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## PREVENTION OF BONE LOSS WITH ALENDRONATE IN POSTMENOPAUSAL WOMEN UNDER 60 YEARS OF AGE

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### ABSTRACT

**Background** Estrogen-replacement therapy prevents osteoporosis in postmenopausal women by inhibiting bone resorption, but the balance between its long-term risks and benefits remains unclear. Whether other antiresorptive therapies can prevent osteoporosis in these women is also not clear.

**Methods** We studied the effect of 2.5 mg or 5 mg of alendronate per day or placebo on bone mineral density in 1174 postmenopausal women under 60 years of age. An additional 435 women who were prepared to receive a combination of estrogen and progestin were randomly assigned to one of the above treatments or open-label estrogen-progestin. The main outcome measure was the change in bone mineral density of the lumbar spine, hip, distal forearm, and total body measured annually for two years by dual-energy x-ray absorptiometry.

**Results** The women who received placebo lost bone mineral density at all measured sites, whereas the women treated with 5 mg of alendronate daily had a mean ( $\pm$ SE) increase in bone mineral density of  $3.5 \pm 0.2$  percent at the lumbar spine,  $1.9 \pm 0.1$  percent at the hip, and  $0.7 \pm 0.1$  percent for the total body (all  $P < 0.001$ ). Women treated with 2.5 mg of alendronate daily had smaller increases in bone mineral density. Alendronate did not increase bone mineral density of the forearm, but it slowed the loss. The responses to estrogen-progestin were 1 to 2 percentage points greater than those to the 5-mg dose of alendronate. Alendronate was well tolerated, with a safety profile similar to that of placebo or estrogen-progestin.

**Conclusions** Alendronate prevents bone loss in postmenopausal women under 60 years of age to nearly the same extent as estrogen-progestin. (N Engl J Med 1998;338:485-92.)

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**O**STEOPOROSIS is a common and important cause of morbidity and mortality among postmenopausal women.<sup>1-3</sup> It arises as a consequence of progressive loss of bone and results in an increased risk of fracture. The destruction of trabecular microarchitecture, which cannot be repaired by currently available therapies, contributes to this mechanical weakness<sup>4</sup> and has been an impetus to the development of strategies to maintain both bone mass and mechanical integrity.

Estrogen-replacement therapy is an established treatment for the prevention of osteoporosis in postmenopausal women.<sup>5-9</sup> It acts by inhibiting bone resorption. Some women, however, cannot tolerate the side effects of estrogen, such as withdrawal bleeding or breast tenderness, and others are reluctant to take estrogen because of the possible risk of breast cancer.<sup>10-12</sup>

Bisphosphonates also inhibit bone resorption and increase bone mineral density in postmenopausal women with osteoporosis.<sup>13-15</sup> Alendronate is a potent amino bisphosphonate<sup>16,17</sup> that increases bone mass<sup>15,18</sup> and reduces the incidence of vertebral and other fractures<sup>15,19</sup> in postmenopausal women with osteoporosis.

The present study was performed to determine whether alendronate prevents bone loss in post-

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menopausal women and to compare the efficacy, safety, and tolerability of alendronate with those of a combination of estrogen and progestin.

## METHODS

### Study Subjects

We studied 1609 women (age, 45 to 59 years) at four study centers. To be eligible for the study they had to have been postmenopausal for at least six months (as confirmed by a high serum follicle-stimulating hormone concentration) and in good health, with no clinical or laboratory evidence of systemic disease. The following were exclusion criteria: abnormal renal function (serum creatinine,  $>1.5$  mg per deciliter [ $130$   $\mu$ mol per liter]), a history of cancer, peptic ulcer or esophageal disease requiring prescription medication within the previous five years, previous treatment with a bisphosphonate or fluoride, regular therapy with a phosphate-binding antacid, estrogen-replacement therapy within the previous three months, and therapy with any other drug that affects the skeleton. To ensure that few women who entered the study had osteoporosis, only 10 percent of the women enrolled at each center were allowed to have a lumbar-spine bone mineral density below  $0.8$  g per square centimeter, as measured by dual-energy x-ray absorptiometry. The women were recruited by direct mailings, advertisements in the media, or telephone. The protocol was approved by the ethics committee or institutional review board at each center, and all the women gave written informed consent.

