

Significant Differential Effects of Alendronate, Estrogen, or Combination Therapy on the Rate of Bone Loss after Discontinuation of Treatment of Postmenopausal Osteoporosis

A Randomized, Double-Blind, Placebo-Controlled Trial

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Background: Combination therapy with alendronate and estrogen for 2 years increases bone mineral density at the spine and hip more than does therapy with either agent alone. Changes in bone mineral density after discontinuation of therapy have not been compared directly.

Objective: To determine the rate of bone loss when therapy with alendronate, estrogen, or both agents is discontinued.

Design: Double-blind, placebo-controlled discontinuation trial.

Setting: 18 U.S. centers.

Patients: 244 postmenopausal, hysterectomized women 44 to 77 years of age.

Intervention: 2 years of therapy with alendronate, 10 mg/d ($n = 92$); conjugated estrogen, 0.625 mg/d ($n = 143$); alendronate and conjugated estrogen ($n = 140$); or placebo ($n = 50$). At year 3, women were allocated into five groups: Twenty-eight women continued to take placebo and 44 women continued to take combination therapy, but 50 women taking alendronate, 81 taking conjugated estrogen, and 41 taking combination therapy were switched to placebo.

Measurements: Bone mineral density and biochemical markers of bone turnover.

Results: Women taking alendronate or combination therapy who

were switched to placebo for year 3 of the study maintained bone mass. Bone mineral density in these women was 4.1% (CI, 2.6% to 5.7%) and 6.6% (CI, 5.0% to 8.2%) higher, respectively, at the spine ($P < 0.001$ for both treatment comparisons) and 3.5% (CI, 2.3% to 4.6%) and 3.0% (CI, 1.8% to 4.2%) higher, respectively, at the trochanter ($P < 0.001$ for both treatment comparisons) than that in women previously taking estrogen who were switched to placebo. In contrast, women who were taking estrogen and were switched to placebo during year 3 experienced a 4.5% decrease at the spine (95% CI, -5.0% to -4.0%) and a 2.4% decrease at the trochanter (CI, -2.7% to -2.1%) ($P < 0.001$ for both changes). Compared with women who took placebo for 3 years, women who took estrogen for 2 years and were then switched to placebo had a bone mineral density that was 2.9% higher (CI, 1.2% to 4.6%) at the spine ($P < 0.05$) and 2.9% higher (CI, 1.6% to 4.2%) at the trochanter ($P < 0.001$). Changes in biochemical markers during year 3 did not differ among the groups that discontinued active treatment.

Conclusions: Accelerated bone loss is seen after withdrawal of estrogen therapy but not after withdrawal of alendronate or combination therapy. The differential effects after withdrawal of therapy should be considered in the management of postmenopausal osteoporosis.

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Several antiresorptive agents have been shown to increase bone mass and reduce osteoporotic fractures (1–3). Because greater improvements in bone mass in women using therapy are associated with greater reductions in fracture (4, 5), investigators have begun to examine combinations of antiresorptive therapies to achieve more substantial gains in bone mass. Lindsay and colleagues demonstrated that addition of alendronate to hormone replacement therapy in postmenopausal women resulted in greater increases in bone mass than did maintenance of estrogen therapy alone (6). We previously showed that administration of alendronate and estrogen for 2 years in postmenopausal women with low bone mass resulted in statistically significantly greater increases in bone mass at the lumbar spine and femoral neck than those seen in women taking either agent alone (7). Furthermore, combination therapy was safe and resulted in normal findings on histologic examination of bone.

In clinical practice, a key concern is the potential for accelerated bone loss when antiresorptive therapy is discon-

tinued. Approximately one third of women discontinue hormone replacement therapy within 1 year of initiation (8). Older studies have demonstrated significant losses in bone mass after discontinuation of hormone replacement therapy (9–11). In contrast, when therapy with oral alendronate, 10 mg/d, is discontinued after osteoporosis treatment, bone mass at the hip and spine are maintained for 1 year (12). However, no head-to-head comparison of hormone replacement therapy and alendronate or the combination of antiresorptive therapy after discontinuation has been done. In addition, future losses in bone mass when patients discontinue therapy must be considered in management of osteoporosis in postmenopausal women.

We therefore sought to examine the rate of bone loss after discontinuation of 2 years of alendronate therapy, hormone replacement therapy, or combination therapy. A subset of participants continued to take combination therapy for a third year to determine whether prolonged therapy remained beneficial.

Context

Alendronate and conjugated estrogen therapy both increase bone mineral density in postmenopausal women, but is the rate of bone loss greater when alendronate or estrogen therapy is discontinued?

Contribution

The discontinuation phase of this double-blind, placebo-controlled trial showed loss of spine and trochanter bone mass in postmenopausal women 1 year after withdrawal of estrogen and no such loss after withdrawal of either alendronate or combination therapy with alendronate and estrogen therapy.

Cautions

The study was not large or long enough to show whether discontinuation of estrogen therapy is associated with more fractures than discontinuation of either alendronate or combination therapy.

—The Editors

METHODS**Study Participants**

Four hundred twenty-five postmenopausal women 42 to 82 years of age who had low bone mass were enrolled in a 2-year randomized, double-blind, placebo-controlled clinical trial conducted at 18 centers in the United States (7). Participants were recruited from clinics, private practices, newspaper advertisements, and targeted mailings. All participants who completed the initial study were asked to enroll in the 1-year extension. Participants were told that if they were taking active treatment, they might be randomly allocated to receive placebo or treatment for the third year and that if they were taking placebo, they would continue to do so.

