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Pretreatment Levels of Bone Turnover and the Antifracture Efficacy of Alendronate: The Fracture Intervention Trial

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ABSTRACT: The influence of pretreatment bone turnover on alendronate efficacy is not known. In the FIT, we examined the effect of pretreatment bone turnover on the antifracture efficacy of daily alendronate given to postmenopausal women. The nonspine fracture efficacy of alendronate was significantly greater among both osteoporotic and nonosteoporotic women with higher baseline levels of the bone formation marker PINP.

Introduction: Previous trials have shown that high bone turnover is associated with greater increases in BMD among bisphosphonate-treated women. The influence of pretreatment bone turnover levels on antifracture efficacy has not been well studied.

Materials and Methods: We randomized women 55–80 years of age with femoral neck BMD T scores ≤ −1.6 to alendronate (ALN), 5–10 mg/day (n = 3105), or placebo (PBO; n = 3081). At baseline, 3495 women were osteoporotic (femoral neck BMD T score ≤ −2.5 or prevalent vertebral fracture), and 2689 were not osteoporotic (BMD T score > −2.5 and no prevalent vertebral fracture). Pretreatment levels of bone-specific alkaline phosphatase (BSALP), N-terminal propeptide of type 1 collagen (PINP), and C-terminal cross-linked telopeptide of type 1 collagen (sCTx) were measured in all participants using archived serum (20% fasting). The risk of incident spine and nonspine fracture was compared in ALN- and PBO-treated subjects stratified into tertiles of baseline bone marker level.

Results and Conclusions: During a mean follow-up of 3.2 years, 492 nonspine and 294 morphometric vertebral fractures were documented. Compared with placebo, the reduction in nonspine fractures with ALN treatment differed significantly among those with low, intermediate, and high pretreatment levels of PINP levels (p = 0.03 for trend). For example, among osteoporotic women in the lowest tertile of pretreatment PINP (<41.6 ng/ml), the ALN versus PBO relative hazard for nonspine fracture was 0.88 (95% CI: 0.65, 1.21) compared with a relative hazard of 0.54 (95% CI: 0.39, 0.74) among those in the highest tertile of PINP (>56.8 ng/ml). Results were similar among women without osteoporosis at baseline. Although they did not reach statistical significance, similar trends were observed with baseline levels of BSALP. Conversely, spine fracture treatment efficacy among osteoporotic women did not differ significantly according to pretreatment marker levels. Spine fracture treatment efficacy among nonosteoporotic women was related to baseline BSALP (p = 0.05 for trend). In summary, alendronate nonspine fracture efficacy is greater among both osteoporotic and non-osteoporotic women with high pretreatment PINP. If confirmed in other studies, these findings suggest that bisphosphonate treatment may be most effective in women with elevated bone turnover.

Key words: alendronate, bone turnover, treatment efficacy, fracture

INTRODUCTION

Clinical trials have shown that alendronate (ALN), a nitrogen-containing bisphosphonate, reduces the risk of spine, hip, and other nonspine fracture among postmenopausal women with existing vertebral fractures and among those with low BMD.¹⁻³ The benefit of ALN seems to be greatest among women with BMD T scores below −2.5.¹⁻³ Among women with existing vertebral fractures, ALN efficacy seems to be unaffected by age, body mass index, or previous nonspine fracture history.¹⁻⁶ ALN treatment reduces biochemical markers of bone turnover.

Dr Bauer has received research funding from MRL, Procter & Gamble, and SKB. Dr Garnero is an employee of Synarc Molecular Markers. Dr Hochberg receives research funding from GSK and Novartis and serves as a consultant for GSK, Novartis, Amgen, Anakin, Astra-Zeneca, Bristol-Myers, MRL, NPS Pharmaceuticals, Scios, Takeda, and Wyeth. Dr Santora is an employee of MRL. Dr Black receives research funding from Novartis, consults for Roche and NPS Pharmaceuticals, and is on the speaker’s bureau for MRL. All other authors have no conflict of interest.

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formation by 30–50% and bone resorption by 50–70%. Several studies have reported that women with higher pretreatment levels of bone turnover have greater increases in BMD while receiving antiresorptive treatment, including ALN and estrogen replacement therapy. Furthermore, those women with greater short-term reductions in bone turnover during ALN treatment have greater increases in BMD. Recently, Siebel et al. reported that baseline levels of urine deoxypyridinoline, a marker of bone resorption, did not influence the antifracture efficacy of risedronate. However, these analyses were limited to the outcome of vertebral fractures and by a relatively small number of events in the risedronate treatment group (N = 62).