### Treatment

There were two treatment strata. In the first, the women were randomly assigned to receive placebo or  $2.5$  mg or  $5$  mg of alendronate daily, with both the women and the investigator being unaware of treatment-group assignment, or open-label estrogen-progestin. Women who had undergone hysterectomy or for whom estrogen-progestin was contraindicated (because of thromboembolic disease or a family history of estrogen-dependent cancer) or unacceptable were enrolled in the second stratum, which was identical to the first except that it did not include estrogen-progestin. In the United States the estrogen and progestin were given as conjugated estrogens (Premarin, Wyeth-Ayerst, Philadelphia,  $0.625$  mg daily), and medroxyprogesterone acetate (Provera, Upjohn, Kalamazoo, Mich.,  $5$  mg daily), respectively. In Europe the estrogen and progestin were given in a cyclical regimen (Trisequens, Novo Nordisk, Copenhagen, Denmark) of  $2$  mg of micronized estradiol per day for 22 days,  $1$  mg of norethindrone acetate per day on days 13 to 22, and  $1$  mg of estradiol per day on days 23 to 28.

Dietary calcium intake was estimated at base line and annually during the study with a food-frequency questionnaire. Women with a calcium intake of less than  $500$  mg per day were advised to increase their intake. Supplements were not provided, because of the limited evidence of benefit in women soon after menopause.

### Measurements of Bone Mineral Density

The bone mineral density of the lumbar spine, hip, forearm, and total body was measured by dual-energy x-ray absorptiometry (model 2000, Hologic, Waltham, Mass.) twice at base line and after one and two years of treatment. The percent change from base line in the measurement of the anteroposterior lumbar spine (vertebrae L1 to L4) was the primary end point, and the changes in the hip (defined as the femoral neck plus trochanter and intertrochanteric area), lateral spine, forearm (measured at the junction of the proximal two thirds and the distal one third of the radial shaft where the radius and ulna meet near the wrist), and total body were secondary end points. Hologic Medical Data Management Services was responsible for handling all aspects of the quality assurance for bone-mineral-density measurements, including calibration of machines, training of technicians, assessment of machine performance, adequacy of the scans obtained, analysis performed at

the various sites, and data management without knowledge of treatment assignment. Positioning of the patients during absorptiometry and data analysis were standardized, as were calibration of the machines and training of the technicians.

### Assessment of Safety of the Treatment

The women were questioned about any symptoms at clinic visits every three months. Standard clinical evaluations and laboratory analyses, including hematologic, renal-function, and liver-function tests, were performed every six months. Physical examinations were performed at base line and yearly thereafter, as was mammography in the women receiving estrogen-progestin. If present, gastrointestinal symptoms were evaluated further if appropriate. All unfavorable or unintended clinical effects, including fractures, and laboratory abnormalities were considered adverse effects and were evaluated by the investigators with respect to severity, duration, seriousness, and relation to the study drug and outcome.

### Statistical Analysis

The two-year data reported here are from two planned interim analyses in this six-year study. The primary evaluation of the efficacy data according to the intention to treat included all 1460 women in whom lumbar-spine bone mineral density was measured at base line and at least once during treatment.

The effect of treatment on bone mineral density was assessed by analysis of variance and included interaction terms for treatment, center, stratum, treatment with center, and treatment with stratum. All statistical tests were two-sided. The interaction terms were removed if the  $P$  value was not significant ( $P>0.10$ ) or the interaction was nonqualitative in nature (according to Simon's test).<sup>20</sup> Because the estrogen-progestin regimens differed in the U.S. and European centers, the comparison with alendronate was evaluated separately for each group.

## RESULTS

The base-line characteristics of the women are shown in Table 1. Women in the first stratum (placebo, alendronate, or estrogen-progestin) had more recently become postmenopausal (mean, four years) than those in the second stratum (placebo or alendronate) (mean, seven years), probably reflecting their higher prevalence of menopausal symptoms and greater willingness to consider estrogen-progestin treatment. There were no significant differences between the treatment groups at base line.

The composition of the subgroups in the two studies and reasons for discontinuation are summarized in Table 2.

