ORIGINAL ARTICLE

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BMD Changes and Predictors of Increased Bone Loss in Postmenopausal Women After a 5-Year Course of Alendronate

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ABSTRACT

Management of women discontinuing bisphosphonates after 3 to 5 years of treatment is controversial. Little is known about how much bone mineral density (BMD) is lost after discontinuation or whether there are risk factors for greater rates of bone loss post-discontinuation. We report patterns of change in BMD and prediction models for the changes in BMD in postmenopausal women during a 5-year treatment-free period after alendronate (ALN) therapy. We studied 406 women enrolled in the Fracture Intervention Trial (FIT) who had taken ALN for a mean of 5 years and were then enrolled in the placebo arm of the FIT Long-Term Extension (FLEX) trial for an additional 5 years, describing 5-year percent changes in total hip, femoral neck, and lumbar spine BMD over the treatment-free period. Prediction models of 5-year percent changes in BMD considered all linear combinations of candidate risk factors for bone loss such as BMD at the start of the treatment-free period, the change in BMD on ALN, age, and fracture history. Serum for three markers of bone turnover was available in 76 women, and these bone turnover markers were included as candidate predictors for these 76 women. Mean 5-year BMD changes were –3.6% at the total hip, –1.7% at the femoral neck, and 1.3% at the lumbar spine. Five-year BMD losses of >5% were experienced by 29% of subjects at the total hip, 11% of subjects at the femoral neck, and 1% of subjects at the lumbar spine. Several risk factors such as age and BMI were associated with greater bone loss, but no models based on these risk factors predicted bone loss rates. Although about one-third of women who discontinued ALN after 5 years experienced >5% bone loss at the total hip, predicting which women will lose at a higher rate was not possible. © 2013 American Society for Bone and Mineral Research.

KEY WORDS: BISPHOSPHONATES; BONE DENSITY; DUAL-ENERGY X-RAY ABSORPTIOMETRY (DXA); DRUG HOLIDAY; ALENDRONATE/THERAPEUTIC USE; OSTEOPOROSIS, POSTMENOPAUSE; OSTEOPOROSIS; OSTEOPOROSIS/TREATMENT

Introduction

Up to half of postmenopausal women will experience fractures during their lives, making postmenopausal osteoporosis a significant source of patient morbidity and mortality.[1,2] Treatment with bisphosphonates such as alendronate (ALN) over 3- to 5-year courses has been shown in multiple large clinical trials to both increase bone mineral density (BMD) and reduce the risk of nonvertebral and vertebral fractures for women with postmenopausal osteoporosis.[3–8] A handful of clinical trials have studied BMD changes and fractures during longer-term bisphosphonate use, comparing women who

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continue treatment beyond 3 to 5 years versus those who stop therapy.[9–12] Results from these trials have been inconclusive regarding the efficacy of bisphosphonates to prevent fractures when used long term. Because of the rising concern for rare but serious adverse events such as osteonecrosis of the jaw[13,14] and atypical fractures[15,16] attributed to bisphosphonates, the United States Food and Drug Administration (FDA) has conducted a systematic review of trials studying the efficacy and safety of bisphosphonate use for longer than 3 to 5 years.[17] The FDA reported that patients at low risk for fracture may be good candidates for discontinuation of bisphosphonate therapy after 3 to 5 years, whereas patients at increased risk for fracture may benefit from continued bisphosphonate therapy.[18] Post hoc analyses of the Fracture Intervention Trial Long-Term Extension (FLEX) trial suggest that women with femoral neck (FN) BMD *T*-score <-2.5 (*T*-score <-2.0 for those with a prevalent vertebral fracture) may have a reduced incidence of clinical vertebral fracture with longer-term bisphosphonate use.[19,20]

Although the recent report by the FDA and concerns for the long-term risks of bisphosphonate use could increase the number of women who stop bisphosphonate therapy, little is known about the natural course of postmenopausal osteoporosis after stopping bisphosphonates. Despite the lack of data directly linking BMD changes in this population to fractures, knowing the rate, variability, and the factors that predict bone loss in women discontinuing bisphosphonates may aid clinical decisions regarding duration of discontinuation and monitoring during bisphosphonate cessation.

Using data from the placebo group from the FLEX trial, we present a descriptive analysis of 5-year percent changes in BMD for postmenopausal women who stopped ALN after an average of 5 years of use. In addition, we performed an exploratory analysis to search for risk factors associated with greater loss of BMD after discontinuation of ALN, and attempted to fit prediction models based on candidate risk factors for the 5-year percent changes in BMD.

