Combination Therapy With Hormone Replacement and Alendronate for Prevention of Bone Loss in Elderly Women
A Randomized Controlled Trial

Susan L. Greenspan, MD
Neil M. Resnick, MD
Robert A. Parker, ScD

The impact of osteoporosis is most pronounced in elderly women who have the greatest risk of fracture.1-2 Available antiresorptive agents increase bone mineral density (BMD) and reduce fractures in women with postmenopausal osteoporosis.3 Although the relationship between BMD and fracture reduction is not linear,4-6 meta-analyses of multiple clinical trials of antiresorptive therapies reveal that an increase in BMD correlates well with the reduction in the rate of vertebral and nonvertebral fractures.6-8 Furthermore, Hochberg et al7 demonstrated that women taking the bisphosphonate alendronate who had the greatest improvement in vertebral BMD also had the greatest reduction in vertebral fractures.

The rationale for combining 2 antiresorptive agents with different mechanisms of action is to induce greater increases in bone mass and, hopefully, greater reduction in fractures than would be observed with a single antiresorptive agent. A 2-year study by Bone et al9 demonstrated that BMD was greater in younger women taking combination therapy than it was in women taking either estrogen or alendronate alone. Fracture reduction was not a primary end point, and no study of combination antiresorptive therapy has had the power to detect a reduction in risk of fracture corresponding to higher bone mass.

Context Therapy with individual antiresorptive agents has been shown to be effective for prevention and treatment of postmenopausal osteoporosis, but whether combination antiresorptive therapy with hormones and bisphosphonates is safe or efficacious or how these agents compare in elderly women is unknown.

Objective To determine whether hormone replacement and the bisphosphonate alendronate sodium in combination are efficacious and safe, and how they compare with monotherapy in community-dwelling elderly women.

Design Randomized, double-blind, placebo-controlled, clinical trial.

Setting and Participants Five hundred seventy-three community-dwelling women age 65 years or older were screened: 485 completed screening and 373 (aged 65 to 90 years) were randomized following a 3-month, open-label, run-in phase with hormone replacement and alendronate placebo. The trial was conducted at a single academic US medical center from January 1996 to May 2001.

Interventions Participants were randomly assigned in a 2 × 2 factorial design to receive hormone replacement (conjugated equine estrogen, 0.625 mg/d, with or without medroxyprogesterone, 2.5 mg/d) and alendronate, 10 mg daily, both agents, or neither. All participants received calcium and vitamin D supplements.

Main Outcome Measures Annualized change in bone mineral density of the hip and spine and occurrence of adverse events.

Results Bone mineral density at 3 years was significantly greater at all femoral and vertebral sites in women treated with combination therapy than with monotherapy, with mean (SD) increases of 5.9% (3.8) at the total hip, 10.4% (5.4) at the posterior-anterior lumbar spine, and 11.8% (6.8) at the lateral lumbar spine. Mean (SD) increases in bone mass at the hip in women treated with alendronate alone were significantly greater than in those treated with hormone replacement therapy alone (4.2% [3.8] vs 3.0% [4.9]; P<.05, respectively), and alendronate resulted in more responders to therapy. All therapies were well tolerated and participant retention was 90% at 3 years.

Conclusions Combination therapy with hormone replacement and alendronate was efficacious and well tolerated in this cohort. Alendronate was superior to hormone replacement, and combination therapy was superior to either therapy alone. Combination therapy may represent an option for women with more severe disease or for those who have failed to achieve an adequate response to monotherapy.

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Moreover, it is not known if improvements in bone mass with combination therapy are relevant to less healthy, older women treated with a standard replacement regimen of estrogen and medroxyprogesterone over 3 years. It is also not known if combination therapy is safe or well tolerated in this group of older women, or if compliance will differ between groups. Finally, it is unknown whether results would be the same with hormone replacement plus bisphosphonates, therefore, our study was designed to examine the efficacy and safety of combination therapy with hormone replacement and alendronate, compared with each agent alone in a group of community-dwelling, elderly women.

METHODS

Participants

We screened 573 community-dwelling women aged 65 or older from the greater Boston area for a single-center clinical trial. Participants were excluded if they had a history of illnesses that could affect bone mineral metabolism (eg, current hyperthyroidism or hyperparathyroidism, renal failure, hepatic failure, and active malignancy) or if they were currently taking medications known to alter bone mineral metabolism (eg, glucocorticoids, anticonvulsants, excess thyroid hormone). Participants were also excluded if they had been treated with osteoporosis medications (eg, bisphosphonates, hormone replacement, or calcitonin) within a year of screening. In addition, women were excluded if they had any contraindications for hormone replacement or alendronate or had a baseline femoral neck BMD of 0.9 g/cm² or greater (ie, zero SD of mean peak BMD using Hologic database prior to the Third National Health and Nutrition Examination Survey database). The protocol was approved by the institutional review board at the Beth Israel Deaconess Medical Center in Boston, Mass. Participants were advised of the nature of the study and provided written informed consent prior to participation.