### Lumbar-Spine Bone Mineral Density

The anteroposterior lumbar-spine bone mineral density decreased steadily in the placebo group (mean [ $\pm$ SE] change for all women given placebo,  $-1.8\pm 0.2$  percent), whereas it increased significantly in both alendronate groups (both strata combined) ( $P<0.001$  for both doses) (Fig. 1A). Most of the gain in lumbar-spine bone mineral density in the alendronate groups occurred during the first year ( $2.0\pm 0.1$  percent in the  $2.5$ -mg group and  $2.7\pm 0.1$  percent in the  $5$ -mg group,  $P<0.001$  for both doses), but there were also significant increases during the second year ( $0.3\pm 0.1$  percentage point in the  $2.5$ -mg group,  $P=0.003$ , and  $0.8\pm 0.1$  percentage point in the  $5$ -mg

**TABLE 1.** BASE-LINE CHARACTERISTICS OF THE WOMEN IN STRATUM 1 (PLACEBO, ALENDRONATE, OR ESTROGEN-PROGESTIN) AND STRATUM 2 (PLACEBO OR ALENDRONATE).\*

CHARACTERISTIC	PLACEBO (N=461)	2.5-mg DOSE OF ALENDRONATE (N=452)	5-mg DOSE OF ALENDRONATE (N=445)	ESTROGEN- PROGESTIN (N=102)
Age (yr)	53±4	53±4	54±4	53±4
Race (%)†				
White	85	87	81	89
Black	0.4	0.4	1	0
Asian	10	10	12	8
Other	5	2	6	3
Oophorectomy (%)	7	7	9	—
Smoking history (%)†				
Never smoked	54	53	51	48
Former smoker	25	25	30	33
Current smoker	21	21	19	19
≥1 alcoholic drinks/wk (%)	45	44	44	51
Body-mass index‡	25±4	26±4	25±4	25±3
Dietary calcium intake (mg/day)	889±445	910±506	971±565	935±594
Years since menopause	6±5	6±5	6±6	4±3
Estrogen-replacement therapy within the past 3 yr (%)	10	13	11	9
Bone mineral density (g/cm <sup>2</sup> )				
Lumbar spine	0.94±0.12	0.93±0.13	0.95±0.14	0.93±0.12
Hip	0.85±0.11	0.84±0.12	0.85±0.12	0.84±0.11
Forearm	0.52±0.05	0.52±0.05	0.52±0.05	0.52±0.05
Total body	1.04±0.09	1.03±0.09	1.04±0.09	1.03±0.09

\*Plus-minus values are means ±SD. The analysis included all 1460 women in whom lumbar-spine bone mineral density was measured at base line and at least once during treatment.

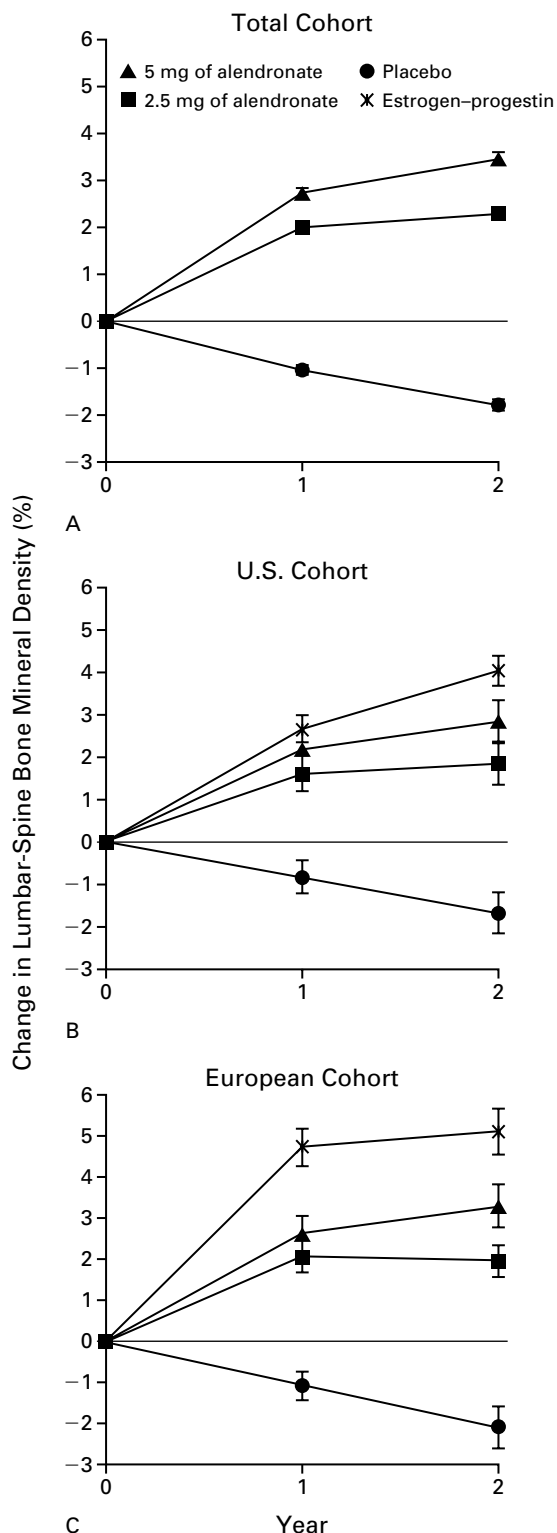
†Percentages may not total 100 because of rounding.