Entry criteria for the initial study are described elsewhere (7). All women had had hysterectomy and had a bone mineral density at the lumbar spine that was less than or equal to a T score of -2.0 SDs below the peak bone mass in young adults. Data on presence or absence of ovaries were not collected. Exclusion criteria were metabolic bone disease, a low serum 25-hydroxyvitamin D level, use of medications known to affect bone turnover, renal insufficiency, severe cardiac disease, and recent major upper gastrointestinal disease.

The institutional review board at each clinical site approved the extension protocol. After signing the extension consent form and undergoing baseline evaluation for the extension, participants were allocated to blinded treatment on the basis of their original treatment in the first 2 years of the study. The randomization process was centrally determined by a statistician; as in the initial study, treatment allocation was concealed.

Design

As described for the initial study at each center, patients were randomly allocated to one of four treatment groups: placebo ($n = 50$); alendronate, 10 mg/d ($n = 92$); conjugated estrogen, 0.625 mg/d ($n = 143$); or alendronate, 10 mg/d, plus conjugated estrogen, 0.625 mg/d ($n = 140$) (Figure 1). The conjugated estrogen used was Premarin (Wyeth-Ayerst, Philadelphia, Pennsylvania). All women received calcium carbonate to provide 500 mg of elemental calcium daily.

At the end of the second year, 244 of the 425 women (57%) continued in a 1-year extension of the study (Figure 1). Of these women, 28 who previously received placebo continued to do so. Women who were taking combination therapy were reallocated to continue taking combination therapy ($n = 44$) or switch to placebo ($n = 41$). In addition, 50 participants taking alendronate alone and 81 participants taking conjugated estrogen alone for the first 2 years were assigned to placebo for the third year. All patients and investigators remained blinded to medication allocation. Patients continued to receive calcium supplementation during the third year.

Outcome Measures

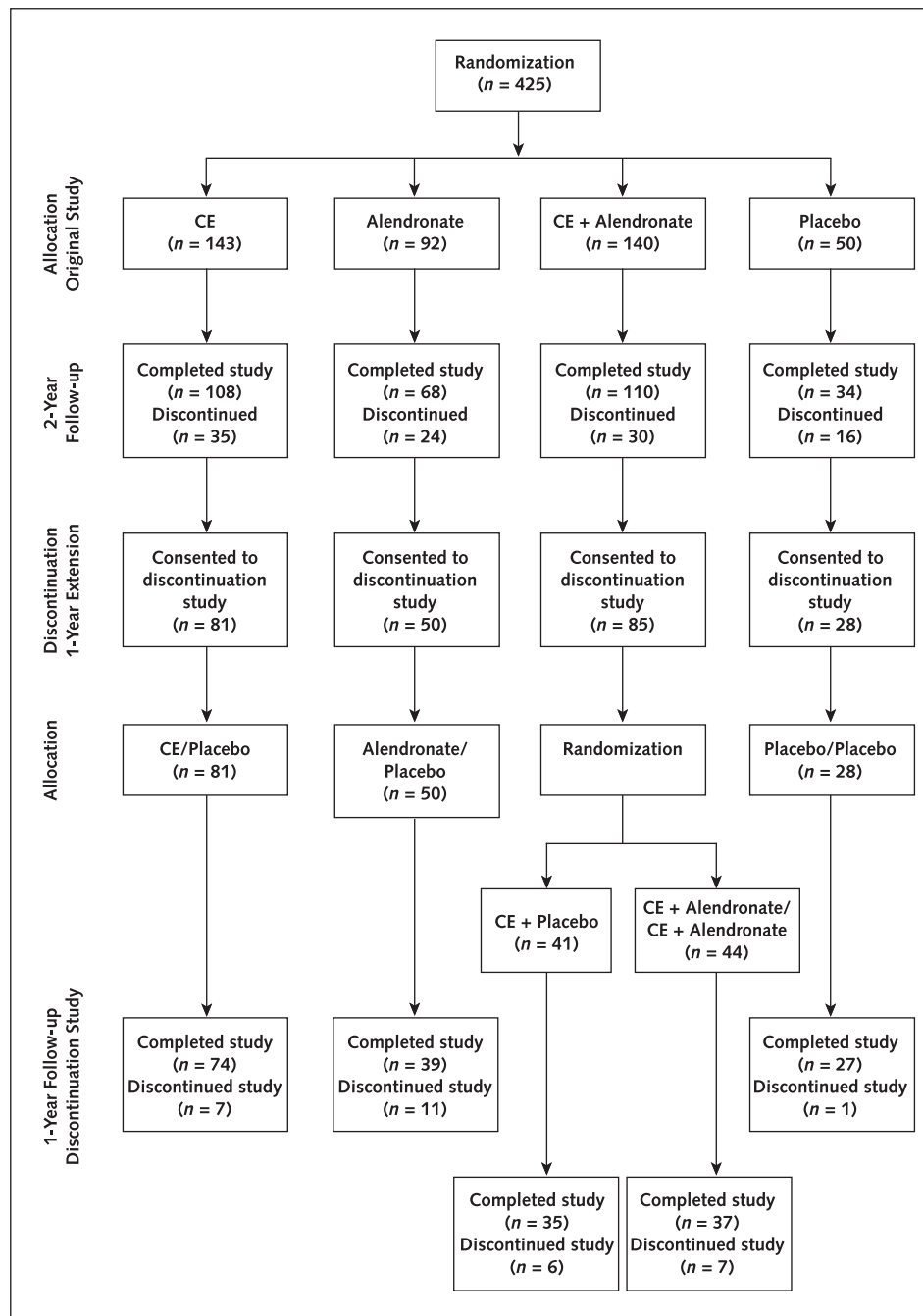
Women were examined at month 24 (baseline of the 1-year extension), month 30, and month 36. Bone mineral density of the lumbar spine, hip (femoral neck, trochanter, total hip), and total body were assessed by using dual-energy x-ray absorptiometry with QDR-1000W, QDR-1500, or QDR-2000 series bone densitometers (Hologic, Inc., Bedford, Massachusetts). A standard phantom was used for cross-calibration at all sites. Serum and urine samples were also obtained at months 24, 30, and 36 for assessment of biochemical markers of bone turnover, namely bone-specific alkaline phosphatase and urinary *N*-telopeptide cross-links of collagen type I, corrected for creatinine.