We used data from the Fracture Intervention Trial (FIT) to determine if pretreatment levels of bone turnover were associated with the antifracture efficacy of ALN among postmenopausal women with osteoporosis (femoral neck T score ≤ −2.5 or prevalent vertebral fracture). Because 44% of FIT participants did not have existing vertebral fractures and had hip BMD T scores between −1.6 and −2.5, we also determined if baseline levels of bone turnover were associated with the antifracture efficacy of ALN among these nonosteooporotic women.

MATERIALS AND METHODS

Study design and subjects

We performed a posthoc analysis of data from the FIT, a randomized, double-blind clinical trial of ALN or placebo (PBO) among 6459 women recruited at 11 U.S. clinical centers. Subjects were postmenopausal women between 55 and 80 years of age with femoral neck BMD (Osteometric; Hologic, Waltham, MA, USA) ≤0.68 g/cm², equivalent to a T score ≤ −1.6 using NHANes normative data. Data from both the vertebral fracture arm, which enrolled women with one or more existing vertebral fractures, and the clinical fracture arm, which enrolled women without baseline vertebral fracture, were included in these analyses. All women provided written informed consent, and the protocol was approved by the appropriate institutional review boards. This analysis is limited to the 6186 women who completed the trial and had complete baseline and follow-up measurements.

Subjects were randomly allocated to daily ALN or PBO. The dose of ALN was initially 5 mg/day for 2 years but was increased to 10 mg/day at the second annual visit, because other trials suggested that 10 mg had greater effects on BMD. Eighty-two percent of participants in each treatment group had dietary calcium intakes at baseline <1000 mg/day; they were asked to take a daily supplement (Ostacal; GSK) containing 500 mg of elemental calcium and 250 IU of vitamin D.

Measurements

Biochemical markers of bone turnover: Each participant provided a serum specimen before randomization that was frozen and transported to a central repository. Twenty percent of randomized subjects, selected at random, were fasting during the baseline visit. Most of the specimens were stored at −20°C for 3 years before they were all placed at −70°C. Archived specimens were thawed and assayed for biochemical markers of bone turnover in 2001.

Bone-specific alkaline phosphatase (BSALP), a marker of bone formation, was measured with a standard assay (Tandem; Hybritech, San Diego, CA, USA). This immunoradiometric assay (IRM) uses two monoclonal antibodies directed against the human bone isoenzyme purified from human SAOS-2 osteosarcoma cells as a standard. This assay has a 16% cross-reactivity with the circulating liver isoenzyme, and the intra- and inter assay CVs were 7% and 12%, respectively. Serum intact N-terminal propeptide of type I collagen (PINP), another marker of bone formation, was measured by radioimmunoassay (Intact PINP; Orion Diagnostica, Upsalla, Finland). The intra- and inter assay CVs of the PINP immunoassay were <5% and 8%, respectively. C-terminal cross-linked telopeptide of type I collagen (sCTx), a marker of bone resorption, was measured using a one-step ELISA assay with reported intra- and inter assay CVs of 5% and 8%, respectively. Because sCTx levels are greatly affected by fasting status, we excluded nonfasting subjects from all sCTx analyses. The manufacturer performed the PINP assays, and the BSALP and sCTx assays were performed at a central facility (Molecular Markers, Synarc, Lyon, France). These biochemical markers are known to be stable in serum stored at −70°C and are believed to be stable at −20°C (P. Garner, personal communication, 2005).

BMD: BMD was measured at the hip and posterior-anterior (PA) spine on all participants using Hologic QDR 2000 densitometers and were repeated annually. Detailed descriptions of these procedures have been previously published. Pathologic fractures or fractures caused by trauma sufficient to fracture a normal bone in most young adults were excluded by a blinded EndpointsAdjudication Committee. Facial and skull fractures were excluded because they are not associated with osteoporosis or low BMD, but all other fracture outcomes were included. Lateral spine radiographs were obtained according to published guidelines at baseline and 3 (vertebral fracture arm) and 4 years (clinical fracture arm) after randomization. The assessment of morphometric vertebral fractures at baseline has been previously described. A new vertebral fracture was defined as a decrease of 20% and at least 4 mm in any vertebral height from baseline to end of the study. All assessments were blinded to treatment allocation.