Study Design

This study used a randomized, double-blind, 2 × 2 factorial design and compared the effect of alendronate or placebo combined with hormone replacement or placebo. We conducted the study from January 1996 through May 2001. Women received alendronate sodium, 10 mg/d (Merck Research Laboratories, Rahway, NJ), or matching placebo. For hormone replacement, women who had had a hysterectomy were given 0.625 mg/d of conjugated equine estrogen (Premarin, Wyeth Ayerst, Philadelphia, Pa) or matching placebo, and women with an intact uterus received conjugated equine estrogen, 0.625 mg/d, with medroxyprogesterone, 2.5 mg/d, (PremPro, Wyeth Ayerst) or matching placebo. A standard food frequency questionnaire was administered, and participants with a daily calcium intake of less than 1000 mg from dietary and supplementary sources were provided with 600 mg per tablet of elemental calcium and 200 IU per tablet of vitamin D (Caltrate Plus D, Wyeth Ayerst) to increase their total daily intake to more than 1000 mg/d. In addition, all participants received a daily multivitamin (400 IU per tablet) so that their daily vitamin D intake was 400 to 800 IU.

Of the 573 women screened, 485 completed screening (Figure 1). To minimize discontinuation following randomization, participants entered a 3-month, open-label, run-in phase prior to randomization, involving hormone replacement, alendronate placebo, calcium (if necessary), and a multivitamin. The rationale behind the run-in phase was to ensure that the 4 groups would be roughly equal after 3 years, such that women taking hormone replacement could be compared with women taking alendronate, combination therapy, or placebo. Three hundred seventy-three women, aged 65 to 90 years, completed the run-in phase and agreed to continue in the study (Figure 1). Reasons for discontinuation during the run-in phase were previously reported. To summarize, 73 participants discontinued secondary to adverse events related to hormone replacement and 39 discontinued for reasons unrelated to hormone replacement. Participants completing the
run-in phase and agreeing to continue in the study were then randomized to 1 of 4 treatment arms: (1) placebo only (hormone replacement placebo and alendronate placebo), (2) hormone replacement only (hormone replacement and alendronate placebo), (3) alendronate only (hormone replacement placebo and alendronate), or (4) combination therapy (hormone replacement and alendronate). All participants continued taking calcium and vitamin D supplementation throughout the study.

After the participant agreed to continue, the study coordinator entered the participant’s data into a computer program and received the participant’s randomization number. Using randomization lists prepared by the study statistician, the research pharmacy determined treatment using the participant’s randomization number. Use of this computer program ensured that participants were randomized only after all procedures were completed and that participants were randomized in strict sequential order at the time they had completed all procedures. Randomization was stratified by prior history of hysterectomy and 3 levels of total hip BMD to ensure balance between groups. Within each strata, randomization was blocked using block sizes of 4, 8, or 12 (block size randomly determined) to reduce the chance that study staff could deduce the treatment assignment. Only the research pharmacist and study statistician had access to the complete randomization code. Sealed, light-proof envelopes were prepared for each participant with their hormone replacement assignment for use by the clinic gynecologist who was not involved in the study outcome activities. Four envelopes were reviewed by the clinic gynecologist during the protocol for safety screening during the course of the study for 3 participants. However, we did not attempt to assess the adequacy of blinding during the study.

Outcome Variables

Bone Mineral Density. Bone mineral density of the hip (total hip, femoral neck, trochanter, intertrochanter, and Ward triangle), lumbar spine (posterior-anterior and lateral), and radius (ultradistal, mid-third, and one-third distal radius) were measured by dual-energy X-ray absorptiometry (DXA) (Hologic QDR 4500A densitometer; Hologic, Inc, Bedford, Mass) at baseline, randomization, and 6-month intervals for 3 years. As previously reported, the coefficients of variation of BMD in elderly women (mean [SD] age, 71 [7] years) using our densitometer were 1.7% for lateral lumbar spine, 1.5% for posterior-anterior lumbar spine, 1.2% for total hip, and 1.9% for femoral neck.13,14 Quality control for bone density scans was performed by Synarc, Inc (San Francisco, Calif), which included visual inspection of the scans for correct scanning and analysis and a review of the quality control database using multivariate Shewart charts.15

Clinical Characteristics. Weight was measured at baseline and every 6 months (Acme Digital In-Bed Scale, model 0501; Acme Medical Scale Co, San Leandro, Calif). Height was measured to the nearest millimeter 3 times per visit and the mean was calculated (Harpenden stadiometer; Holtrain Ltd, Croymych, Dyfed, United Kingdom). Body mass index (BMI) was calculated as kilograms per square meter. We assessed daily activity with the 27-point Instrumental Activities of Daily Living from Laughton and Brody,16 which measures a set of behaviors, including telephoning, shopping, food preparation, housekeeping, laundry, use of transportation, use of medicines, and financial behavior. We also administered the 30-point Folstein Mini-Mental State examination,17 which assesses cognitive function.

Sample Size

A priori, we specified that the study needed to randomize 92 participants to each treatment group (total 368 participants) to provide 80% power to detect a difference of 3% (or 90% power to detect a difference of 4% between each treatment group and the placebo group, with \( \alpha = .05 \) [2-sided]). These calculations were based on variance estimates found in a previous study at our site18 and incorporated a 24% dropout rate (8% per year) during the 3 years after randomization.