Statistical Analysis

We used SAS software, version 6.12, TSLevel 0060, PROCEDUREGLM (SAS Institute, Inc., Cary, North Carolina) to analyze the data. The primary efficacy end point was the mean difference between groups in the percentage change in bone mineral density at the lumbar spine from month 24 to month 36. Secondary efficacy end points were the mean percentage changes in bone mineral density of the hip and total body and biochemical markers of bone turnover. Overall percentage changes from month 0 to 36 in spine, hip, and total-body bone mineral density were also analyzed.

The prespecified analysis was based on an intention-to-treat approach. At study design, we prespecified that all patients who had a baseline measurement and at least one measurement during treatment would be included in the analysis according to the group to which they were randomly allocated. The missing data were approximated by carrying forward the last available value on treatment forward to the missing time point. No data from the original

Figure 1. Design of original 2-year study and reallocation to extension phase for year 3.



CE = conjugated estrogen.

2-year study were carried forward to the extension period for any assessment of change. Women who violated the protocol were excluded from analysis of biochemical markers, as previously reported (7).

Between-group comparisons of bone mineral density and biochemical measures were made by using analysis of variance techniques, with treatment, center, and treatment-by-center as factors. The assumption of homoscedasticity for the analysis of variance model was assessed by using the Levene test, and the normality assumption was assessed by

using the Shapiro–Wilk test (13). If the assumptions were violated, a nonparametric method was used to corroborate the parametric results. The Fisher exact test was used to compare treatment groups for the proportion of participants who exceeded predefined limits of change in laboratory safety variables (13). Power calculations based on estimated sample sizes of 56 and 84 participants in the alendronate/placebo and estrogen/placebo treatment groups, respectively, yielded an estimate of 92% power to detect a 1.5% difference between mean percentage changes from

Table 1. Baseline Characteristics of Participants in the Extension Study*

Variable	Placebo/Placebo Group (n = 28)	Alendronate/Placebo Group (n = 50)	Estrogen/Placebo Group (n = 81)	Combination Therapy/Combination Therapy Group (n = 44)	Combination Therapy/Placebo Group (n = 41)
Age, y	64 ± 9	63 ± 8	62 ± 8	65 ± 7	64 ± 8
Time since menopause, y	26 ± 11	24 ± 7	22 ± 9	25 ± 10	22 ± 9
White ethnicity, %	86	88	86	89	95
Smoking, %	11	8	15	18	10
Alcohol consumption, %	7	10	7	11	10
Height, mm	1589 ± 58	1593 ± 66	1597 ± 64	1594 ± 69	1615 ± 51
Body mass index, kg/m ²	30.0 ± 7.1	25.8 ± 4.3	26.6 ± 5.4	26.9 ± 3.8	26.7 ± 4.6
Daily calcium intake, mg	1457 ± 552	1300 ± 488	1273 ± 424	1343 ± 1200	1200 ± 414
Bone mineral density, g/cm ²					
Lumbar spine	0.76 ± 0.09	0.83 ± 0.07	0.80 ± 0.08	0.83 ± 0.08	0.85 ± 0.07
Femoral neck	0.66 ± 0.11	0.64 ± 0.08	0.65 ± 0.09	0.66 ± 0.08	0.67 ± 0.10
Total hip	0.76 ± 0.09	0.78 ± 0.10	0.80 ± 0.08	0.83 ± 0.08	0.85 ± 0.07
Urinary N-telopeptide cross-linked collagen type 1 level, nmol BCE/mmol creatinine	49.3 ± 23.0	19.8 ± 8.8	26.0 ± 14.5	13.6 ± 8.1	13.8 ± 5.3
Serum bone-specific alkaline phosphatase level, ng/mL	12.7 ± 5.2	7.1 ± 2.0	8.0 ± 4.2	5.4 ± 1.8	6.0 ± 2.2
Serum calcium level, mmol/L (mg/dL)	2.28 ± 0.1 (9.1 ± 0.4)	2.30 ± 0.13 (9.2 ± 0.5)	2.28 ± 0.1 (9.1 ± 0.4)	2.28 ± 0.1 (9.1 ± 0.4)	2.25 ± 0.1 (9.0 ± 0.4)
Serum phosphate level, mmol/L (mg/dL)	1.16 ± 0.16 (3.6 ± 0.5)	1.10 ± 0.16 (3.4 ± 0.5)	1.10 ± 0.16 (3.4 ± 0.5)	1.10 ± 0.16 (3.4 ± 0.5)	1.07 ± 0.13 (3.3 ± 0.4)

* Unless otherwise indicated, data are presented as the mean ± SD.

month 24 to month 36 in bone mineral density at the lumbar spine ($\alpha = 0.05$, two-tailed test).