Analysis

Baseline characteristics of ALN- and PBO-treated women were compared with χ² and t-tests. Results were similar with or without log transformation of marker levels; only untransformed data are presented. Randomized subjects were divided into tertiles based on baseline levels of biochemical marker among both osteoporotic and non-osteoporotic women (see below).
The primary analysis examined the relationship between pretreatment marker levels and the antifracture efficacy of ALN among osteoporotic women (femoral neck BMD T score ≤ −2.5 or prevalent vertebral fracture); these women form the osteoporotic cohort from FIT and have been described.\(^3\) All nonspine (including hip) fracture outcomes were examined in age-adjusted proportional hazards models, using time to event after the randomization visit. Incident vertebral fractures were analyzed with age-adjusted logistic regression models.

To test for interactions between baseline levels of biochemical markers and ALN versus PBO treatment efficacy, our initial models included interaction terms using the baseline marker level as a continuous variable. Interaction term \( p < 0.10 \) were considered statistically significant. We searched for similar interactions using tertiles of baseline marker and tested the significance of different treatment effect across tertiles of baseline marker levels with a trend statistic. Trend statistics \( p < 0.05 \) were considered statistically significant. Parallel analyses were performed in women without osteoporosis at baseline (femoral neck BMD T score > −2.5 and no prevalent vertebral fracture). All models were adjusted for age and performed with and without adjustment for baseline hip BMD. We examined the effect of specific marker cut-points selected a priori (above or below premenopausal mean values ± 2 SD) based on normative data from the OFELY study.\(^2\) Secondary analyses using ALN- and PBO-related changes in hip and spine BMD from baseline until the end of follow-up, stratified by tertile of baseline marker, were performed using linear regression. The results of these analyses are presented as the absolute difference in annualized percent change in BMD between ALN- and PBO-treated subjects.

**RESULTS**

**Baseline characteristics**

Baseline characteristics of both the osteoporotic subjects (femoral neck BMD T score ≤ −2.5 or prevalent vertebral fracture) and the nonosteorotic subjects (BMD T score between −1.6 and −2.5 and no prevalent vertebral fracture) were similar in the ALN and PBO groups (Table 1). Within both osteoporotic and nonosteorotic subgroups, baseline biochemical markers were similar in the ALN and PBO groups. Tertiles of baseline markers for the osteoporotic and nonosteorotic groups, derived from the pooled results from the ALN and PBO groups at baseline, are shown in Table 2.

**Pretreatment marker levels and treatment efficacy in osteoporotic women**

Among all osteoporotic women, ALN reduced the risk of nonspine (relative hazard [RH] = 0.69; 95% CI: 0.58, 0.83) and morphometric vertebral fractures (OR = 0.50; 95% CI: 0.39, 0.65). Compared with PBO-treated women, ALN-treated osteoporotic women with higher baseline levels of PINP had a greater reduction in nonspine fracture risk than those with lower baseline levels of PINP (Table 3; Fig. 1). Compared with PBO-treated women, the RH for nonspine fracture among osteoporotic ALN-treated women in the lowest tertile of pretreatment PINP was 0.88 (95% CI: 0.65, 1.21) and was 0.54 (95% CI: 0.39, 0.74) in the highest tertile \( (p \text{ for trend } = 0.03) \). When baseline PINP level was analyzed as a continuous variable among osteoporotic women, the nonspine fracture PINP × treatment interaction \( p \text{ value} \) was 0.02. Results using pretreatment BSALP and sCTx were in the same direction as those for PINP, but the relationships between tertile of BSALP or sCTx and the risk of