Statistical Analysis

Analyses used treatment as assigned (ie, the intention-to-treat framework). Results are presented as mean (SD) in text and tables. Figures display mean (SEM). For comparisons of baseline values among all 4 groups, we used the Kruskal-Wallis test or \( \chi^2 \) test as appropriate. Percentage changes from baseline at initiation of the run-in phase were calculated from participants with the measurement, without imputation for missing values. Statistical significance for changes from baseline within a group was tested using the Wilcoxon rank sum test. For comparisons between groups, we used a Bonferroni correction to adjust for the 3 primary treatment comparisons in the analysis: combined therapy vs alendronate alone, combined therapy vs hormone replacement alone, and alendronate alone vs hormone replacement alone. Binary variables (eg, clinical response) were compared using the Fisher exact test. For continuous variables (eg, BMD measures), we present results from a mixed-models analysis of variance of percentage change from baseline. We did not impute missing data because the mixed-models analysis of variance does not require complete data on each participant. Our analysis adjusted for time trend using date of bone density scan.
and an AR(1) correlation structure between measurements within a partici- pant. The rate of change per year in BMD was calculated from this mixed-models analysis of variance separately for each group. For comparisons between 2 treatment groups, our initial model adjusted for time trend, included an indicator variable to allow for differences between the intercepts (value at the end of the run-in phase) for the 2 treatment groups, and included a time × treatment group interaction.

Conceptually, this model is equivalent to fitting 2 nonparallel lines with different intercepts in an analysis of covariance. If the indicator variable for differences in the intercept was not statistically significant (P > .05), it was excluded and differences in time trend were assessed from a final model, including an overall time trend and the time × treatment group interaction. Similar results (not shown) were found when we imputed missing data using a last-value-carried-forward approach. The response to therapy was analyzed from participants who had a measurement at 36 months. A participant was considered a responder if, after 3 years, the change in BMD at the spine or hip was greater (more positive) than −1.0%.19 Cochran Mantel-Haenszel statistics were used to test for a trend over age groups adjusted for treatment groups. All analyses were performed using SAS version 8.1 (SAS Institute, Cary, NC).

RESULTS

No statistically significant differences were found in baseline characteristics or BMD between the 4 groups (Table 1). Baseline levels of serum calcium, albumin, parathyroid hormone, and 25-hydroxyvitamin D were within the normal range (Table 1). The mean (SD) dietary intake of calcium was 890 (437) mg/d and mean (SD) vitamin D intake was 252 (230) IU/d. Thirty-two percent of participants (120/373) were taking nonsteroidal anti-inflammatory medications or aspirin. Thirty-five percent (130/373) of women had had a hysterectomy and the distribution between estrogen or estrogen plus progesterone (or placebo) was similar across groups. The mean (SD) bone mass of the entire cohort was in the osteopenic classification by World Health Organization criteria; 34% (128/373) of the group had osteoporosis.20,21 Compliance and retention were similar in all groups. Fifty-one percent (489/949) to 63% (599/933) of participants were adherent, which was defined as taking 80% of both medications during the study (Table 2) (criteria previously cited in other estrogen trials22,23). Retention was 90% (337/373) for all participants after 3 years (Figure 1).

Bone Mineral Density

After 3 years, total hip BMD showed a mean (SD) increase of 5.9% (3.8) with combination therapy, an increase of 4.2% (3.8) with alendronate, and an increase of 3.0% (4.9) with hormone replacement (all P <.001), with maintenance of BMD in the placebo group. Similar trends were observed for the BMD of the femoral neck and trochan-

### Table 1. Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 93)</th>
<th>HRT (n = 93)</th>
<th>ALN (n = 93)</th>
<th>HRT + ALN (n = 94)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>72 (5)</td>
<td>71 (5)</td>
<td>71 (4)</td>
<td>72 (6)</td>
<td>.24</td>
</tr>
<tr>
<td>Height, cm</td>
<td>159 (7)</td>
<td>158 (5)</td>
<td>159 (6)</td>
<td>158 (6)</td>
<td>.38</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>69 (18)</td>
<td>69 (12)</td>
<td>71 (17)</td>
<td>70 (15)</td>
<td>.84</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27 (6)</td>
<td>28 (5)</td>
<td>28 (7)</td>
<td>27 (5)</td>
<td>.83</td>
</tr>
<tr>
<td>Dietary calcium, mg/d</td>
<td>969 (456)</td>
<td>859 (416)</td>
<td>856 (421)</td>
<td>877 (452)</td>
<td>.31</td>
</tr>
<tr>
<td>Dietary vitamin D, IU/d</td>
<td>258 (193)</td>
<td>234 (180)</td>
<td>264 (320)</td>
<td>252 (201)</td>
<td>.82</td>
</tr>
<tr>
<td>Serum hematocrit (%)</td>
<td>39.5 (2.8)</td>
<td>39.7 (2.7)</td>
<td>39.9 (3.0)</td>
<td>40.4 (2.8)</td>
<td>.13</td>
</tr>
<tr>
<td>Serum 25-hydroxyvitamin D, ng/mL</td>
<td>37.9 (16.1)</td>
<td>39.5 (19.4)</td>
<td>36.1 (15.8)</td>
<td>36.6 (14.9)</td>
<td>.56</td>
</tr>
<tr>
<td>Serum albumin, g/dL</td>
<td>4.4 (0.3)</td>
<td>4.4 (0.3)</td>
<td>4.4 (0.3)</td>
<td>4.5 (0.3)</td>
<td>.64</td>
</tr>
<tr>
<td>Serum calcium, mg/dL</td>
<td>9.1 (0.4)</td>
<td>9.1 (0.4)</td>
<td>9.1 (0.4)</td>
<td>9.1 (0.3)</td>
<td>.56</td>
</tr>
<tr>
<td>Serum PTH, pg/mL</td>
<td>37.9 (16.1)</td>
<td>39.5 (19.4)</td>
<td>36.1 (15.8)</td>
<td>36.6 (14.9)</td>
<td>.56</td>
</tr>
<tr>
<td>Serum 25-hydroxyvitamin D, ng/mL</td>
<td>17.9 (7.2)</td>
<td>18.2 (8.2)</td>
<td>17.7 (9.0)</td>
<td>19.4 (9.3)</td>
<td>.54</td>
</tr>
<tr>
<td>IADL score (9-27)</td>
<td>26.9 (0.5)</td>
<td>26.9 (0.5)</td>
<td>26.8 (0.8)</td>
<td>26.9 (0.6)</td>
<td>.40</td>
</tr>
<tr>
<td>FMMS Score (0-30)</td>
<td>28.9 (1.7)</td>
<td>29.3 (1.0)</td>
<td>28.9 (2.4)</td>
<td>29.3 (0.9)</td>
<td>.24</td>
</tr>
</tbody>
</table>