Materials and Methods

Study participants

The design and results of both the Fracture Intervention Trial (FIT) and the FLEX trial from which our study group is derived have been previously reported.[4,5,9,11] The FLEX trial included postmenopausal women aged 61 to 86 years who were randomized to ALN (5 mg/day for 2 years, 10 mg/day thereafter) in the FIT ($n = 3236$) and were subsequently rerandomized to either 5 more years of ALN ($n = 662$) or to placebo ($n = 437$). We analyzed women from the placebo group who each contributed up to 5 yearly BMD measurements. To avoid including data from women on open-label osteoporosis therapy, we excluded individual BMD measurements performed after discontinuing the study drug (placebo). We analyzed all women from the placebo group who had at least one eligible BMD measurement after FLEX randomization (406, 93%) (Fig. 1). Initial inclusion criteria before the administration of ALN during the parent trial (FIT) included women with baseline BMD ≤ 0.68 g/cm^2 (*T*-score ≤ -1.6). Exclusion criteria at the beginning of the treatment-free period (FLEX baseline) included total hip (TH) BMD <0.515 g/cm^2 (*T*-score <-3.5),[21] TH BMD being lower than before ALN treatment, or having received ALN for less than a total of 3 years. Each participant was offered a daily supplement containing 500 mg of calcium and 250 IU of vitamin D3.

Of the 437 women considered for analysis, 100 participants had had bone turnover markers (BTMs) measured. These participants had a complete set of blood samples drawn at each time point of interest (before starting ALN, after completion of trial-administered ALN at 36 or 48 months, and at baseline,

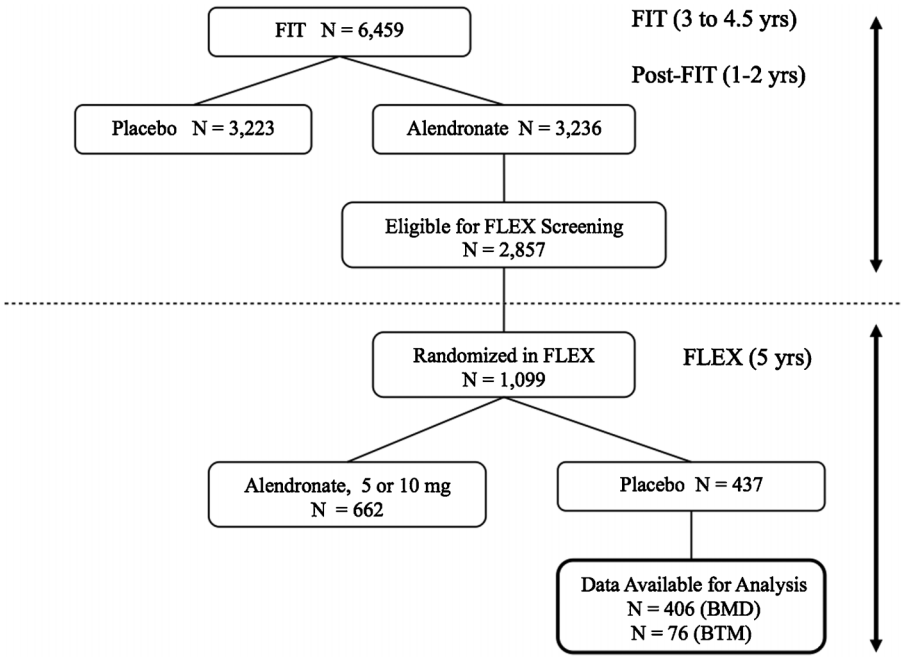

Fig. 1. Design of trials from which the study group is derived. FIT = Fracture Intervention Trial; FLEX = FIT Long-Term Extension; BMD = bone mineral density; BTM = bone turnover markers.

month 36, and month 60 of the treatment-free period) and were adherent with both trial-administered ALN before the treatment-free period and placebo given throughout the treatment-free period (defined as taking >75% of the assigned medication). Of this sample, only 76 women were on ALN at the baseline of the treatment-free period (defined as reporting both that the last dose of ALN was taken within 90 days of the study baseline and that ≥180 days of ALN was taken in the time period between the end of the parent trial and baseline of the treatment-free period) and had their BTM data analyzed.