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

**TABLE 2.** DISTRIBUTION OF THE WOMEN AMONG THE TREATMENT GROUPS IN STRATUM 1 (PLACEBO, ALENDRONATE, OR ESTROGEN-PROGESTIN) AND STRATUM 2 (PLACEBO OR ALENDRONATE) AND REASONS FOR DISCONTINUATION OF TREATMENT BEFORE TWO YEARS.

VARIABLE	ALL WOMEN	PLACEBO	2.5-mg DOSE OF ALENDRONATE	5-mg DOSE OF ALENDRONATE	ESTROGEN- PROGESTIN
No. randomized					
Stratum 1	435	109	109	107	110
Stratum 2	1174	393	390	391	—
Total	1609	502	499	498	110
No. included in analysis of lumbar-spine bone mineral density					
Stratum 1	390	101	94	93	102
Stratum 2	1070	360	358	352	—
Total	1460	461	452	445	102
No. with no data on lumbar-spine bone mineral density after base line	149	41	47	53	8
No. completing 24 mo of treatment	1303	409	407	396	91
No. completing <24 mo of treatment and reason for discontinuation					
Protocol violation	30	9	12	9	0
Adverse effects					
Drug-related	40	11	6	10	13
Non-drug-related	69	16	20	31	2
Laboratory abnormalities	2	1	0	1	0
Loss to follow-up	26	10	8	8	0
Withdrawal*	139	46	46	43	4
Total	306	93	92	102	19

\*Reasons for withdrawal included social or work constraints, poor control of menopausal symptoms, and move from study locality.



**Figure 1.** Mean ( $\pm$ SE) Percent Change from Base Line in Lumbar-Spine Bone Mineral Density after One and Two Years of Treatment with Placebo, 2.5 mg or 5 mg of Alendronate, or Estrogen-Progestin in the Total Cohort (Panel A), the U.S. Cohort (Panel B), and the European Cohort (Panel C). Results for the two strata were combined according to treatment.

group,  $P < 0.001$ ). At both times the increases in the 5-mg group were greater ( $P < 0.001$ ) than those in the 2.5-mg group. The total gain at two years was  $3.5 \pm 0.2$  percent in the 5-mg group and  $2.3 \pm 0.2$  percent in the 2.5-mg group. The proportion of women who lost more than 2 percent of bone mineral density at the lumbar spine was 46 percent in the placebo group, 9 percent in the group given the 2.5-mg dose of alendronate, and 5 percent in the group given the 5-mg dose of alendronate (Fig. 2).

In the first stratum, the response at two years to estrogen-progestin in the U.S. women (Fig. 1B) was slightly greater than the response to the 5-mg dose of alendronate ( $4.0 \pm 0.3$  vs.  $2.9 \pm 0.5$  percent,  $P = 0.06$ ), whereas the response to estrogen-progestin in the European cohort was significantly greater than that to 5 mg of alendronate ( $5.1 \pm 0.5$  vs.  $3.3 \pm 0.5$  percent,  $P = 0.008$ ) (Fig. 1C).