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**Table 1. Baseline Characteristics of Study Population**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Osteoporotic subjects (BMD T score ≤ −2.5 or prevalent spine fracture)</th>
<th>Non-osteoporotic subjects (BMD T score &gt; −2.5 and no prevalent spine fracture)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years ± SD)</td>
<td>ALN group (N = 1764) 69.8 ± 5.9</td>
<td>PBO group (N = 1731) 70.0 ± 5.9</td>
</tr>
<tr>
<td></td>
<td>ALN group (N = 1341) 66.9 ± 6.1</td>
<td>PBO group (N = 1348) 67.0 ± 6.0</td>
</tr>
<tr>
<td>BMI (kg/m² ± SD)</td>
<td>ALN group (N = 1764) 24.7 ± 4.0</td>
<td>PBO group (N = 1731) 24.9 ± 4.0</td>
</tr>
<tr>
<td></td>
<td>ALN group (N = 1341) 25.7 ± 4.0</td>
<td>PBO group (N = 1348) 25.7 ± 4.1</td>
</tr>
<tr>
<td>Existing vertebral fracture</td>
<td>ALN group (N = 1764) 97.9 (55.5%)</td>
<td>PBO group (N = 1731) 95.2 (55.0%)</td>
</tr>
<tr>
<td></td>
<td>ALN group (N = 1341) 0</td>
<td>PBO group (N = 1348) 0</td>
</tr>
<tr>
<td>Femoral neck BMD (g/cm² ± SD)</td>
<td>ALN group (N = 1764) 0.55 ± 0.06</td>
<td>PBO group (N = 1731) 0.55 ± 0.06</td>
</tr>
<tr>
<td></td>
<td>ALN group (N = 1341) 0.63 ± 0.03</td>
<td>PBO group (N = 1348) 0.63 ± 0.03</td>
</tr>
<tr>
<td>Baseline BSALP (ng/ml ± SD)</td>
<td>ALN group (N = 1764) 14.0 ± 4.5</td>
<td>PBO group (N = 1731) 14.1 ± 4.6</td>
</tr>
<tr>
<td></td>
<td>ALN group (N = 1341) 13.3 ± 4.2</td>
<td>PBO group (N = 1348) 13.4 ± 4.3</td>
</tr>
<tr>
<td>Baseline PINP (ng/ml ± SD)</td>
<td>ALN group (N = 1764) 52.1 ± 21.3</td>
<td>PBO group (N = 1731) 52.1 ± 20.2</td>
</tr>
<tr>
<td></td>
<td>ALN group (N = 1341) 50.6 ± 19.4</td>
<td>PBO group (N = 1348) 51.2 ± 19.5</td>
</tr>
<tr>
<td>Baseline sCTx (fasting)</td>
<td>ALN group (N = 1764) 3329.4 ± 1680.9</td>
<td>PBO group (N = 1731) 3341.4 ± 1901.7</td>
</tr>
<tr>
<td></td>
<td>ALN group (N = 1341) 3243.3 ± 1681.4</td>
<td>PBO group (N = 1348) 3301.3 ± 1584.4</td>
</tr>
</tbody>
</table>

* Fasting sCTx available among 699 osteoporotic subjects and 537 non-osteoporotic subjects.

**Table 2. Tertile of Pretreatment Marker Level Between Osteoporotic and Non-Osteoporotic Subjects**

<table>
<thead>
<tr>
<th>Tertile 1</th>
<th>Tertile 2</th>
<th>Tertile 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>PINP (ng/ml)</td>
<td>&lt;41.6</td>
<td>41.6–56.8</td>
</tr>
<tr>
<td>BSALP (ng/ml)</td>
<td>&lt;11.7</td>
<td>11.7–14.9</td>
</tr>
<tr>
<td>sCTx (fasting)*</td>
<td>&lt;2337</td>
<td>2337–3665</td>
</tr>
<tr>
<td>PINP (ng/ml)</td>
<td>&lt;41.1</td>
<td>41.1–55.7</td>
</tr>
<tr>
<td>BSALP (ng/ml)</td>
<td>&lt;11.2</td>
<td>11.2–14.2</td>
</tr>
<tr>
<td>sCTx (fasting)*</td>
<td>&lt;2385</td>
<td>2385–3663</td>
</tr>
</tbody>
</table>

* Fasting sCTx available among 699 osteoporotic subjects and 537 non-osteoporotic subjects.
nonspine fracture did not reach statistical significance. When baseline BSALP level was analyzed as a continuous variable among osteoporotic women, the nonspine fracture BSALP × treatment interaction p value was 0.70. There was no relationship between pretreatment PINP, BSALP, or sCTx and ALN efficacy for incident spine fractures among osteoporotic women (Table 3).