BMD measurements

At the ALN treatment-free period baseline, BMD was measured at the TH, FN, and posteroanterior lumbar spine (LS), using dual-energy X-ray absorptiometry (DXA). Measurements were made with the same Hologic QDR 2000 densitometers used during the parent trial (FIT) when participants received active ALN therapy (Hologic, Inc., Bedford, MA, USA). TH and FN BMD were measured annually. LS BMD was measured at months 36 and 60, and was the average of the individual BMDs from L_2 to L_4 vertebral bodies. Individual vertebral bodies were excluded if vertebral fracture was present, leading to 13.1%, 12.5%, and 12.1% of participants having one or more vertebral bodies excluded at baseline, month 36, and month 60, respectively. Phantom-based reproducibility of LS BMD was 0.4% to 0.5%, and for similar machines in other studies, in vivo reproducibility has been reported as about 1%.[22–24] If a participant experienced bone loss at the TH >8% over 1 year, >10% over 2 years, >12% over 3 years, etc., or three or more new fractures, the participant was deemed to have experienced "excessive bone loss" and the investigator was notified without disclosing treatment assignment. Risks and benefits associated with study continuation were discussed with the participant. Discontinuation from the study drug was required if any TH BMD measurement was more than 5% below the FIT baseline value. Women who discontinued the study drug were strongly encouraged to remain in the trial and have BMD measured at the usual scheduled intervals to preserve the ability to perform an "intention to treat" analysis. A common reason for discontinuing the study drug was a decision to use open-label ALN. In these analyses, we have therefore excluded any BMD measurements obtained after women discontinued the study drug (placebo) because participants were likely no longer treatment-free.

Bone turnover markers

After completion of the observation period, analyses of BTMs were performed in one batch using stored serum drawn both during the active administration of ALN and across the ALN treatment-free period. Specimens were obtained in a nonfasting state and stored at −70°C over the treatment-free period. During the parent trial, samples were also stored at −70°C with the exception of 2 years at −20°C. All assays were performed at a central laboratory (Synarc, Lyon, France). Serum C-terminal telopeptide of type 1 collagen (CTX), a marker of bone resorption, and N-propeptide of type 1 collagen (PINP), a marker of bone formation, were measured by electrochemiluminescent immunoassay (Roche Elecsys Analyzer, Roche Diagnostics, Mannheim, Germany) with intra-assay and interassay coefficients of variability of approximately 4% and 6%, respectively. Bone-specific alkaline phosphatase (bone ALP), another marker of bone formation, was measured by paramagnetic particle immunoassay (Beckman, San Diego, CA, USA).

Statistical methods

Five-year percent changes were estimated for each participant with at least one qualifying follow-up BMD measurement using linear mixed models for log-transformed BMD. TH and FN BMD were measured annually during the observation period, and LS BMD at years 0, 3, and 5. Models for each BMD measure included linear, quadratic, and cubic terms in time as fixed effects to accommodate nonlinearity in the average trajectory, and random intercepts and slopes to model subject-specific departures from the population trajectory. We obtained participant-specific estimates of 5-year percent change by back-transforming best linear unbiased predictions (BLUPs) provided by the mixed model, using the following formula: percent change = 100*[exp(5-year change in log-BMD)-1].

We also used linear mixed models for repeated measures of log-transformed BMD during the 5-year treatment-free period to assess the independent associations of risk factors measured before the treatment-free period with bone loss during the treatment-free period. Specifically, these associations were estimated by interactions of the risk factors with the linear, quadratic, and cubic time variables used to model changes in BMD. Candidate risk factors included age, body mass index (BMI), total duration of ALN use, BMD before ALN use, percent change in BMD during ALN use, daily calcium intake, self-reported general health status, fracture history, smoking, alcohol use, self-reported walking for exercise, history of falls, and levels of CTX, bone ALP, and PINP measured at baseline of the treatment-free period. All risk factors associated with change in BMD at the TH, FN, or LS at a significance of $p < 0.1$ were included in the final adjusted models for BMD change at each of the three BMD locations.

Finally, we assessed the ability of the same risk factors to provide clinically useful predictions of future bone loss. Statistically significant independent associations, even those plausibly interpretable as causal, may have limited utility in clinical prediction. To assess potential predictive accuracy, we exhaustively screened candidate models for our BLUP-based estimates of 5-year percent bone loss in the 406 women studied. These models included one to eight predictors amongst the candidate risk factors listed above (excluding BTM levels), and allowed for interactions between them. To assess whether prediction of the trajectory of BMD changes over a shorter period would differ from prediction of 5-year percent bone loss, we performed a sensitivity analysis using estimates of 2-year percent bone loss to look for differences in predictive accuracy. The screening procedure was repeated on the sample of 76 women with BTM data including treatment-free period baseline (FLEX baseline) BTM levels as additional predictors. We did not allow interactions for the models fit to the sample of 76 women, and only one BTM was included in each model screened. R^2, corrected for optimism using 10-fold cross-validation, served as our measure of predictive accuracy. All analyses were performed using Stata Version 12 (Stata Corp., College Station, TX, USA).