Table 1. Baseline Clinical Characteristics

Abbreviations: ALN, alendronate; BMI, body mass index; FMMS, Folstein Mini-Mental Status; HRT, hormone replacement therapy; IADL, Instrumental Activities of Daily Living; NSAI, nonsteroidal anti-inflammatory drugs; PTH, parathyroid hormone.

SI conversion factors: To convert serum calcium from mg/L to mmol/L, multiply by 0.25; serum albumin from g/dL to g/L, multiply by 10; serum PTH from pg/mL to mg/L, multiply by 1.0; and serum 25-hydroxyvitamin D from ng/mL to nmol/L, multiply by 2.496.

*Values expressed as mean (SD) unless otherwise noted.
†P value: overall comparison across groups.
§Fracture after age 50 years.
‡At least 1 drink per week.
¥Hormone replacement and alendronate therapy for prevention of bone loss

HORMONE REPLACEMENT AND ALENDRONATE THERAPY FOR PREVENTION OF BONE LOSS

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After 12 months and for the remainder of the study, the percentage change in total hip BMD was significantly greater in each of the 3 active treatment groups than in the placebo group ($P<.001$). At 36 months, the women treated with combination therapy had a significantly greater increase in total hip BMD than those on either alendronate or hormone replacement alone ($P<.01$). The rate of change of BMD (percentage per year) at the total hip was greater with combination therapy than with either active therapy alone ($P<.01$) (Table 3). These differences were statistically significant for combined therapy vs hormone replacement alone at all hip sites and for combined therapy vs alendronate alone for the total hip and trochanter.

At 3 years, women in the treatment groups had significant increases in posteroanterior and lateral lumbar spine BMD ($P<.001$), with maintenance of vertebral BMD in the placebo group (Figure 2). At all time points after randomization, BMD was greater in each treatment group than in the placebo group. At the posteroanterior lumbar spine, mean (SD) change BMD increased 10.4% (5.4) in the combination group, 7.7% (5.2) in the alendronate group, 7.1% (5.8) in the hormone replacement group (all $P<.001$), and 1.1% (4.6) in the placebo group ($P<.05$). Mean (SD) changes at the lateral lumbar spine reflected changes at the posteroanterior lumbar spine, with an increase of 11.8% (6.8) in women receiving combination therapy. The gain in vertebral BMD and the rate of change was greater in women taking

<table>
<thead>
<tr>
<th>Table 2. Adherence and Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>HRT</td>
</tr>
<tr>
<td>ALN</td>
</tr>
<tr>
<td>HRT + ALN</td>
</tr>
<tr>
<td>Adherence, No./total (%)</td>
</tr>
<tr>
<td>ALN or placebo</td>
</tr>
<tr>
<td>HRT or placebo</td>
</tr>
<tr>
<td>HRT + ALN</td>
</tr>
<tr>
<td>Responders, No./total (%)*</td>
</tr>
<tr>
<td>Total hip</td>
</tr>
<tr>
<td>Trochanter</td>
</tr>
<tr>
<td>Intertrochanter</td>
</tr>
<tr>
<td>Posteroanterior lumbar spine</td>
</tr>
<tr>
<td>Lateral lumbar spine</td>
</tr>
</tbody>
</table>

Abbreviations: ALN, alendronate; HRT, hormone replacement therapy.

*Responders is the percentage change of ≥−1.0% after 3 years.

†$P<.05$ compared with HRT, adjusted for 3 multiple comparisons.

‡$P<.01$ compared with HRT, adjusted for 3 multiple comparisons.
Combination therapy had an additive effect on BMD, but the changes were not significant. The combination therapy group showed greater improvements in BMD at the spine and total hip than did hormone replacement alone. No significant differences were found in the response rate between the 3 groups (Table 2). The combination therapy group had a significantly higher response rate than hormone replacement alone for the total hip (P<.05) but not for the lumbar spine. The women taking alendronate alone had a higher response rate at the intertrochanter (P<.05) than women taking hormone replacement alone. No significant differences were found between BMD increases for women taking estrogen plus progesterone vs women taking unopposed estrogen (data not shown).