The changes in bone mineral density of the lateral spine at two years were similar to those of the anteroposterior spine (data not shown).

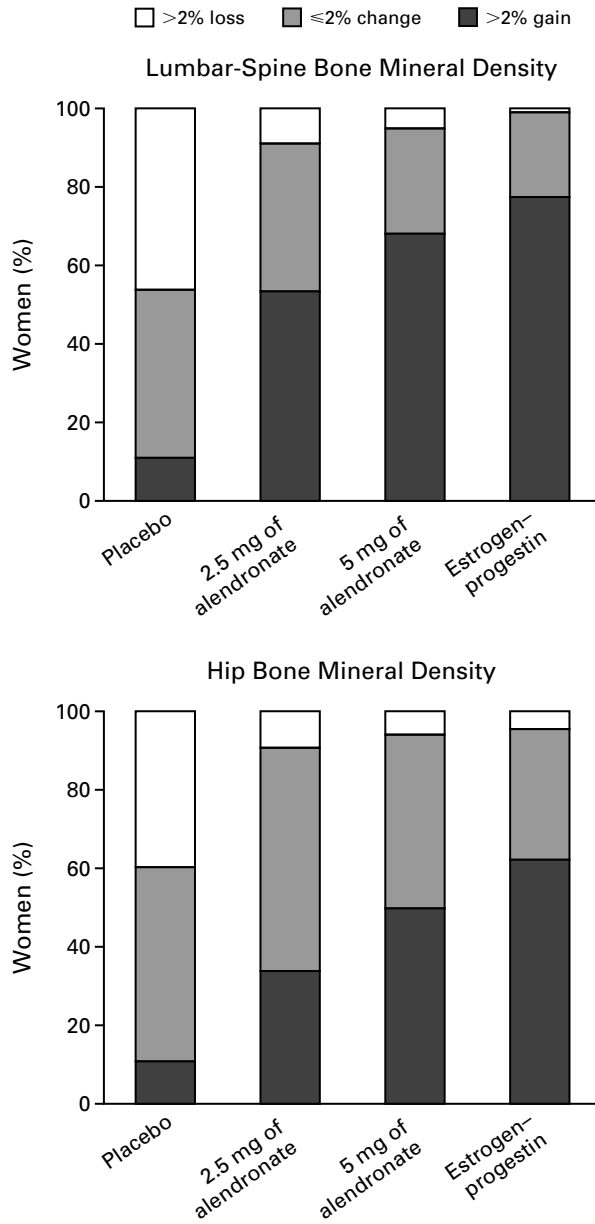
#### Hip Bone Mineral Density

The changes in the bone mineral density of the hip and its subregions (femoral neck and trochanter) were qualitatively similar to those at the lumbar spine, with the main increase occurring within the first year (Fig. 3). At two years, for both strata combined, the changes from base line in the hip, femoral neck, and trochanter were  $-1.4 \pm 0.1$  percent,  $-1.6 \pm 0.2$  percent, and  $-0.9 \pm 0.2$  percent (all  $P < 0.001$ ), respectively, in the placebo group and  $1.9 \pm 0.1$  percent,  $1.3 \pm 0.2$  percent, and  $3.0 \pm 0.1$  percent (all  $P < 0.001$ ), respectively, in the group given the 5-mg dose of alendronate. The differences between treatment groups were significant ( $P < 0.001$ ) at each of these sites. The proportion of women who lost more than 2 percent of bone mineral density at the hip was 40 percent in the placebo group, 10 percent in the group given the 2.5-mg dose of alendronate, and 6 percent in the group given the 5-mg dose of alendronate (Fig. 2).

In the U.S. cohort, estrogen-progestin increased hip bone mineral density at two years by  $1.8 \pm 0.3$  percent, as compared with  $1.3 \pm 0.3$  percent in the group receiving 5 mg of alendronate per day ( $P = 0.21$ ). In the European cohort, the respective increases were  $3.2 \pm 0.3$  percent and  $1.6 \pm 0.3$  percent ( $P < 0.002$ ).