Table 1. Baseline Characteristics at the Start of Treatment-Free Period After a 5-Year Course of ALN

Baseline characteristic ($n = 406$)	Mean (SD) or *n* (%)
Age (years)	73.6 (5.9)
BMI (kg/m^2)	25.8 (4.3)
Race	
White	391 (96)
Self-reported general health	
Very good/excellent	236 (58)
Good	145 (36)
Fair/Poor	24 (6)
Walk for exercise	225 (57)
Fall in last 12 months	94 (23)
History of fracture	236 (58)
Smoking	
Never	208 (51)
Former/current	197 (49)
Drank alcohol in last 30 days	212 (52)
Dietary calcium (mg/d)	628 (383)
Years of ALN use	5.1 (0.7)
On ALN at baseline	320 (79)
Time since FIT baseline (years)	5.7 (0.3)
Time since FIT closeout (years)	1.9 (0.5)
BMD	
Total hip (gm/cm^2)	0.724 (0.089)
Femoral neck (gm/cm^2)	0.612 (0.073)
Lumber spine (gm/cm^2)	0.907 (0.145)
Total HIP *T*-score	−1.94 (0.82)
≤−2.5	89 (22)
>−2.5 to ≤−2.0	95 (24)
>−2.0	220 (54)
Femoral neck *T*-score	−2.17 (0.67)
≤−2.5	120 (30)
>−2.5 to ≤−2.0	121 (30)
>−2.0	163 (40)
% Change in BMD after 5 years of ALN	
Total hip	3.53 (4.69)
Femoral neck	4.21 (5.96)
Lumbar spine	9.57 (6.60)
Bone turnover marker[a]	
CTX (ng/mL)	0.117 (0.065)
Bone ALP (ng/mL)	8.55 (2.86)
PINP (ng/mL)	24.7 (11.8)

ALN = alendronate; SD = standard deviation; BMI = body mass index; FIT = Fracture Intervention Trial; BMD = bone mineral density; CTX = serum C-terminal telopeptide of type 1 collagen; Bone ALP = bone-specific alkaline phosphatase; PINP = N-propeptide of type 1 collagen.

[a]Based on a subset of 76 women with available data.

Results

Study participants

Of the 437 women from the FLEX placebo group, 406 (93%) women had at least one eligible BMD measurement within the treatment-free period at the TH, FN, or LS (see Table 1 for baseline characteristics). There were 404 (92%) women with eligible TH and FN BMD data, and 351 (80%) with eligible LS BMD data. For the 406 women studied, the average age at treatment-free period baseline (FLEX baseline) was 73.6 years, the average BMI was 25.8 kg/m^2, the average FN BMD was 0.612 g/cm^2 (*T*-score –2.17), and the average duration of ALN use (the sum of duration of treatment during participation in the parent trial and the duration of use of ALN in the time between closeout of the parent trial and baseline of the treatment-free period) was 5.1 years. There was a history of fracture defined as having prevalent vertebral fracture before ALN initiation, a history of clinical fracture after age 45, or having experienced either a clinical vertebral, morphometric vertebral, or clinical, nonvertebral fracture during the parent trial (FIT) in 236 (58%) women.

There were 76 (76%) women of the sample of participants with BTM data who were receiving ALN at the treatment-free period baseline (FLEX baseline). All of them had treatment-free period BMD data available, and all were included in the analysis.

Changes in BMD after discontinuation of ALN

After an average course of 5 years of ALN, the 5-year TH BMD decreased by an average of 3.62% (SD 3.41%), FN BMD decreased by an average of 1.69% (SD 2.94%), and LS BMD increased by an average of 1.27% (SD 2.93%) (Table 2). The 5-year percent changes in BMD were normally distributed (Fig. 2). Estimated 5-year percent change in TH BMD was <–5% for 118 (29%) women, whereas at the LS, 29 (8%) women had estimated BMD gains of >5% at 5 years (Table 3).