Response to Therapy

Most women receiving active treatment responded to therapy, but significant differences were found in the response rate between the 3 active groups (Table 2). The combination therapy group had a significantly higher response rate than hormone replacement alone for the total hip (P<.05) but not for the lumbar spine. The women taking alendronate alone had a higher response rate at the intertrochanter (P<.05) than women taking hormone replacement alone. No significant differences were found between BMD increases for women taking estrogen plus progesterone vs women taking unopposed estrogen (data not shown). The response to therapy was unrelated to baseline BMD, BMI, hysterectomy, dietary calcium and vitamin D intake, baseline vitamin D levels, or use of NSAIDs or aspirin. However, at the total hip, trochanter, and intertrochanter, the response was related to age at consent, with older participants responding less often. For example, in the 3 active treatment groups, the proportion responding at the total hip was 93% in women younger than 70 years, 88% in women aged 70 to 75 years, and 80% in women older than 75 years (P<.01).

Adverse Events

Women receiving hormone replacement (with or without alendronate) had the expected increased incidence of menstrual spotting, cramps, and breast tenderness when compared with women in the 2 groups not receiving hormone replacement (Table 4). Adverse events with combination therapy were similar to those with hormone replacement alone (Table 4). We observed no between group differences in potential adverse effects associated with alendronate (ie, esophagitis, indigestion, heartburn, or dysphagia) (Table 4).

COMMENT

This is the first study to date to compare the efficacy of hormone replacement, the bisphosphonate alendronate, and combined therapy with both agents in community-dwelling, elderly women. We found that combination therapy yielded greater improvements in BMD at the spine and total hip than did monotherapy with hormone replacement or alendronate. Moreover, at 3 years, the BMD increases observed with combination therapy exceeded those seen in most clinical trials of women with osteoporosis whether treated with alendronate, risedronate, or raloxifene hydrochloride. Furthermore, hormone replacement plus alendronate was safe and well tolerated. Finally, in this head-to-head comparison of alendronate and hormone replacement, we found greater improvements in BMD at the hip, and more responders to therapy with alendronate.

Previous studies with younger women have suggested trends similar to those observed in this trial. Bone et al demonstrated in a group of women, all of whom had had a prior hysterectomy and were a decade younger than our cohort, that com-

Table 3. Bone Mineral Density Based on Mixed Models Analysis of Variance

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>HRT</th>
<th>ALN</th>
<th>HRT + ALN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total hip</td>
<td>−0.81</td>
<td>0.48</td>
<td>0.97</td>
<td>1.43</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>−0.68</td>
<td>0.27</td>
<td>0.59</td>
<td>1.00</td>
</tr>
<tr>
<td>Trochanter</td>
<td>−0.98</td>
<td>0.54</td>
<td>1.39</td>
<td>1.91</td>
</tr>
<tr>
<td>Intertrochanter</td>
<td>−0.77</td>
<td>0.48</td>
<td>0.97</td>
<td>1.36</td>
</tr>
<tr>
<td>Ward triangle</td>
<td>−1.04</td>
<td>0.21</td>
<td>1.40</td>
<td>1.38</td>
</tr>
<tr>
<td>Posteroanterior lumbar spine</td>
<td>−0.12</td>
<td>1.61</td>
<td>1.76</td>
<td>2.58</td>
</tr>
<tr>
<td>Lateral lumbar spine</td>
<td>−0.53</td>
<td>1.30</td>
<td>1.65</td>
<td>2.49</td>
</tr>
<tr>
<td>Ultradistal radius</td>
<td>−1.55</td>
<td>0.53</td>
<td>0.58</td>
<td>−0.16</td>
</tr>
</tbody>
</table>

Abbreviations: ALN, alendronate; HRT, hormone replacement therapy.
*Combined group significantly different from HRT alone, adjusted for 3 multiple comparisons; P<.001.
†Combined group significantly different from ALN alone, adjusted for 3 multiple comparisons; P<.05.
‡Not significantly different from zero (P > .05). All other groups significantly changed over time.
§Combined group significantly different from HRT alone, adjusted for 3 multiple comparisons; P<.05.
¶Combined group significantly different from ALN alone, adjusted for 3 multiple comparisons; P<.05.

Bone loss was greater in the active treatment groups but was stable in the placebo groups, and decreased in the placebo group (−3.0% [5.8]; Figure 2). The BMD for the one-third distal radius remained stable in the active treatment groups but decreased in the placebo group (data not shown).

When the analysis comparing alendronate with hormone replacement therapy was performed as a head-to-head analysis without adjustment for multiple comparisons, BMD of the total hip, trochanter, intertrochanter, and Ward triangle were significantly higher in women in the 2 groups not receiving hormone replacement (Table 4). The changes in mean (SD) BMD were related to adherence; BMD was higher in participants who were adherent in all 3 treatment groups (data not shown).

