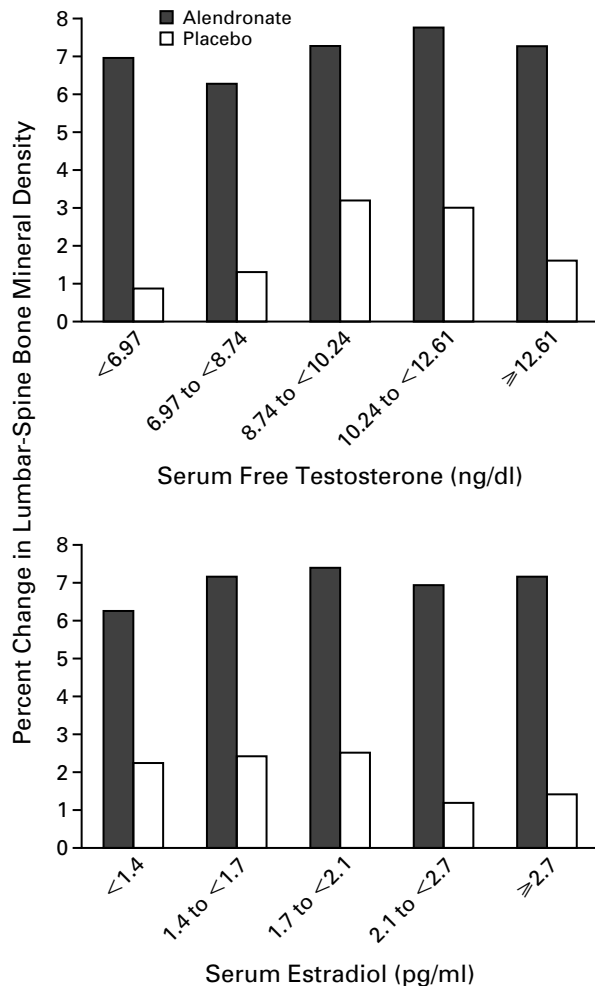
**Biochemical Markers of Bone Turnover and Indexes of Calcium Homeostasis**

After two years of treatment, there was a small (9 percent) decrease in urinary excretion of type I collagen N-telopeptides in the placebo group as compared with a 59 percent decrease in the alendronate group ( $P < 0.001$  for both comparisons with base-line values and the comparison with the placebo group). Virtually all the decline had occurred by the third month. After two years, serum bone-specific alkaline phosphatase concentrations had decreased by 5 percent in the placebo group and 38 percent in the alendronate group ( $P < 0.001$ ). Serum calcium concen-



**Figure 2.** Mean ( $\pm$ SE) Percent Changes from Base Line in the Bone Mineral Density of the Lumbar Spine, Hip, Femoral Neck, Trochanter, and Total Body in the Alendronate and Placebo Groups.

The analyses were conducted according to the intention to treat. Asterisks indicate significant differences between the groups ( $P \leq 0.001$ ).



**Figure 3.** Mean Percent Changes in Lumbar-Spine Bone Mineral Density from Base Line to Year 2, According to the Quintile of Serum Free Testosterone and Estradiol Concentrations at Base Line.

To convert values for serum free testosterone to picomoles per liter, multiply by 34.67. To convert values for estradiol to picomoles per liter, multiply by 36.71. The serum free testosterone and estradiol concentrations in these men ranged from 0.4 to 26 ng per deciliter (14 to 902 pmol per liter) and 4 to 50 pg per milliliter (15 to 184 pmol per liter), respectively.

trations did not change significantly in either group, but serum phosphate concentrations decreased slightly in both groups (by 4 percent in the placebo group and by 9 percent in the alendronate group,  $P=0.10$ ).

#### Changes in Height

After two years of treatment, the men in the placebo group lost 2.4 mm in stature ( $P<0.001$  for the comparison with base line), as compared with a non-significant change of 0.6 mm in the alendronate group ( $P=0.02$  for the difference between groups).

The proportion of men whose height decreased by at least 10 mm over the two-year period was 13 percent in the placebo group and 3 percent in the alendronate group. Alendronate had similar effects on height in men with androgen deficiency and those with no deficiency (data not shown).

The decrease in height was more pronounced among men who had a new vertebral fracture during the study: the decrease was 6.9 mm among men in the placebo group and 3.3 mm among men in the alendronate group who had vertebral fractures, as compared with respective decreases of 1.7 mm and 0.3 mm among those without vertebral fractures. Thus, the decrease in height appeared to be associated with vertebral deformity irrespective of treatment.

#### Fractures

Using semiquantitative methods, we found that vertebral fractures occurred in 8.1 percent of men in the placebo group and 3.1 percent of men in the alendronate group ( $P=0.12$ ). However, quantitative methods revealed that the incidence of vertebral fractures was 7.1 percent in the placebo group and 0.8 percent in the alendronate group ( $P=0.02$ ). Four men had painful vertebral fractures: three (3.2 percent) in the placebo group and 1 (0.7 percent) in the alendronate group ( $P=0.3$ ). Nonvertebral fractures occurred in five men (5.3 percent) in the placebo group and six men (4.1 percent) in the alendronate group ( $P=0.8$ ).

#### Adverse Effects

Fourteen men withdrew from the study because of adverse effects: 10 (11 percent) in the placebo group and 4 (3 percent) in the alendronate group ( $P=0.02$ ). The reason for withdrawal was different for each man. In addition, one man in the alendronate group discontinued therapy because of high serum aspartate aminotransferase concentrations. Five men (5.3 percent) in the placebo group and nine (6.2 percent) in the alendronate group withdrew from the study for personal reasons, and five men (one in the placebo group and four in the alendronate group) were lost to follow-up.