Table 2. Percent Changes in BMD at Total Hip, Femoral Neck, and Lumbar Spine During a 5-Year ALN Treatment-Free Period After a Mean of 5 Years of ALN Therapy

	% Change, mean (SD)		
Parameter at study baseline (*n*)	Total hip	Femoral neck	Lumbar spine
Whole study group (406)	−3.62 (3.41)	−1.69 (2.94)	1.27 (2.93)
Age (years)			
<70 (100)	−2.54 (2.86)	−1.67 (2.46)	0.75 (2.51)
70 to 74 (127)	−3.69 (3.57)	−1.26 (3.05)	1.39 (2.90)
75 to 79 (106)	−4.08 (3.31)	−2.04 (2.62)	1.71 (2.72)
≥80 (73)	−4.34 (3.70)	−1.95 (3.67)	1.13 (3.78)
BMI (kg/m^2)			
<20 (28)	−5.48 (3.31)	−3.44 (2.49)	−0.17 (2.79)
20 to <25 (160)	−3.85 (3.56)	−2.17 (2.55)	0.99 (2.69)
25 to <30 (153)	−3.44 (3.27)	−1.33 (3.20)	1.48 (3.04)
≥30 (65)	−2.71 (3.10)	−0.60 (2.87)	2.03 (3.09)
Femoral Neck *T*-score			
>−2.0 (164)	−2.91 (3.13)	−1.08 (2.97)	1.26 (2.74)
>−2.5 to ≤−2.0 (121)	−3.98 (3.32)	−1.59 (2.91)	1.73 (3.30)
≤−2.5 (121)	−4.23 (3.71)	−2.61 (2.71)	0.84 (2.79)

BMD = bone mineral density; ALN = alendronate; 95% CI = 95% confidence interval; BMI = body mass index.

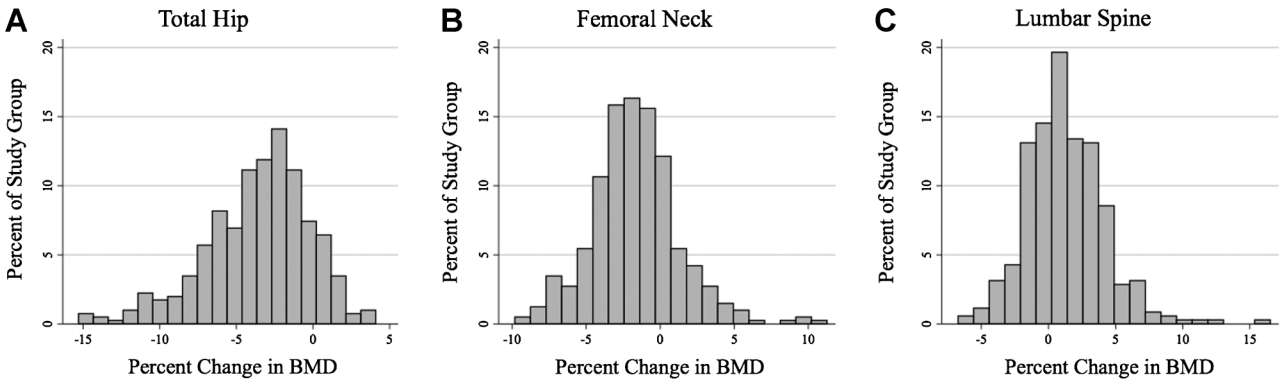

Fig. 2. Distribution of 5-year % change in bone mineral density (BMD) after discontinuing alendronate at the total hip (*A*), femoral neck (*B*), and lumbar spine (*C*).

Associations between BMD changes and candidate risk factors

Age and smoking were negatively associated with 5-year BMD percent change at the TH (Table 4). BMI was positively associated with estimated 5-year percent change in BMD at the FN and LS (Tables 5 and 6). Unadjusted and adjusted associations of the candidate risk factors with 5-year percent change in BMD are presented in Tables 4 to 6.

Exploratory analysis to find predictive model

Less than 15% of the variability in the 5-year percent changes in BMD during the treatment-free period could be predicted from non-BTM factors for the 406 women analyzed (best cross-validated R^2 6.3% for TH, 10.8% for FN, and 13.6% for LS) (Table 7). The percent of the variability that could be explained in the 76 women with available BTM data was slightly improved at the LS and TH and slightly worse at the FN (best cross-validated R^2 9.2% for TH, 6.8% for FN, and 26.4% for LS) (Table 7). The sensitivity analysis assessing predictive accuracy for 2-year percent changes in BMD did not differ from the results assessing for the predictive accuracy for 5-year percent changes. This implies no difference between predicting the BMD change 5 years after alendronate discontinuation or the trajectory of BMD change over a 5-year period.