The number of hospitalizations, myocardial infarctions, falls, and clinical fractures was similar in all 4 groups. Participants in all groups lost height (range, −0.4 to −1.1 cm), but the differences between groups were not significant.
HORMONE REPLACEMENT AND ALENDRONATE THERAPY FOR PREVENTION OF BONE LOSS

Combined estrogen and alendronate resulted in greater improvements in BMD at the spine and femoral neck than either agent alone. However, they did not find differences between BMD increases at 2 years in women receiving estrogen vs alendronate. Women were excluded if they had moderate hypertension, recent cardiac disease, dyspepsia, or if they were recently taking aspirin or nonsteroidal anti-inflammatory medications. In contrast, we included such participants. Harris et al administered conjugated estrogen with or without risedronate to 524 postmenopausal women for 1 year. Lumbar spine BMD was not found to be significantly different between the 2 groups, but femoral neck BMD in the combination therapy group was approximately 1% greater than in women taking estrogen alone. In our study, not only was the greatest response noted with combination therapy at all sites, but alendronate therapy resulted in a greater increase in BMD at the hip than hormone replacement therapy.

Investigators have reported that more than 95% of women taking alendronate respond to therapy. Our study confirmed the high response rate that has been observed with alendronate in younger postmenopausal women. However, few data are available in older women receiving hormone replacement or combination therapy. In the Postmenopausal Estrogen/Progestin Intervention trial with younger women (mean age, 56 years), approximately 1.5% of participants receiving hormone replacement therapy had a reduction in spine BMD in the first 12 months (defined as BMD loss of 1% or more in the trial), and 5% to 8% had a reduction in spine BMD from months 12 to 36. At the hip, women showed a reduction in BMD of 14.5% in the first 12 months and of 11.8% from months 12 to 36. To our knowledge, our study is the first long-term clinical trial using standard doses of combined continuous hormone replacement therapy in older women with and without a uterus, and it suggests that over 3 years, 19% of participants had a reduction in BMD at the total hip, and 23% had a reduction in BMD at the trochanter. Only 7% had a reduction in BMD at the posterolateral lumbar spine (Table 2). However, because women often have atypical calcifications outside of the spine that falsely elevate the posterolateral lumbar spine measurements, the lateral lumbar spine nonresponse rate of 16% may be a more appropriate reflection of the impact on vertebral bone mass.

Our study has several limitations. First, it was not powered to examine fractures as an outcome. Although the increases of bone mass with combination therapy are greater than with single therapy, use of combination therapy may not translate to greater fracture reduction. Applying a logistic model developed from a meta-analysis of 12 trials modeling the relationship between improvement in vertebral bone mass and reduction in vertebral fractures, combination therapy would provide an additional 10% fracture reduction over hormone replacement and an additional 8% fracture reduction over alendronate. Both of these translate into clinically relevant benefits. Second, this study may be generalized only to women tolerating hormone replacement for at least the run-in phase. The rationale behind the run-in phase was to minimize withdrawal following randomization. The run-in phase ensured that the 4 groups were of similar size after 3 years, such that women taking hormone replacement could be compared with women taking alendronate, combination therapy, or placebo. Moreover, this study has limited power to examine differences in outcomes of women taking estrogen plus progesterone vs unopposed estrogen. Finally, this study did not have the power to measure differences among treatment groups in the occurrence of rare but serious adverse events, such as myocardial infarction or venous thrombosis. However, data are available from the Women’s Health Initiative and Heart and Estrogen/Progestin Replacement Study that address the risk of

Table 4. Adverse Events Following Randomization

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n = 93)</th>
<th>HRT (n = 93)</th>
<th>ALN (n = 93)</th>
<th>HRT + ALN (n = 94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants with potential HRT events (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menstrual spotting</td>
<td>9 (10)</td>
<td>29 (31)*</td>
<td>7 (8)†</td>
<td>31 (33)$</td>
</tr>
<tr>
<td>Menstrual cramps</td>
<td>0</td>
<td>6 (6)*</td>
<td>0†</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Endometrial biopsy</td>
<td>1 (1)</td>
<td>12 (13)*</td>
<td>2 (2)†</td>
<td>11 (12)$</td>
</tr>
<tr>
<td>Breast tenderness</td>
<td>16 (17)</td>
<td>52 (56)*</td>
<td>22 (24)†</td>
<td>50 (53)$</td>
</tr>
<tr>
<td>Bloating</td>
<td>2 (2)</td>
<td>9 (10)</td>
<td>4 (4)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>12 (13)</td>
<td>13 (14)</td>
<td>9 (10)</td>
<td>11 (12)</td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td>0</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Weight gain</td>
<td>8 (9)</td>
<td>8 (9)</td>
<td>6 (6)</td>
<td>8 (9)</td>
</tr>
<tr>
<td>No. of participants with other adverse events (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophagitis</td>
<td>21 (23)</td>
<td>17 (18)</td>
<td>26 (28)</td>
<td>20 (21)</td>
</tr>
<tr>
<td>Indigestion</td>
<td>4 (4)</td>
<td>5 (5)</td>
<td>6 (6)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Heartburn</td>
<td>15 (16)</td>
<td>11 (12)</td>
<td>17 (18)</td>
<td>16 (17)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td>3 (3)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>3 (3)</td>
<td>6 (6)</td>
<td>5 (5)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>26 (28)</td>
<td>40 (43)</td>
<td>34 (37)</td>
<td>32 (34)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1 (1)</td>
<td>0</td>
<td>2 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>13 (14)</td>
<td>10 (11)</td>
<td>16 (17)</td>
<td>9 (10)</td>
</tr>
<tr>
<td>Falls</td>
<td>42 (45)</td>
<td>44 (47)</td>
<td>52 (56)</td>
<td>49 (52)</td>
</tr>
<tr>
<td>Clinical fractures</td>
<td>9 (10)</td>
<td>5 (5)</td>
<td>7 (8)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Height loss, cm, mean (SD)</td>
<td>−1.1 (1.6)</td>
<td>−0.7 (1.5)</td>
<td>−0.9 (2.0)</td>
<td>−0.4 (2.4)</td>
</tr>
</tbody>
</table>

Abbreviations: ALN, alendronate; HRT, hormone replacement therapy.
*P<.05 hormone replacement vs placebo.
†P<.05 alendronate vs hormone replacement.
‡P<.05 combination therapy vs placebo.
§P<.05 combination therapy vs alendronate.