There were no significant differences in the incidence of serious adverse effects, drug-related adverse effects, drug-related withdrawals from therapy, or laboratory abnormalities between the alendronate and placebo groups (Table 3). The frequency of adverse gastrointestinal effects in the two groups was similar despite the fact that 36 percent of the men in the placebo group and 41 percent of those in the alendronate group reported taking nonsteroidal antiinflammatory drugs during the study.

#### DISCUSSION

In this study of men with osteoporosis, 10 mg of alendronate daily for two years increased bone min-

TABLE 3. INCIDENCE OF ADVERSE EFFECTS.\*

ADVERSE EFFECT	PLACEBO GROUP (N=95)	ALENDRONATE GROUP (N=146)
	no. (%)	
Drug-related†	13 (14)	25 (17)
Serious	22 (23)	27 (18)
Cardiovascular system	16 (17)	23 (16)
Digestive system	37 (39)	51 (35)
Upper gastrointestinal tract		
Any event	21 (22)	37 (25)
Abdominal pain	4 (4)	12 (8)
Acid regurgitation	5 (5)	7 (5)
Esophagitis	1 (1)	1 (1)
Dyspepsia	1 (1)	9 (6)
Musculoskeletal system	50 (53)	68 (47)
Nervous system	19 (20)	37 (25)
Respiratory system	47 (49)	66 (45)
Skin	21 (22)	33 (23)
Urogenital system	16 (17)	25 (17)

\*There were no significant differences ( $P>0.05$ ) between the groups.

†These events were determined by the investigators to be possibly, probably, or definitely related to the study drug. Examples include skin cancer, prostate cancer, benign prostatic hypertrophy, lymphoma, lung cancer, osteoarthritis, coronary artery disease, and cholelithiasis.

eral density of the spine, hip, and total body. The effects of alendronate were evident after six months of therapy and were independent of base-line serum free testosterone or estradiol concentrations. The decreases in bone turnover, as reflected by changes in biochemical markers, were consistent with the effects of alendronate previously reported in postmenopausal women.<sup>7</sup> Alendronate reduced the incidence of vertebral fractures and prevented decreases in height. It was generally well tolerated in these men, and few men withdrew from the study because of an adverse effect.

Primary osteoporosis (which includes age-related and idiopathic forms) and hypogonadism together account for approximately 60 percent of all cases of osteoporosis in men.<sup>3</sup> Glucocorticoid-induced osteoporosis accounts for approximately 20 percent of all cases,<sup>3</sup> and alendronate and other bisphosphonates have been reported to be beneficial in men with glucocorticoid-induced osteoporosis.<sup>17-20</sup> Thus, on the basis of our findings and those of other studies, alendronate appears to be effective in the majority of men with osteoporosis.

The benefits of alendronate therapy in men with osteoporosis were very similar to those in postmenopausal women. In such women alendronate increased bone mineral density and decreased the incidence of vertebral fractures, hip fractures, and any type of non-vertebral fractures.<sup>8-11,21</sup> The magnitude of the effects of alendronate on bone mineral density in the men in our study was very similar to that reported in post-

menopausal women with osteoporosis after two years of therapy,<sup>8</sup> and the reduction in the incidence of vertebral fractures in the alendronate group relative to that in the placebo group is consistent with the reduction in the incidence of vertebral fractures among postmenopausal women with osteoporosis.<sup>8</sup>

Our trial has several limitations. Most of the men were white, and the increases in bone mineral density, the decreases in the incidence of fractures, and the maintenance of height might not occur in other racial groups. However, in a recent study of black postmenopausal women with osteoporosis, the effects of alendronate on bone mineral density were similar to those previously reported in white women.<sup>22</sup> Our study lasted only two years, and we evaluated only a single dose of alendronate (10 mg); thus, longer-term responses and the relative efficacy of other doses are unknown. In previous dose-ranging studies, a 10-mg dose of alendronate was optimal for the treatment of osteoporosis in postmenopausal women,<sup>9</sup> and the bioavailability of alendronate is similar in men and women.<sup>23</sup> Moreover, similar results were obtained with this dose of alendronate in men and women who had Paget's disease of bone.<sup>24</sup>

In summary, in men with osteoporosis, alendronate increased lumbar-spine and hip bone mineral density, reduced the rate of vertebral fractures, and prevented decreases in height.

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Drs. Orwoll, Ettlinger, Weiss, Miller, Kendler, Graham, Adami, Weber, and Pietschmann have served as consultants to Merck, the manufacturer of alendronate, have been members of speakers' bureaus sponsored by Merck, or have done both for Merck, as well as for other companies making products for the treatment of osteoporosis. Dr. Ettlinger owns stock in Merck.

## APPENDIX

The following investigators also participated in the study: J.D. Adachi, McMaster University, Hamilton, Ont., Canada; N. Bell, Medical University of South Carolina, Charleston; J.-J. Body, Institut Bordet, Brussels, Belgium; A. Castro, Hospital De S. Antonio dos Capuchos, Lisbon, Portugal; A. Daifotis, Merck, Rahway, N.J.; D. Felsenberg, University of Berlin, Berlin, Germany; N. Gilchrist, Princess Margaret Hospital, Christchurch, New Zealand; A. Hoffman, University of Graz, Graz, Austria; M. Maricic, University of Arizona, Tucson; R. Rizzoli, Hôpital Cantonal, Geneva; S. Silverman, University of California and West Los Angeles Veterans Affairs Medical Center, Los Angeles; and J. Valeriano, University of South Florida, Tampa.

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