Discussion

It has been previously reported from the FLEX trial that the mean 5-year percent change in BMD in those who discontinued ALN is –3.4% at the TH, –1.4% at the FN, and 1.5% at the LS.[11] This was calculated as the percent change from FLEX baseline to year 5. The current analysis estimates 5-year percent change in BMD, attempting to limit the estimate to women known not to be taking open-label anti-osteoporosis therapy during the 5-year treatment-free period, and also including bone loss data from women who experienced "excessive bone loss" as defined in the FLEX trial who were likely selectively excluded from contributing year 5 BMD data. The estimates we present for the mean percent change in BMD after 5 years off ALN therapy (3.6% loss at TH, 1.7% loss at FN, and 1.3% gain at LS) are close to those originally presented. These losses of BMD are similar to what might be expected in treatment naïve women at the TH, but less than what would be expected at the FN.[25] The lack of accelerated bone loss after ALN discontinuation may be a reflection of the small amounts of bisphosphonates retained in bone after treatment.[26] We also show that there is a normal distribution of the individual 5-year percent changes in BMD with a standard deviation of 2.9% to 3.4%, meaning many women experienced >5% BMD loss at the TH and FN. These findings suggest that the long-term kinetics of ALN can be quite variable from patient to patient. The gain of BMD at the spine may be the result of osteophyte accumulation and other degenerative changes known to be both age and BMD related.[27,28]

Our exploratory search for risk factors that predict greater loss of BMD during the treatment-free period yielded several significant results. Specifically, age and smoking had negative effects on bone loss at the TH, higher BMIs were protective against bone loss at the FN and LS, a history of falls had negative effects at the LS, and, paradoxically, alcohol use and age were protective at the LS. Higher treatment-free period PINP levels were protective at the FN only. Increased BMD gain while on ALN was associated with higher losses of BMD during the treatment-free period at the LS only. Interestingly, BMD gained during ALN treatment was not associated with BMD loss after ALN discontinuation at the TH and FN. This differs from what happens upon discontinuation of estrogen, where gains are lost within a few years[29] and could be related to retention of ALN in newly formed bone. The increases in spine BMD associated with age and BMI may not represent a physiologic process pertaining to postmenopausal osteoporosis or ALN treatment, as both risk factors are associated with degenerative

Table 3. Proportion of Study Group That Gained or Lost ≥5% BMD Over a 5-Year Treatment-Free Period After a Mean of 5 Years of ALN

BMD location	Lost ≥5%, *n* (%)	Gained ≥5%, *n* (%)
Total hip	118 (29)	0 (0)
Femoral neck	45 (11)	9 (2)
Lumbar spine	5 (1)	29 (8)

BMD = bone mineral density; ALN = alendronate.

Table 4. Associations of Candidate Predictors With % Change in Total Hip BMD Over a 5-Year Treatment-Free Period After a Mean of 5 Years of ALN

	% Change in BMD associated with each increase in predictor			
	Unadjusted		Adjusted[a]	
Candidate predictor	Estimate (95% CI)	*p* Value	Estimate (95% CI)	*p* Value
Age (5 years)	−0.51 (−0.95 to −0.07)	0.023	−0.49 (−0.94 to −0.03)	0.038
BMI (5 kg/m^2)	0.62 (0.01 to 1.24)	0.047	0.44 (−0.24 to 1.12)	0.21
BMD before ALN (0.1 gm/cm^2)[b]	0.76 (0.13 to 1.4)	0.018	0.42 (−0.29 to 1.14)	0.24
% Change in BMD on ALN	0.05 (−0.07 to 0.17)	0.42	0.03 (−0.09 to 0.15	0.66
Current smoker	−2.14 (−4.23 to −0.01)	0.049	−2.13 (−4.29 to 0.09)	0.06
Current alcohol use	−0.14 (−1.18 to 0.91)	0.79	0.13 (−0.92 to 1.19)	0.81
History of falls	−0.36 (−1.59 to 0.89)	0.57	−0.56 (−1.78 to 0.69)	0.38
BTM[c]				
CTX (0.065 ng/mL)[d]	−0.70 (−1.69 to 0.29)	0.17	−0.65 (−1.67 to 0.37)	0.21
Bone ALP (2.86 ng/mL)[d]	−0.25 (−1.25 to 0.76)	0.63	−0.24 (−1.30 to 0.83)	0.66
PINP (11.8 ng/mL)[d]	0 (−1.01 to 1.02)	1	−0.15 (−1.19 to 0.91)	0.79

BMD = bone mineral density; ALN = alendronate; 95% CI = 95% confidence interval; TH = total hip; FN = femoral neck; LS = lumbar spine; BMI = body mass index; BTM = bone turnover marker; CTX = serum C-terminal telopeptide of type 1 collagen; Bone ALP = bone-specific alkaline phosphatase; PINP = N-propeptide of type 1 collagen.