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complications with hormone therapy. There is no reason to suppose that the risk would differ substantially with the addition of a bisphosphonate to the hormone regimen. The main results of this study (bone mass density with combination therapy) can help answer the question of whether the potential risk of hormone treatment is worth the estimated 8% reduction in fracture risk when combination therapy is used compared with alendronate alone.

This study has several unique features. While the Women’s Health Initiative excluded women older than 79 years of age, we included a cohort approximately a decade older than women in the Women’s Health Initiative. We included elderly postmenopausal women receiving a standard dose of conjugated estrogen with or without medroxyprogesterone. We also included women with osteopenia or osteoporosis. In addition, we included less-healthy elderly women compared with the majority of other trials for postmenopausal osteoporosis. Participants with cardiovascular disease, hypertension, gastrointestinal tract disorders, mild renal insufficiency, or those who were taking aspirin or nonsteroidal anti-inflammatory medications were allowed to participate, reflecting typical participants in clinical practice. In addition, the study was performed at a center using 1 bone mineral densitometer with daily quality control. Analysis was performed with a conservative mixed-models approach, which incorporated all data available. Similar results (not shown) were found using a last-observation-carried-forward analysis. Furthermore, another advantage of the study is the duration of 3 years. Since the changes in BMD in 1 year are of similar magnitude to the coefficient of variation for the dual-energy X-ray absorptiometry scan used to measure bone mass density, an interval greater than 1 year is needed to assess changes in BMD. Moreover, despite 3 years of therapy in an elderly population, the completion rate was 90%. Finally, this study is the first long-term, head-to-head comparison of hormone replacement and alendronate in elderly women.

In summary, in community-dwelling elderly women, combination therapy with alendronate and hormone replacement is safe and efficacious. Monotherapy with alendronate was shown to be superior to hormone replacement, and combination therapy with both was shown to be superior to either alone. This study provides additional information for the growing body of data on the risks and benefits of hormone replacement therapy. Although findings from the Women’s Health Initiative suggest an increased risk when hormone replacement is used for prevention of chronic disease, the study also demonstrated a statistically significant reduction in hip and vertebral fractures. Recently, investigators from the Heart Estrogen/Progestin Replacement Study reported that hormone replacement therapy resulted in a 35% lower risk of type 2 diabetes mellitus during the 4-year trial. More information is needed regarding other potential benefits of hormones or unopposed estrogen, such as improvement in cognitive function, quality of life, mobility, or reduction in depression, falls, and colon cancer in older women. However, for elderly women in whom hormone or estrogen replacement is a therapeutic alternative, combination therapy with a bisphosphonate can be considered to further improve skeletal integrity and may be an option for women who fail to achieve an adequate response on monotherapy or for patients with more severe disease for whom monotherapy would be less desirable.

Author Contributions: Study concept and design: Greenspan, Resnick, Parker. Acquisition of data: Greenspan, Parker. Analysis and interpretation of data: Greenspan, Resnick, Parker. Drafting of the manuscript: Greenspan, Resnick, Parker. Critical revision of the manuscript for important intellectual content: Greenspan, Resnick, Parker. Statistical expertise: Parker. Obtained funding: Greenspan, Resnick. Administrative, technical, or material support: Greenspan, Parker. Study supervision: Greenspan, Parker. Funding/Support: The study was conducted at the Harvard-Thorndike General Clinical Research Center, Beth Israel Deaconess Medical Center, Massachusetts General Hospital, and Wyeth-Ayerst Laboratories (Philadelphia, Pa) provided the Premarin and Prempro, matching placebo, and Os-Cal Plus D, and Merck Research Laboratories (Rahway, NJ) provided the alendronate and matching placebo used in this study.

Disclaimer: The funding organizations and companies providing study drug and placebo had no role in the study design; study conduct; data collection or analysis; interpretation of the data; or preparation, review, or approval of the manuscript.

Acknowledgments: We gratefully acknowledge the assistance of the nursing, nutrition, study, and administrative staff of the Harvard-Thorndike General Clinical Research Center and the Osteoporosis Prevention and Treatment Center at the Beth Israel Deaconess Medical Center where the study was conducted.

Members of the Data and Safety Monitoring Board: Robert A. Heaney, MD (Chair); Clifford J. Rosen, MD; Marcia L. Stefanick, PhD; Siu L. Hui, PhD; Peggy A. Norton, MD; and Sherry Sherman, PhD.

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13. Greenspan SL, Maitland LA, Myers ER, Krasnow
HORMONE REPLACEMENT AND ALENDRONATE THERAPY FOR PREVENTION OF BONE LOSS


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widely, with particularly high rates of use by internists and physicians in the Northeast and the South.