**Pretreatment marker levels and treatment efficacy in nonosteoporotic women**

Among nonosteoporotic subjects, the overall effect of ALN versus PBO was not statistically significant for nonspine fractures (RH = 1.11; 95% CI: 0.88, 1.40) or incident vertebral fractures (OR = 0.65; 95% CI: 0.37, 1.16). We found that pretreatment levels of bone turnover were associated with ALN efficacy among FIT participants without osteoporosis, but the effects were less consistent than among osteoporotic women. Compared with PBO-treated women, ALN-treated nonosteoporotic women with higher pretreatment levels of PINP had a greater reduction in nonspine fracture risk (Table 4). For example, the RH for nonspine fracture among nonosteoporotic ALN-treated women in the lowest tertile of pretreatment PINP was 1.46 (95% CI: 0.98, 2.17) compared with 0.77 (95% CI: 0.51, 1.17) in the highest tertile (p for trend = 0.03). When baseline PINP level was analyzed as a continuous variable among nonosteoporotic women, the nonspine PINP × treatment interaction p value was 0.08. We found no evidence of a relationship between baseline BSALP levels or sCTx and ALN treatment efficacy for nonspine fracture. Interestingly, among nonosteoporotic women, higher pretreatment levels of BSALP, but not PINP, were associated with greater ALN efficacy for incident spine fracture (Table 4). The OR for incident vertebral fracture was 1.22 (95% CI: 0.45, 3.33) in the lowest tertile of BSALP compared with 0.25 (95% CI: 0.07, 0.88) in the highest tertile (p for trend = 0.05). When baseline BSALP level was analyzed as a continuous variable among nonosteoporotic women, the incident vertebral fracture BSALP × treatment interaction p value was 0.08. The number of women with fasting baseline sCTx levels was too small to definitively evaluate the relationship with incident vertebral fracture.

**Additional analyses**

We performed several additional analyses to test the robustness of our results. We repeated these analyses after adjusting for baseline hip BMD, and the results did not change (data not shown). Results were similar when we dichotomized baseline bone turnover into low and high groups rather than using tertiles. For example, using normative data from healthy young women in the OFELY cohort, a population-based sample of French women, we calculated a PINP cut-point that represented the mean premenopausal level plus 2 SD. In age-adjusted analyses among the osteoporotic women in FIT, the nonspine fracture risk reduction for ALN was 52% (95% CI: 25%, 69%)
among women with pretreatment PINP >67 ng/ml compared with a risk reduction of 23% (95% CI: 6%, 37%) if pretreatment PINP was <67 ng/ml (p = 0.05 for interaction between high and low PINP level and ALN versus PBO efficacy).

To determine if the relationships between baseline turnover and treatment-related changes in axial BMD in FIT were consistent with the observed relationships between baseline turnover and fracture efficacy, we analyzed change in BMD during the entire study among ALN- and PBO-treated women within each tertile of baseline turnover marker. Consistent with the nonspine fracture results among osteoporotic women, higher levels of PINP were associated with a greater difference in change in total spine BMD among ALN- and PBO-treated women (Table 5), but the associations with BSALP and sCTx, and the associations between baseline markers and hip BMD, were not statistically significant. Among nonosteoporotic women, higher baseline levels of all three markers were associated with greater ALN versus PBO increases in hip BMD (Table 6). Similar associations were found among nonosteoporotic women for baseline PINP and treatment-related changes in spine BMD.

**DISCUSSION**

In this posthoc analysis of data from a large, placebo-controlled, randomized trial of postmenopausal women with low BMD, we found that, among osteoporotic women (femoral neck BMD T score ≤−2.5 or prevalent vertebral fracture), the nonspine fracture efficacy of ALN was greater in those with higher pretreatment levels of PINP. A similar trend was observed with another marker of bone formation, BSALP, although the relationship did not reach statistical significance. Among these osteoporotic women, we found no relationship between pretreatment level of bone turnover and vertebral fracture treatment efficacy. Interestingly, among nonosteoporotic women (hip BMD T score between −1.6 and −2.5 and no prevalent vertebral fractures), the nonspine fracture efficacy of ALN was also greater among those with higher pretreatment levels of PINP, whereas spine fracture efficacy was greater among those with higher levels of BSALP. Our sCTx results are difficult to interpret because the analyses were limited to the 20% of subjects fasting at baseline. Although not completely consistent across all three markers, our results suggest that pretreatment levels of bone turnover may influence the antifracture effectiveness of ALN therapy, particularly for nonspine fractures. Consistent with the fracture data, we also found that, among nonosteoporotic women, higher baseline levels of all three markers were associated with greater treatment-related increases in hip BMD. Among nonosteoporotic women, higher baseline PINP was also associated with greater treatment-related increases in spine BMD, and among osteoporotic women, higher PINP was associated with greater increases in spine BMD.