[a]All predictors adjusted for age, BMI, history of falls, smoking status, and alcohol use. All predictors except % change in BMD on ALN are also adjusted for baseline BMD before alendronate use.

[b]BMD measured before alendronate therapy (FIT baseline).

[c]Based on a subset of 76 women with available data.

[d]One standard deviation increase.

changes that may confound the interpretation of LS DXA BMD.[27,28]

We caution the interpretation of these associations as we tested multiple hypotheses, increasing the chances of type I error. Also, the measurement of BTMs in only approximately 20% of patients may have limited the ability to detect statistically significant associations between BMD changes and these factors. The fact that CTX was often collected in the nonfasting state

Table 5. Associations of Candidate Predictors With % Change in Femoral Neck BMD Over a 5-Year Treatment-Free Period After a Mean of 5 Years of ALN

	% Change in BMD associated with each increase in predictor			
	Unadjusted		Adjusted[a]	
Candidate predictor	Estimate (95% CI)	*p* Value	Estimate (95% CI)	*p* Value
Age (5 years)	0.24 (−0.30 to 0.78)	0.39	0.30 (−0.26 to 0.86)	0.29
BMI (5 kg/m^2)	1.05 (0.30 to 1.81)	0.006	1.13 (0.33 to 1.93)	0.006
BMD before ALN (0.1 gm/cm^2)[b]	0.47 (−0.55 to 1.5)	0.37	0.27 (−0.85 to 1.39)	0.64
% Change in BMD on ALN	−0.07 (−0.18 to 0.05)	0.25	−0.10 (−0.21 to 0.01)	0.086
Current smoker	−1.34 (−3.89 to 1.28)	0.32	−0.31 (−2.95 to 2.41)	0.82
Current alcohol use	−0.15 (−1.39 to 1.10)	0.81	0.04 (−1.22 to 1.32)	0.95
History of falls	0.24 (−1.25 to 1.74)	0.76	0.01 (−1.46 to 1.51)	0.99
BTM[c]				
CTX (0.065 ng/mL)[d]	−0.73 (−2.07 to 0.63)	0.29	−0.64 (−2.07 to 0.80)	0.38
Bone ALP (2.86 ng/mL)[d]	0.98 (−0.41 to 2.39)	0.17	0.64 (−0.86 to 2.17)	0.40
PINP (11.8 ng/mL)[d]	1.45 (0.05 to 2.87)	0.042	1.17 (−0.31 to 2.67)	0.12

BMD = bone mineral density; ALN = alendronate; 95% CI = 95% confidence interval; TH = total hip; FN = femoral neck; LS = lumbar spine; BMI = body mass index; BTM = bone turnover marker; CTX = serum C-terminal telopeptide of type 1 collagen; Bone ALP = bone-specific alkaline phosphatase; PINP = N-propeptide of type 1 collagen.

[a]All predictors adjusted for age, BMI, history of falls, smoking status, and alcohol use. All predictors except % change in BMD on ALN are also adjusted for baseline BMD before alendronate use.

[b]BMD measured before alendronate therapy (FIT baseline).

[c]Based on a subset of 76 women with available data.

[d]One standard deviation increase.

Table 6. Associations of Candidate Predictors With % Change in Lumbar Spine BMD Over a 5-Year Treatment-Free Period After a Mean of 5 Years of ALN

	% Change in BMD associated with each increase in predictor			
	Unadjusted		Adjusted[a]	
Candidate predictor	Estimate (95% CI)	*p* Value	Estimate (95% CI)	*p* Value
Age (5 years)	0.50 (−0.03 to 1.03)	0.063	0.54 (0.02 to 1.07)	0.044
BMI (5 kg/m^2)	0.91 (0.17 to 1.65)	0.015	1.08 (0.32 to 1.84)	0.005
BMD before ALN (0.1 gm/cm^2)[b]	0.39 (−0.12 to 0.90)	0.13	0.33 (−0.18 to 0.84)	0.20
% Change in BMD on ALN	−0.07 (−0.17 to 0.02)	0.13	−0.12 (−0.22 to −0.02)	0.015
Current smoker	−0.19 (−2.75 to 2.43)	0.89	0.77 (−1.8 to 3.42)	0.56
Current alcohol use	1.07 (−0.15 to 2.31)	0.085	1.27 (0.05 to 2.50)	0.04
History of falls	−1.42 (−2.83 to 0.01)	0.051	−1.64 (−3.01 to −0.24)	0.022
BTM[c]				
CTX (0.065 ng/mL)[d]	−0.07 (−1.43 to 1.30)	0.92	−0.24 (−1.56 to 1.10)	0.72
Bone ALP (2.86 ng/mL)[d]	−0.30 (−1.64 to 1.07)	0.67	0.06 (−1.28 to 1.41)	0.93
PINP (11.8 ng/mL)[d]	0.64 (−0.71 to 2.00)	0.36	0.52 (−0.82 to 1.88)	0.45