#### Forearm Bone Mineral Density

Bone mineral density of the distal forearm at two years decreased by  $2.5 \pm 0.1$  percent in the placebo group and  $1.4 \pm 0.1$  percent in the group given the 5-mg dose of alendronate ( $P < 0.001$  for both) (Fig. 3). The change in the U.S. cohort was  $-0.3 \pm 0.2$  percent among those receiving estrogen-progestin, as compared with  $-1.7 \pm 0.3$  percent among those receiving the 5-mg dose of alendronate ( $P < 0.001$ ),

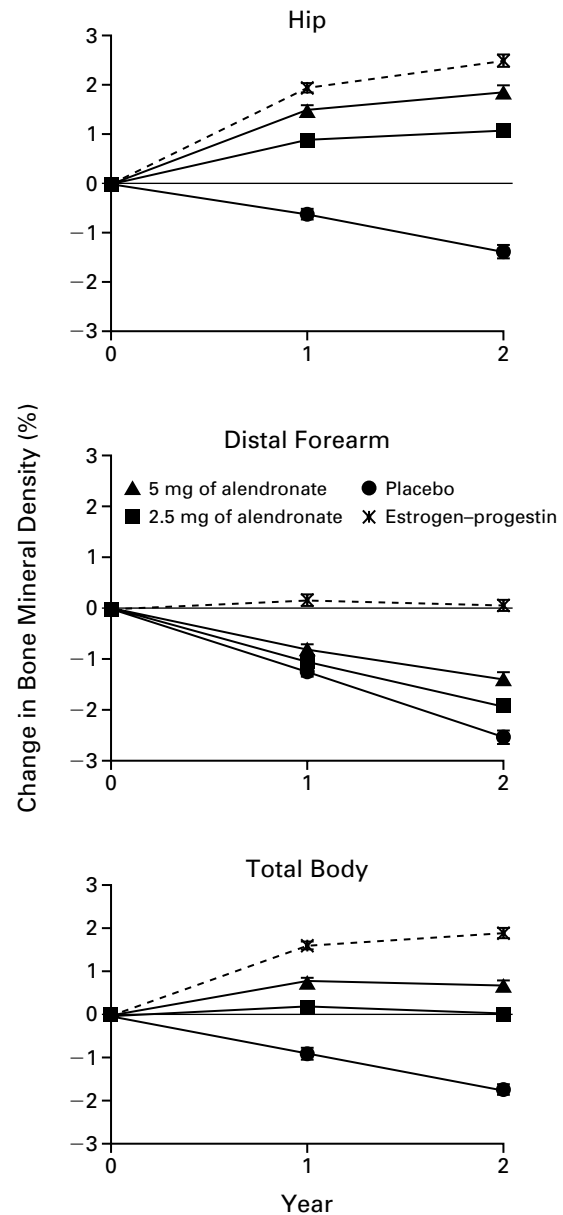


**Figure 2.** Proportion of Women with a Loss of More Than 2 Percent, a Change of 2 Percent or Less, or a Gain of More Than 2 Percent in Bone Mineral Density of the Lumbar Spine and Hip after Two Years of Treatment with Placebo, 2.5 mg or 5 mg of Alendronate, or Estrogen-Progestin. Results for the two strata were combined according to treatment.

whereas in the European cohort the respective changes were  $0.5 \pm 0.2$  percent and  $-1.1 \pm 0.4$  percent ( $P < 0.001$ ).

**Total-Body Bone Mineral Density**

After two years of treatment, total-body bone mineral density decreased in the placebo group ( $-1.8 \pm 0.1$  percent,  $P < 0.001$ ), did not change signif-



**Figure 3.** Mean ( $\pm$ SE) Change from Base Line in the Bone Mineral Density of the Hip, Distal Forearm, and Total Body after One and Two Years of Treatment with Placebo, 2.5 mg or 5 mg of Alendronate, or Estrogen-Progestin. Results for the two strata were combined according to treatment.

icantly in the group receiving 2.5 mg of alendronate daily, and increased  $0.7 \pm 0.1$  percent in the group given 5 mg of alendronate daily ( $P < 0.001$ ) (Fig. 3). Estrogen-progestin induced significantly larger increases in total-body bone mineral density than 5 mg of alendronate in the European group ( $2.6 \pm 0.2$  vs.  $0.6 \pm 0.3$  percent,  $P < 0.001$ ), but not in the U.S. group ( $1.2 \pm 0.2$  vs.  $0.8 \pm 0.3$  percent,  $P = 0.29$ ).