Previous studies found that among estrogen-,<sup>6,9,10</sup> calcitonin-,<sup>22</sup> and bisphosphonate-treated women,<sup>23</sup> higher pretreatment levels of bone turnover were associated with greater increases in bone mass. Few data exist, however, on the relationship between pretreatment levels of bone turnover and the antifracture efficacy of antiresorptive treatment. Recently, Siebel et al.<sup>13</sup> reported that, in a pooled analysis of several risedronate versus placebo trials, the spine fracture risk reduction with risedronate therapy was similar among women with low and high pretreatment bone turnover. In that study, 1593 osteoporotic postmenopausal women received risedronate, 5 mg/day, or PBO, and were followed for up to 3 years for the development of new morphometric vertebral fractures. Baseline bone turnover was assessed with a urine marker bone resorption, deoxypyridinoline (DPD). Among the women with baseline DPD levels below the median (15.4 nmol/nmol creatinine), the relative risk for a new vertebral fracture with risedronate therapy was 0.52 (95% CI: 0.30, 0.92), whereas among those with baseline DPD levels above the median, the relative risk was 0.54 (95% CI: 0.36, 0.80). These analyses were based on a relative small number of fractures (51 in the low turnover group and 116 in the high turnover group), but are consistent with our vertebral fracture results among osteoporotic women. The study of Siebel et al. did not report the relationship between baseline turnover and nonspine fracture efficacy or the relationship between baseline turnover and change in BMD.

In previous analyses in the FIT population, we found
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that, among ALN-treated women, greater short-term reductions in bone turnover markers were associated with fewer hip, spine, and nonspine fractures.<sup>34</sup> We further reported that, contrary to most cohort studies,<sup>21,25-27</sup> baseline turnover in the PBO group was not associated with a higher risk of fracture. This study extends these earlier findings and suggests that the magnitude of antifracture effects of ALN is influenced by pretreatment levels of bone turnover, particularly for nonspine fracture.

The strengths of our study include the large size, a well-characterized population, and the careful assessment of the fracture outcomes.<sup>1,23</sup> Our study did have several weaknesses that should be noted. We could not reliably measure bone resorption in this cohort, because urine specimens were not available, and 80% of the baseline serum was collected in a nonfasting state. Thus, we are unable to provide definitive data on the relationship between baseline markers of bone resorption and ALN treatment efficacy. Despite the large number of nonspine fractures (492 among osteoporotic women and 294 among nonosteooporotic women), there were insufficient numbers of hip fractures to assess the relationship between baseline turnover and those events. Our results only apply to postmenopausal women treated with ALN and may not apply to other bisphosphonates, other antiresorptive treatments, or other populations, such as men or premenopausal women. The number of fractures was insufficient to determine if the effects of baseline turnover were similar during the first 2 years of the trial, when ALN-treated women received 5 mg/day, and in subsequent years, when subjects received 10 mg/day. Last, the stability of serum turnover markers stored at −20°C has not been adequately studied, and suboptimal serum storage may have attenuated the relationships we observed.

Many experts agree that osteoporotic postmenopausal women, specifically those with existing vertebral fractures or with low BMD (T score ≤ −2.5), benefit most from bisphosphonate therapy.<sup>28-30</sup> Unfortunately, approximately one-half of all fractures occur among women without osteoporosis.<sup>31-33</sup> Our findings suggest that, similar to prevalent vertebral fracture or low BMD, higher levels of bone turnover may identify postmenopausal women most likely to benefit from ALN treatment. If confirmed in other studies, future practice guidelines may eventually incorporate measurement of both BMD and bone turnover thresholds to optimize patient selection for bisphosphonate treatment.