Michael A. Steinman, MD
C. Seth Landefeld, MD
San Francisco VA Medical Center
San Francisco, Calif
Ralph Gonzales, MD, MSPH
University of California, San Francisco


CORRECTIONS

Name Omitted: In the Original Contribution entitled “Combination Therapy With Hormone Replacement and Alendronate for Prevention of Bone Loss in Elderly Women: A Randomized Controlled Trial” published in the May 21, 2003, issue of THE JOURNAL (2003;289:2525-2533), Michael McClurg, MD, should be added to the list of members of the Data and Safety Monitoring Board on page 2532 after Peggy A. Norton, MD.

Error in Author’s Name: In the Review article entitled “Alcohol Consumption and Risk of Stroke: A Meta-analysis” published in the February 5, 2003, issue of THE JOURNAL (2003;289:579-588) in the byline, the initial letter “L.” was incorrectly placed in front of the name of author Brian Lewis, MPH.

CME ANNOUNCEMENT

Online CME to Begin in Mid-2003

In mid-2003, online CME will be available for JAMA/Archives journals and will offer many enhancements:

- Article-specific questions
- Hypertext links from questions to the relevant content
- Online CME questionnaire
- Printable CME certificates and ability to access total CME credits

We apologize for the interruption in CME and hope that you will enjoy the improved online features that will be available in mid-2003.
Author Contributions: Dr Furukawa had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Furukawa, Watanabe, Montori, Guyatt.

Acquisition of data: Furukawa, Watanabe, Omori.

Analysis and interpretation of data: Furukawa, Watanabe, Omori.

Drafting of the manuscript: Furukawa, Watanabe, Omori.

Critical revision of the manuscript for important intellectual content: Furukawa, Watanabe, Omori, Montori, Guyatt.

Financial Disclosures: Dr Furukawa reports that he has received research funds and speaking fees from Asahi Kasei, Astellas, Dai-Nippon, Eisai, Eli Lilly, GlaxoSmithKline, Janssen, Kyowa Hakko, Meiji, Organon, Pfizer, Tsumura, Yoshitomi, and Zelia and that the Japanese Ministry of Education, Science, and Technology and the Japanese Ministry of Health Labor and Welfare have also funded his research. Dr Watanabe reports that he received a grant from the Cochrane Child Health Field bursary scheme. Dr Montori reports receiving research funding from the Mayo Foundation, the Endocrine Society, and the American Diabetes Association. Dr Guyatt reports that he has received grant funding from Pfizer, Lotte and John Hecht Foundation, Bristol-Myers Squibb, Aventis, Pharmacia, Leo Pharma, AstraZeneca AB, and Eli Lilly Canada. He has also received consultation fees from Up-to-Date. All authors have written Cochrane protocols and/or reviews. Dr Furukawa is an editor of 1 Cochrane review group and Dr Guyatt is a co-convener of 2 Cochrane methods groups. No other disclosures were reported.

Funding/Support: No external funding was used for this study.


CORRECTIONS

Error in Wording: In the Research Letter entitled “Trends in the Diffusion of Laparoscopic Nephrectomy” published in the June 7, 2006, issue of JAMA (2006;295:2480-2482), an error occurred in wording. In the second paragraph on page 2480 (“Methods” section), the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) procedure code “55.3” for nephrectomies should have been “55.52.” The sentence should have read “International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) procedure codes were used to determine the annual number of . . . nephrectomies (55.52, 55.4, 55.5, 55.54, 55.91).”

Incorrect Funding Listed: In the Original Contribution entitled “Combination Therapy With Hormone Replacement and Alendronate for Prevention of Bone Loss in Elderly Women: A Randomized Controlled Trial” published in the May 21, 2003, issue of JAMA (2003;289:2525-2533), Wyeth-Ayerst Laboratories did not provide Os-Cal Plus D. On page 2532, under Funding/Support, the last sentence should read “Wyeth-Ayerst Laboratories (Philadelphia, Pa) provided the Premarin and Prempro, matching placebo, and Caltrate Plus D, and Merck Research Laboratories (Rahway, NJ) provided the alendronate and matching placebo used in this study.”

Incorrect Reference Citation: In the Letter entitled “Use of Children as Interpreters” published in the December 20, 2006, issue of JAMA (2006;296:2802), a reference was incorrectly cited. The authors in reference 1 should have been listed in the following order: Lee KC, Winickoff JP, Kim MK, et al.

Incorrect Date Listed: In the Original Contribution entitled “Long-term Proton Pump Inhibitor Therapy and Risk of Hip Fracture” published in the December 27, 2006, issue of JAMA (2006;296:2947-2953), the inclusion dates of the database used were incorrect. On page 2947, under Design, Setting, and Patients, the first sentence should read “A nested case-control study was conducted using the General Practice Research Database (1987-2002), which contains information on patients in the United Kingdom.” On page 2948, under Study Cohort, the first sentence should read “From the 9.4 million patients who started follow-up in the full version of the GPRD between May 1987 and April 2002, we excluded individuals meeting at least 1 of the following 4 criteria: . . . .” On page 2952, in the first column, first paragraph, the third sentence should read “The maximum follow-up and duration of potential PPI exposure in our cohort were close to 14 years (1988-2002) . . . .”