As requested by the journal editors, data on bone mineral density were also analyzed by using a mixed-model analysis, and results of this analysis are presented. An appropriate curvilinear function was fitted to the actual data, and the function was estimated by using all data available across time points for each participant. A model that regressed bone mineral density versus log (month + 1) provided the appropriate fit for the 3-year data and was used to analyze these data. The variable log (month + 1) was used because log (month) is undefined when month is 0, and log (month + 1) yields the value 0 at baseline. The fitted values from the model were used to obtain the percentage change during the period of interest. Data on bone mineral density from the mixed-model analyses are presented unless otherwise specified.

Role of the Funding Source

Data were collected by investigators at each study site with the support of Merck Research Laboratories, Rahway, New Jersey. Analyses were performed by statisticians at Merck & Co., Inc. Data were interpreted by the authors, who submitted the manuscript for publication.

RESULTS

Patient Characteristics and Retention

Baseline randomization characteristics did not differ between participants who entered the extension phase and those who did not. Baseline demographic characteristics of the 244 women who entered the extension phase were similar in all treatment groups (Table 1). Two hundred twelve

women completed the extension phase, including 39 in the alendronate/placebo group, 74 in the conjugated estrogen/placebo group, 35 in the combination therapy/placebo group, 27 in the placebo/placebo group, and 37 in the combination therapy/combination therapy group (Figure 1). In the active treatment group, compliance (defined as taking the study drug for at least 75% of the time spent in the study) was 100%. No compliance data were collected for calcium supplementation.

Bone Mineral Density and Markers of Bone Turnover

During the extension period, women who received estrogen during the first 2 years and were then switched to placebo showed significant losses in bone mineral density at the spine (−4.5% [95% CI, −5.0% to −4.0%]), total hip (−1.8% [CI, −2.1% to −1.6%]), femoral neck (−2.4% [CI, −2.7% to −2.2%]), and trochanter (−2.4% [CI, −2.7% to −2.1]) (all $P < 0.001$) (Figures 2 and 3). Patients in the alendronate/placebo or combination/placebo group showed no significant change in bone mineral density at any of the skeletal sites studied. During the third year, the difference in bone mineral density between women in the alendronate/placebo group and those in the estrogen/placebo group was 3.5% (CI, 2.6% to 4.3%) at the spine, 2.5% (CI, 2.0% to 3.0%) at the trochanter, 2.0% (CI, 1.5% to 2.4%) at the total hip, and 2.1% (CI, 1.7% to 2.5%) at the femoral neck. Compared with the placebo/placebo group, women in the estrogen/placebo group had losses in bone mineral density of 4.4% (CI, −5.3% to −3.4%) at the spine and 2.4% (CI, −3.0% to −1.8%) at the trochanter. No significant differences in bone mass at the spine or hip were observed between the

alendronate/placebo group and the placebo/placebo group, the combination therapy/placebo group and the placebo/placebo group, or the combination therapy/combo combination therapy group and the placebo/placebo group.

Analyses using the last value carried forward provided similar results. For example, the difference in bone mineral density between women in the alendronate/placebo group versus the estrogen/placebo group was 3.6% at the spine (CI, 2.4% to 4.8%), 2.5% at the trochanter (CI, 1.2% to 3.7%), 1.9% at the total hip (CI, 0.9% to 3.0%), and 2.2% at the femoral neck (CI, 0.7% to 3.6%).

During the extension phase, levels of urinary *N*-telopeptide cross-links of collagen type I did not change significantly in the placebo/placebo group or combination therapy/combo combination therapy group but increased significantly in the estrogen/placebo group (increase, 66.1% [CI, 48.3% to 85.9%]), alendronate/placebo group (72.3% [CI, 48.2% to 100.3%]), and combination/placebo group (84.4% [CI, 57.6% to 115.8%]) (all $P < 0.001$) (Figure 4). The increases in urinary *N*-telopeptide cross-links of collagen type I levels in patients who discontinued active treatment did not differ among groups. However, an 83.8% difference (CI, 54.2% to 113.5%) was observed between the alendronate/placebo group and the placebo/placebo group, and an 80.4% difference (CI, 56.8% to 104.0%) was observed between the estrogen/placebo group and the placebo/placebo group.

Serum levels of bone-specific alkaline phosphatase increased significantly in the placebo/placebo group (17.2% [CI, 4.1% to 32.1%]; $P = 0.005$), estrogen/placebo group (66.5% [CI, 54.5% to 79.5%]; $P < 0.001$), alendronate/placebo group (58.2% [CI, 42.8% to 75.2%]; $P < 0.001$), combination therapy/placebo group (66.3% [CI, 45.9% to 85.0%]; $P < 0.001$), and combination therapy/combo combination therapy group (21.1% [CI, 9.2% to 34.3%]; $P < 0.001$) (Figure 4). The increases in serum levels of bone-specific alkaline phosphatase in the estrogen/placebo, alendronate/placebo, and combination therapy/placebo groups were significantly greater than those observed in the placebo/placebo group (differences of 40.1% to 51.7%; all $P < 0.001$) but did not differ significantly.

At the conclusion of the study (3 years), women treated with alendronate or combination therapy for 2

years who were then switched to placebo showed significant increases in bone mineral density of the spine (6.0% [CI, 4.7% to 7.3%] and 8.5% [CI, 7.1% to 9.8%], respectively; both $P < 0.001$); the net difference between the two groups was 2.5 percentage points (CI, 0.7 to 4.3 percentage points). Women who received estrogen for 2 years and were then switched to placebo had a significant change of 1.9% (CI, 1.0% to 2.8%) in bone mineral density of the spine over 3 years; the net difference compared with the placebo group was 2.9% (CI, 1.1% to 4.6%). At 3 years, bone mineral density of the spine in the alendronate/placebo group was 4.1% (CI, 2.6% to 5.6%) higher than that in the estrogen/placebo group. Bone mass at the spine in women who took combination therapy for all 3 years was 11.2% higher (CI, 9.2% to 13.2%) than that in the placebo group.