In summary, in this posthoc analysis of data from a placebo-controlled clinical trial with fracture outcomes, we found that the nonspine fracture efficacy of ALN therapy was greater among women with higher pretreatment levels of PINP. This effect was observed in both osteoporotic and nonosteoporotic women. We did not find that higher bone turnover was associated with greater spine fracture efficacy among osteoporotic women, but among nonosteoporotic women, we did show that higher pretreatment levels of BSALP were associated with greater spine fracture efficacy. If confirmed in other studies, bone turnover may

### Table 5. Difference in Mean Percent Change in BMD for ALENDRONATE vs. PLACEBO by TERTILE of PRETREATMENT MARKER LEVEL Among Osteoporotic Women (N = 3495)

<table>
<thead>
<tr>
<th>Tertile</th>
<th>Pretreatment Difference (95% CI)</th>
<th>Pretreatment Difference (95% CI)</th>
<th>Pretreatment Difference (95% CI)</th>
<th>p trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.09 (0.91, 1.28)</td>
<td>1.39 (1.18, 1.59)</td>
<td>1.25 (1.06, 1.45)</td>
<td>0.26</td>
</tr>
<tr>
<td>PINP</td>
<td>1.31 (1.13, 1.48)</td>
<td>1.20 (1.00, 1.40)</td>
<td>1.22 (1.02, 1.43)</td>
<td>0.56</td>
</tr>
<tr>
<td>BSALP</td>
<td>1.06 (0.62, 1.51)</td>
<td>1.04 (0.64, 1.45)</td>
<td>1.60 (1.18, 2.01)</td>
<td>0.08</td>
</tr>
<tr>
<td>sCTx (fasting)</td>
<td>1.77 (1.57, 1.96)</td>
<td>2.09 (1.87, 2.31)</td>
<td>2.11 (1.89, 2.32)</td>
<td>0.02</td>
</tr>
<tr>
<td>PINP</td>
<td>1.86 (1.66, 2.06)</td>
<td>2.05 (1.85, 2.25)</td>
<td>2.07 (1.84, 2.30)</td>
<td>0.16</td>
</tr>
<tr>
<td>BSALP</td>
<td>2.16 (1.61, 2.70)</td>
<td>2.26 (1.78, 2.73)</td>
<td>2.10 (1.64, 2.56)</td>
<td>0.85</td>
</tr>
</tbody>
</table>

* Age-adjusted.

### Table 6. Difference in Mean Percent Change in BMD for ALENDRONATE vs. PLACEBO by TERTILE of PRETREATMENT MARKER LEVEL Among Non-Osteoporotic Women (N = 2689)

<table>
<thead>
<tr>
<th>Tertile</th>
<th>Pretreatment Difference (95% CI)</th>
<th>Pretreatment Difference (95% CI)</th>
<th>Pretreatment Difference (95% CI)</th>
<th>p trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.01 (0.84, 1.18)</td>
<td>1.14 (0.97, 1.32)</td>
<td>1.33 (1.17, 1.49)</td>
<td>0.01</td>
</tr>
<tr>
<td>PINP</td>
<td>1.06 (0.90, 1.22)</td>
<td>1.08 (0.91, 1.24)</td>
<td>1.34 (1.16, 1.52)</td>
<td>0.02</td>
</tr>
<tr>
<td>sCTx (fasting)</td>
<td>0.88 (0.54, 1.23)</td>
<td>0.95 (0.61, 1.29)</td>
<td>1.39 (1.03, 1.75)</td>
<td>0.04</td>
</tr>
<tr>
<td>PINP</td>
<td>1.47 (1.31, 1.64)</td>
<td>1.61 (1.43, 1.79)</td>
<td>1.97 (1.79, 2.16)</td>
<td>0.0001</td>
</tr>
<tr>
<td>BSALP</td>
<td>1.56 (1.40, 1.72)</td>
<td>1.67 (1.50, 1.85)</td>
<td>1.80 (1.61, 1.99)</td>
<td>0.06</td>
</tr>
<tr>
<td>sCTx (fasting)</td>
<td>1.63 (1.22, 2.04)</td>
<td>1.93 (1.53, 2.33)</td>
<td>1.98 (1.56, 2.40)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

* Age-adjusted.
prove to be a useful measurement to help target women who are likely to derive the greatest benefit from bispho-
phonate therapy.

REFERENCES


9. Rosen CJ, Chesnut CH III, Mallinak NJ 1997 The predictive value of biochemical markers of bone turnover for bone mineral density in early postmenopausal women treated with hormone replacement or calcium supplementation. J Clin Endo-
crinol Metab 82:1904–1910. [see comments]


12. Black DM, Reiss TF, Nevitt MC, Cauley J, Karpf D, Cums-
nings SR 1993 Design of the Fracture Intervention Trial. Osteo-


poros Int 11:76–82.


29. Anonymous 2002 Screening for osteoporosis in postmeno-


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