**TABLE 3.** SUMMARY OF ADVERSE EVENTS AMONG THE TREATMENT GROUPS IN BOTH STRATA.\*

TYPE OF ADVERSE EVENT OR SYSTEM AFFECTED	PLACEBO (N = 502)	2.5-mg	5-mg	ESTROGEN- PROGESTIN (N = 110)
		DOSE OF ALENDRONATE (N = 499)	DOSE OF ALENDRONATE (N = 498)	
		number (percent)		
Type of adverse event				
Any type of clinical event	468 (93)	476 (95)	474 (95)	109 (99)
Drug-related event	56 (11)	59 (12)	58 (12)	96 (87)
Serious event†	30 (6)	41 (8)	36 (7)	5 (5)
Laboratory	82 (16)	82 (16)	74 (15)	18 (16)
System affected				
Cardiovascular system	47 (9)	50 (10)	49 (10)	15 (14)
Digestive system	263 (52)	258 (52)	265 (53)	56 (51)
Musculoskeletal system	299 (60)	319 (64)	308 (62)	62 (56)
Nervous system and psychiatric	156 (31)	149 (30)	163 (33)	36 (33)
Respiratory system	387 (77)	374 (75)	370 (74)	78 (71)
Skin	166 (33)	159 (32)	162 (33)	31 (28)
Urogenital system	168 (33)	181 (36)	164 (33)	99 (90)
Upper gastrointestinal symptoms				
Any type	148 (29)	152 (30)	148 (30)	31 (28)
Abdominal pain	60 (12)	50 (10)	45 (9)	12 (11)
Acid regurgitation	22 (4)	23 (5)	24 (5)	0
Dyspepsia	49 (10)	46 (9)	46 (9)	6 (5)
Nausea	37 (7)	38 (8)	38 (8)	8 (7)
Vomiting	17 (3)	17 (3)	24 (5)	3 (3)

\*Adverse events could be classified in more than one category.

†A serious event was defined as death, permanent or substantial disability, cancer, a life-threatening adverse effect, or an adverse effect requiring hospitalization.

The proportion of women who lost more than 2 percent of total-body bone mineral density was 42 percent in the placebo group, 19 percent in the group given the 2.5-mg dose of alendronate, and 9 percent in the group given the 5-mg dose of alendronate.

Overall, there were no strong correlations between base-line characteristics and the changes in bone mineral density at two years.

#### Adverse Effects

Both doses of alendronate were well tolerated, and their safety profile was similar to that of placebo (Table 3). There were no significant differences in the incidence of serious clinical effects or laboratory abnormalities between the alendronate, estrogen-progestin, and placebo groups. The rates of drug-related adverse events were similar in the alendronate and placebo groups, but those attributed to estrogen-progestin cannot be directly compared because this treatment was open label. There was no significant difference between groups in the proportion of women with any adverse effect when effects were analyzed according to body system, including the upper gastrointestinal tract (Table 3), and there was no significant trend with increasing dose. The numbers of drug-related withdrawals were similar in the alendronate and placebo groups and higher in the estrogen-progestin group (Table 2), but the to-

tal withdrawal rates were similar for each treatment because of a balancing effect of non-drug-related withdrawals due to menopausal symptoms in the alendronate groups.

Sixty-one women had fractures during the study, none of which were considered to be drug-related: 14 (3 percent) in the placebo group, 22 (4 percent) in the group receiving 2.5 mg of alendronate per day, 22 (4 percent) in the group receiving 5 mg of alendronate per day, and 3 (3 percent) in the estrogen-progestin group. All were traumatic nonvertebral fractures.