Similar results were obtained with last-value-carried-forward analyses. After 3 years of treatment, bone mass at the spine was 4.4% higher (CI, 2.8% to 6.0%) in the alendronate/placebo group than in the estrogen/placebo group and 11.4% higher (CI, 9.3% to 13.5%) in the combination therapy group than in the placebo group.

Women treated with alendronate/placebo or combination therapy/placebo showed significant increases in bone mineral density at the total hip (4.5% [CI, 3.9% to 5.2%] and 4.4% [CI, 3.7% to 5.0%], respectively) at 3 years (both $P < 0.001$). Over 3 years, total-hip bone mineral density increased significantly by 2.6% (CI, 2.1% to 3.0%) in women treated with estrogen/placebo; the net change was similar to that in the placebo group. By comparison, total-hip bone mineral density was 4.0% higher (CI, 3.0% to 5.0%) in the alendronate/placebo group than the placebo/placebo group. Women who took combination therapy for all 3 years had a total-hip bone mineral density that was 6.4% higher (CI, 5.4% to 7.5%) than that in the placebo/placebo group. Similar trends were noted at the femoral neck. Compared with the estrogen/placebo group, bone mineral density at the trochanter was 3.4% higher (CI, 2.3% to 4.6%) in the alendronate/placebo group and 3.0% higher (CI, 1.8% to 4.2%) in the combination therapy/placebo group.

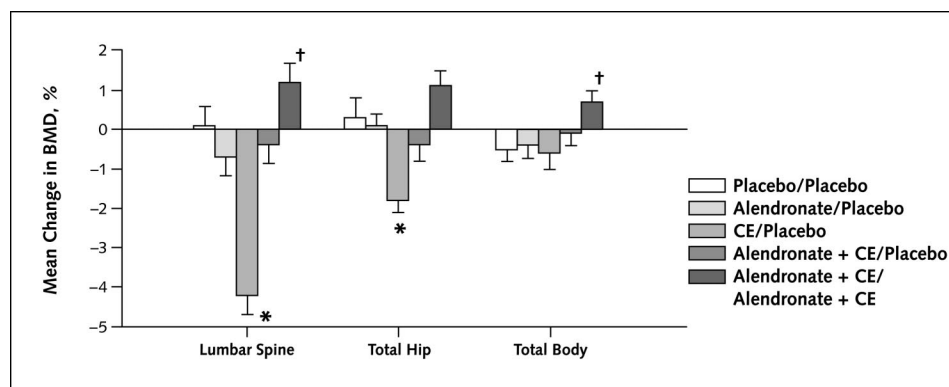
Few differences among groups were noted for total-body bone mineral density at 3 years. However, total-body

Table 2. Between-Treatment Differences at 36 Months*

Between-Treatment Comparison	Mean Difference in Bone Mineral Density (95% CI), %		
	Lumbar Spine	Trochanter	Total Hip
Alendronate/placebo group vs. placebo/placebo group	7.0 (5.0 to 8.9)	6.4 (4.9 to 7.9)	4.0 (3.0 to 5.0)
Estrogen/placebo group vs. placebo/placebo group	2.9 (1.2 to 4.6)	2.9 (1.6 to 4.3)	2.1 (1.2 to 3.0)
Combination therapy/placebo group vs. placebo/placebo group	9.5 (7.4 to 11.5)	5.9 (4.4 to 7.4)	3.9 (2.9 to 4.9)
Combination therapy/combo combination therapy group vs. placebo/placebo group	11.2 (9.3 to 13.2)	9.1 (7.6 to 10.6)	6.5 (5.4 to 7.5)
Alendronate/placebo group vs. estrogen/placebo group	4.1 (2.6 to 5.6)	3.4 (2.3 to 4.6)	1.9 (1.1 to 2.7)
Combination therapy/placebo group vs. alendronate/placebo group	2.5 (0.7 to 4.3)	-0.4 (-1.8 to 0.9)	-0.1 (-1.1 to 0.8)
Combination therapy/placebo group vs. estrogen/placebo group	6.6 (5.0 to 8.2)	3.0 (1.8 to 4.2)	1.8 (1.0 to 2.6)

* Mixed-models analysis.

Figure 2. Mean (\pm SE) percentage change from year 2 to year 3 in bone mineral density (BMD) at the lumbar spine, total hip, and total body.



Vertical lines represent SEs. * $P \leq 0.001$; † $P \leq 0.01$. CE = conjugated estrogen.

bone mineral density was 2.8% (CI, 2.3% to 3.3%) higher in the combination therapy/combotherapy group than in the placebo/placebo group. Last-value-carried-forward analyses provided similar results.

Over 3 years, urinary levels of *N*-telopeptide cross-links of collagen type I did not change significantly in the placebo/placebo group but decreased significantly in the estrogen/placebo group (−15% [CI, −24.7% to −4.1%]; $P = 0.005$), alendronate/placebo group (−38.6% [CI, −47.8% to −27.7%]; $P < 0.001$), combination therapy/placebo group (−38.4% [CI, −47.9% to −27.1%]; $P < 0.001$), and combination therapy/combotherapy group (−75.0% [CI, −78.8% to −70.6%]; $P < 0.001$). The decrease in the estrogen/placebo group at month 36 was significantly less than that in the alendronate/placebo group (difference, −24.1% [CI, −37.6% to −10.6%]; $P < 0.001$) or the combination therapy/placebo group (difference, −24.1% [CI, −38.2% to −10.1%]; $P = 0.001$) but did not differ from that in the placebo group (Figure 4). Similar trends were observed for levels of bone-specific alkaline phosphatase.

Safety and Tolerability

Concomitant therapy with alendronate and estrogen for up to 3 years was well tolerated and had a favorable safety profile, consistent with those of the individual treatments (7). During year 3, the overall proportion of all clinical adverse experiences was similar among patients who were switched from treatment groups to placebo. The proportion of gastrointestinal adverse events was also similar in all groups. Although women who continued to receive combination therapy during year 3 experienced a greater number of serious adverse events than did women taking placebo, these events were not related to any specific medical problem or single organ system. The only serious upper gastrointestinal adverse event, erosive esophagitis, occurred in one patient who received placebo during year 3. Similar proportions of patients in the five treatment groups discontinued therapy because of a clinical adverse

event. During year 3, no clinically meaningful differences were seen among the groups in laboratory adverse events.

DISCUSSION

Postmenopausal women with hysterectomy who received estrogen for 2 years and were then switched to placebo for year 3 had a statistically significant loss of bone mineral density at the spine (4.5%), total hip (1.8%), femoral neck (2.4%), and trochanter (2.4%) during the third year. In contrast, women who received alendronate alone or in combination with conjugated estrogens for 2 years and were then switched to placebo for year 3 maintained gains in spine and hip bone mineral density that were attained during the preceding 2 years. At 3 years, bone mineral density at the spine, femoral neck, and trochanter was significantly higher in the group taking alendronate or combination therapy and switched to placebo than in the group previously taking estrogen. Women who continued taking combination therapy with alendronate and conjugated estrogen for a third year had a spine bone mineral density that was 11.3% higher and a hip bone mineral density that was 6.6% higher than those in the placebo group.

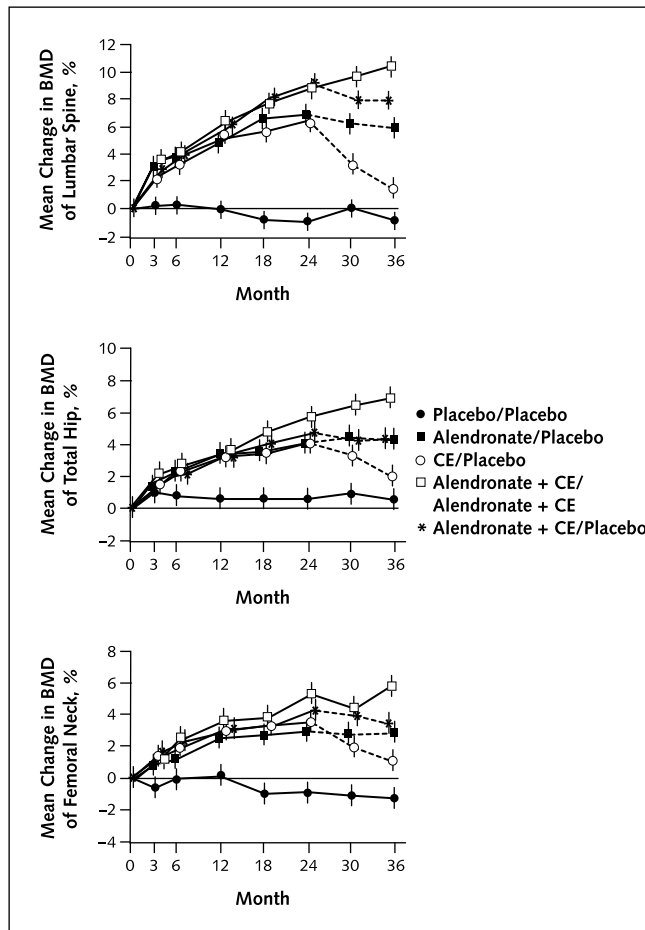
The finding of accelerated bone loss after discontinuation of hormone replacement therapy supports results of previous epidemiologic studies and clinical investigations. The Framingham Study, an epidemiologic study begun in 1948, assessed bone mineral density 40 years later in the female half of the cohort that was still alive. Of the 670 women examined, no differences in bone mass were observed between those who had taken hormone replacement therapy for less than 7 years and those who had never taken hormone replacement therapy (14). In a clinical trial by Christiansen and colleagues, 18 postmenopausal women who crossed over from estrogen–progesterone therapy to placebo after 2 years lost 2.3% of spine bone mass the following year (9), compared with a continued increase in

vertebral bone density in the 16 women who continued therapy during year 3. Moreover, in the Postmenopausal Estrogen/Progestin Intervention trial, women randomly assigned to the placebo group who had used hormone replacement therapy before enrollment lost more bone mineral density at the spine (-5.3%) and hip (-3.9%) than did women who had not previously used hormone replacement (-3.9% from the spine and -1.5% from the hip) (11). In contrast, postmenopausal osteoporotic women who took alendronate, 10 mg/d, for 2 years maintained bone mass for 1 year after therapy was discontinued (12).

Of note, women who took placebo (with calcium supplementation) for 3 years maintained bone mass at the spine and hip. This observation has been noted in other studies, in which older postmenopausal women taking supplementary calcium maintain or have a slight increase in vertebral bone mineral density (1-3) and maintain or lose bone at different regions of the hip (1-3).