#### DISCUSSION

We found that in postmenopausal women without osteoporosis, alendronate increases bone mineral density at most sites and that a daily dose of 5 mg was more effective than a dose of 2.5 mg. The increments in bone mineral density in the 5-mg group approached those in the estrogen-progestin group and were similar to those achieved with the same dose in two studies of older women with osteoporosis.<sup>15,18</sup> In the second study, 10 mg of alendronate daily produced the greatest gains in bone mineral density,<sup>18</sup> but our study was designed to identify the lowest dose that would maintain or increase bone density in a substantial majority of women rather than produce the maximal gain. In contrast to the results at most sites, forearm bone mineral density

decreased in the alendronate-treated women, but not as much as in those given placebo. In a recent placebo-controlled study of alendronate, there was a 48 percent reduction in the incidence of forearm fractures in the context of a gain of about 1 percent in forearm bone mineral density,<sup>19</sup> suggesting that increments in bone mineral density may account only in part for the antifracture efficacy of alendronate.

Estrogen-progestin prevented bone loss at all sites to an extent similar to that reported previously.<sup>7,21-23</sup> The gain in bone mineral density was 1 to 2 percentage points greater than that achieved with alendronate. Some women in both alendronate groups lost bone mass. This effect of alendronate has to be accepted, since the aim of prevention is to achieve a moderate increase in bone density on average or at least to prevent ongoing bone loss.

Since both the 5-mg dose of alendronate and estrogen-progestin prevent bone loss in postmenopausal women under the age of 60 years, the choice of therapy for any woman may well be determined by the safety and tolerability of the treatment. In view of reports of esophageal ulceration with alendronate,<sup>24</sup> upper gastrointestinal symptoms were carefully monitored and, when present, were investigated as clinically appropriate. We found, however, that the safety and tolerability of a 5-mg dose of alendronate were similar to those of placebo. Caution should be used in interpreting the safety and tolerability of open-label estrogen-progestin, because of the potential for investigator reporting bias. The adverse effects of estrogen-progestin reported were typical of known effects, such as withdrawal bleeding and breast tenderness, and as a consequence were more likely to be classified as drug-related.

Estrogen-progestin is recommended for women who want control of menopausal symptoms and protection from osteoporosis. The probable benefit of estrogen with respect to coronary heart disease<sup>25,26</sup> may also attract women with risk factors for this condition. Among women who have not had a hysterectomy, however, these advantages may be offset by side effects from the addition of progestins or withdrawal bleeding.<sup>27</sup> Fear of breast cancer is also a disincentive to some women, although there is no consensus on the magnitude of the risk.<sup>11,12,28</sup>

In conclusion, alendronate is effective in preventing bone loss in postmenopausal women and therefore provides an alternative to estrogen (with or without progestin) in women for whom the therapeutic goal is to maintain bone mass and thus reduce the risk of future fractures.

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## APPENDIX

The following investigators also participated in the study: *Hawaii Osteoporosis Center, Honolulu*: D. Uyeda, L. Medina, J. Silva, J. Carlson, M. Chong, G. Gibb, S. Caindec-Ranchez, N. Inuma, B. Choo; *Oregon Osteoporosis Center, Portland*: B. Love, P. Workman, N. Parkins, E. Stephens, E. Kingston, R. Mansfield, C. Kowalski; *Bone and Mineral Unit, Nottingham City Hospital and School of Community Health Sciences, Medical School, Nottingham, United Kingdom*: A. Lyons, S. Patel, C. Coupland, D. Green, P. San, A. Worley, S. Cliffe, S. Cawte, N. Keating; *Center for Clinical and Basic Research, Ballerup, Denmark*: B. Clemmesen, P. Alexandersen, L. Petersen, J. Jorgensen, I. Bergmann, L. Vilstrup Moller, G. Hansen, A. Pedersen, M. Jakobsen, K. Overgaard, K. Bjarnson, A. Mollgaard Jensen; *Hologic, Medical Data Management Division, Waltham, Mass.*: P. Steiger, E. Yapchian, S. Steiger; *Merck Research Laboratories, Rahway, N.J.*; *Hoddesdon, United Kingdom*; and *Copenhagen, Denmark*: A. Maragoto, E. Weinberg, G. Cizza, C. Allen, M. Stephens, J. Butcher, S. Marquiss, J. Dollerup, R. Elkjaer, I. Byback.

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