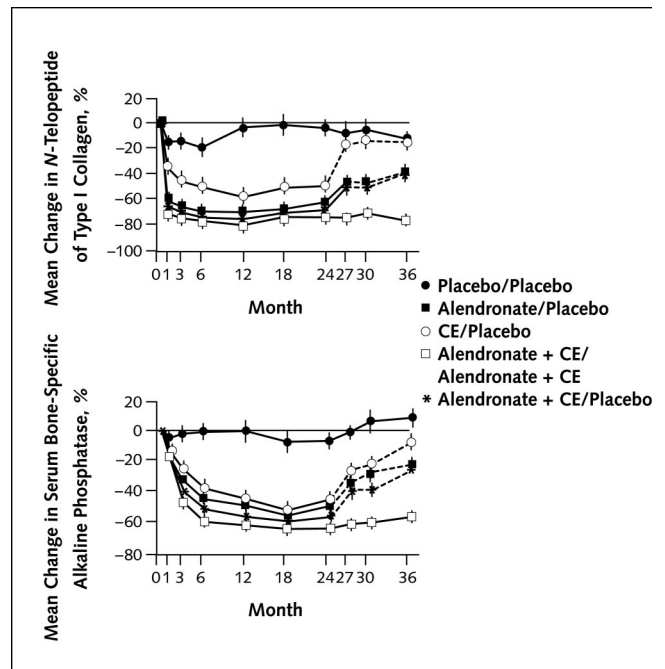
More important, several epidemiologic studies have demonstrated that previous use of hormone replacement therapy does not decrease a woman's risk for fracture (15-

Figure 3. Mean percentage change from baseline to year 3 in bone mineral density (BMD).



Vertical lines represent SEs. Dotted lines represent placebo period. CE = conjugated estrogen.

Figure 4. Mean percentage change from baseline to year 3 in biochemical markers of bone turnover.



Data were obtained from per-protocol analyses. Data on urinary *N*-telopeptide cross-links of collagen type I and serum bone-specific alkaline phosphatase, respectively, were available in the following numbers of patients: 26 and 27 in the placebo/placebo group, 38 and 39 in the alendronate/placebo group, 72 and 74 in the conjugated estrogen (CE)/placebo group, 35 and 36 in the combination therapy/combotherapy group, and 32 and 33 in the combination therapy/placebo group. Dotted lines represent placebo period.

17). In a subset of 1720 women from the Framingham observational cohort study, use of estrogen during the 2 years before the study visit resulted in a statistically significant 66% reduction in hip fracture, whereas no significant reduction was noted in patients with past estrogen use (16). In the Study of Osteoporotic Fractures, a lower incidence of nonvertebral fractures was associated only with current use of hormone replacement therapy, not with previous use (17). A study of 1327 Swedish women 50 to 81 years of age showed that current users of hormone replacement therapy had a 65% lower incidence of hip fracture than did women who had never used estrogen. Former users within the past 5 years had a 24% lower incidence of hip fracture, but this value was not statistically significant (15). Our data may explain the finding that current estrogen use is necessary for reduction in fractures. When estrogen therapy is discontinued, bone mass decreases and protection against fracture may be diminished.

Our study has several limitations. First, we focused on differences in bone mineral density and safety of therapy. Measurement of fracture as an outcome was not a primary objective. However, recent data suggest that greater improvements in bone mass with alendronate therapy lead to greater reduction in fractures (4, 5). Second, of the 425

postmenopausal women in the original study, 320 (75%) completed 2 years of treatment and 244 (57%) consented to the third year. Nevertheless, the study retained the power to show important differences regarding accelerated bone loss after discontinuation of hormone replacement therapy and continued improvement in bone mass during the third year of combination therapy. In addition, at the beginning of year 3, bone mineral density was similar in women taking estrogen or alendronate who were switched to placebo. The difference in the rate of bone loss in the estrogen group does not appear to be due to a difference in bone mineral density between the estrogen and alendronate groups at the beginning of year 3. Finally, the changes in bone mineral density represent mean changes of a group and may not be significant for a single patient, in whom the least significant change must be taken into account. For example, as a group, women who were taking estrogen and switched to placebo lost 1.8% of bone mineral density at the total hip, a statistically significant decrease. If the calculated precision error at the total hip was 1.2%, a difference of 3.3% would be needed to be 95% confident of a statistically significant change in total-hip bone mineral density for an individual patient at follow-up.

The biochemical markers of bone turnover in our study help explain some of the changes in bone mineral density observed during year 3. Women in the estrogen/placebo group had an increase in urinary levels of *N*-telopeptide cross-links of collagen type I, a marker of bone resorption, that reached the postmenopausal baseline level, while bone mineral density decreased significantly at the spine and hip. However, increases in urinary levels of *N*-telopeptide cross-links of collagen type I were also noted in the other groups that discontinued active therapy, although the absolute level was less than that found in the estrogen/placebo group and bone mineral density in these women did not change significantly. In contrast, women who continued to take combination therapy for the third year maintained the previous level of urinary *N*-telopeptide cross-links of collagen type I in a premenopausal range, and bone mass of the spine and hip continued to improve. Although biochemical markers vary significantly from day to day (18–20), group changes in these markers with therapy are predictive of changes in bone mass (19) and partially reflect the changes in bone mass that we observed. Because a higher level of bone resorption may be an independent risk factor for fracture (21), further studies are needed to determine the clinical effect of an increase in bone resorption after discontinuation of antiresorptive therapy.

Our study lays the foundation for a new and important area of investigation that is relevant to clinical practice. In addition to examining bone mass improvements and fracture reduction with treatment, we must examine these outcomes when antiresorptive therapy is discontinued.

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References

- Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. *Lancet*. 1996;348:1535-41. [PMID: 8950879]
- Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. *JAMA*. 1999;282:1344-52. [PMID: 10527181]
- Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *JAMA*. 1999;282:637-45. [PMID: 10517716]
- Hochberg MC, Ross PD, Black D, Cummings SR, Genant HK, Nevitt MC, et al. Larger increases in bone mineral density during alendronate therapy are associated with a lower risk of new vertebral fractures in women with postmenopausal osteoporosis. Fracture Intervention Trial Research Group. *Arthritis Rheum*. 1999;42:1246-54. [PMID: 10366118]
- Wasnich RD, Miller PD. Antifracture efficacy of antiresorptive agents are related to changes in bone density. *J Clin Endocrinol Metab*. 2000;85:231-6. [PMID: 10634392]
- Lindsay R, Cosman F, Lobo RA, Walsh BW, Harris ST, Reagan JE, et al. Addition of alendronate to ongoing hormone replacement therapy in the treatment of osteoporosis: a randomized, controlled clinical trial. *J Clin Endocrinol Metab*. 1999;84:3076-81. [PMID: 10487668]
- Bone HG, Greenspan SL, McKeever C, Bell N, Davidson M, Downs RW, et al. Alendronate and estrogen effects in postmenopausal women with low bone mineral density. Alendronate/Estrogen Study Group. *J Clin Endocrinol Metab*. 2000;85:720-6. [PMID: 10690882]
- Ravnikar VA. Compliance with hormone therapy. *Am J Obstet Gynecol*. 1987;156:1332-4. [PMID: 3578453]
- Christiansen C, Christensen MS, Transbøl I. Bone mass in postmenopausal women after withdrawal of oestrogen/gestagen replacement therapy. *Lancet*. 1981;1:459-61. [PMID: 6110089]
- Lindsay R, Hart DM, Forrest C, Baird C. Prevention of spinal osteoporosis in oophorectomised women. *Lancet*. 1980;2:1151-4. [PMID: 6107766]
- Effects of hormone therapy on bone mineral density: results from the postmenopausal estrogen/progestin interventions (PEPI) trial. The Writing Group for the PEPI. *JAMA*. 1996;276:1389-96. [PMID: 8892713]

12. Stock JL, Bell NH, Chesnut CH 3rd, Ensrud KE, Genant HK, Harris ST, 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;103:291-7. [PMID: 9382121]
13. Neter J, Wasserman W, Kutner M. *Applied Linear Statistical Models.* Boston: Richard D. Irwin; 1990.
14. Felson DT, Zhang Y, Hannan MT, Kiel DP, Wilson PW, Anderson JJ. The effect of postmenopausal estrogen therapy on bone density in elderly women. *N Engl J Med.* 1993;329:1141-6. [PMID: 8377776]
15. Michaëlsson K, Baron JA, Farahmand BY, Johnell O, Magnusson C, Persson PG, et al. Hormone replacement therapy and risk of hip fracture: population based case-control study. The Swedish Hip Fracture Study Group. *BMJ.* 1998;316:1858-63. [PMID: 9632404]
16. Kiel DP, Felson DT, Anderson JJ, Wilson PW, Moskowitz MA. Hip fracture and the use of estrogens in postmenopausal women. The Framingham Study. *N Engl J Med.* 1987;317:1169-74. [PMID: 3657888]
17. Cauley JA, Seeley DG, Ensrud K, Ettinger B, Black D, Cummings SR. Estrogen replacement therapy and fractures in older women. Study of Osteoporotic Fractures Research Group. *Ann Intern Med.* 1995;122:9-16. [PMID: 7985914]
18. Eastell R, Mallinak N, Weiss S, Ettinger M, Pettinger M, Cain D, et al. Biological variability of serum and urinary N-telopeptides of type I collagen in postmenopausal women. *J Bone Miner Res.* 2000;15:594-8. [PMID: 10750575]
19. Miller PD, Baran DT, Bilezikian JP, Greenspan SL, Lindsay R, Riggs BL, et al. Practical clinical application of biochemical markers of bone turnover: consensus of an expert panel. *J Clin Densitom.* 1999;2:323-42. [PMID: 10548827]
20. Greenspan SL, Dresner-Pollak R, Parker RA, London D, Ferguson L. Diurnal variation of bone mineral turnover in elderly men and women. *Calcif Tissue Int.* 1997;60:419-23. [PMID: 9115158]
21. Garnero P, Hausherr E, Chapuy MC, Marcelli C, Grandjean H, Muller C, et al. Markers of bone resorption predict hip fracture in elderly women: the EPIDOS Prospective Study. *J Bone Miner Res.* 1996;11:1531-8. [PMID: 8889854]

She works, always, against the fear of relapse. First come the headaches, which are not in any way ordinary pain ("headache" has always seemed an inadequate term for them, but to call them by any other would be too melodramatic). They infiltrate her. They inhabit rather than merely afflict her, the way viruses inhabit their hosts. Strands of pain announce themselves, throw shivers of brightness into her eyes so insistently she must remind herself that others can't see them. Pain colonizes her, quickly replaces what was Virginia with more and more of itself, and its advance is so forceful, its jagged contours so distinct, that she can't help imagining it as an entity with a life of its own.

Michael Cunningham
The Hours
 New York: Farrar, Straus and Giroux; 1998:70

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