BMD = bone mineral density; ALN = alendronate; 95% CI = 95% confidence interval; TH = total hip; FN = femoral neck; LS = lumbar spine; BMI = body mass index; BTM = bone turnover marker; CTX = serum C-terminal telopeptide of type 1 collagen; Bone ALP = bone-specific alkaline phosphatase; PINP = N-propeptide of type 1 collagen.

[a]All predictors adjusted for age, BMI, history of falls, smoking status, and alcohol use. All predictors except % change in BMD on ALN are also adjusted for baseline BMD before alendronate use.

[b]BMD measured before alendronate therapy (FIT baseline).

[c]Based on a subset of 76 women with available data.

[d]One standard deviation increase.

further complicates the interpretation of the associations between BMD changes and this specific BTM. But most importantly, we show that the best possible prediction of 5-year percent change in BMD from using all candidate risk factors is relatively weak. We would like to point out that the measured risk factors' (BMD, BTMs, etc.) ability to predict not only depends on their biologic association to the outcome but also on the precision of the methods by which they are measured. Overall, given the unlikely possibility of a substantial portion of variability in BMD changes being explained by candidate risk factors as measured in this study, we believe that these risk factors are presently of limited clinical utility for predicting bone loss during the subsequent treatment-free period.

Table 7. Maximum % of Variability of 5-Year, Treatment-Free, Post-ALN Therapy % Change in BMD Explained by All Possible Combinations of Candidate Predictors

	Top-Model Cross-Validated R^2, %	
BMD location	Without BTM predictors[a]	With BTM predictors[b]
Total hip	6.3	9.2
Femoral neck	10.8	6.8
Lumbar spine	13.6	26.4

ALN = alendronate; BMD = bone mineral density; BTM = bone turnover marker.

[a]Based on 406 patients with available data.

[b]Based on a sample of 76 patients with available BTM data.

Post hoc analyses of the FLEX trial suggest that BMD values at the time of discontinuation are capable of differentiating women who will benefit from longer-term bisphosphonate therapy when considering clinical vertebral fractures as the outcome.[19,20] These studies have proposed some specific BMD thresholds for deciding whether patients should continue ALN after 5 years, but we currently have no data on if and when to resume anti-osteoporosis therapy. Despite there also being no data to support an association of BMD changes after ALN discontinuation to fracture outcomes, we feel one reasonable criterion for resumption of therapy would be having BMD as measured by DXA drop below the threshold where continued therapy beyond 5 years seems to be effective. This would imply that women who discontinue bisphosphonates should be monitored periodically with DXA, although the frequency of monitoring is not certain. Future research can use the mean and SD of the rate of bone loss calculated in this analysis to develop a reasonable monitoring algorithm, perhaps based on BMD at the time of discontinuation.

There are several additional caveats to this analysis. The population studied consisted entirely of women aged 61 to 86 years. It may not be appropriate to extrapolate these results, particularly for the estimated 5-year percent bone loss, to men or younger women. The original FLEX trial had a protocol for those who lost high amounts of bone (defined above and called "excessive bone loss.") This protocol likely led to women with high bone loss being less likely to have follow-up BMD measurements, or to be switched to open-label anti-osteoporosis therapy, ultimately biasing estimates of 5-year percent changes. We attempted to account for this influence in two ways:

1) we excluded BMD measurements performed after study drug (placebo) was discontinued; 2) our longitudinal approach estimated a 5-year percent change for every patient who contributed data, thereby including the early data from the women with ''excessive bone loss.'' If anything, we expected our estimates of 5-year percent bone loss to be pessimistic, as the women with ''excessive bone loss'' are less likely to contribute BMD data past being identified as an ''excessive bone loser,'' which may have allowed their individual estimations of 5-year percent changes in BMD to regress away from the extreme of high bone loss.

In summary we have presented the distribution of change in BMD over a 5-year treatment-free period after 5 years of ALN therapy. Several risk factors, especially BMI, may be significantly related to bone loss during the treatment-free period. However, because no combination of risk factors can generate a prediction model that accounts for a meaningful proportion of variability in 5-year percent BMD changes, these risk factors are unlikely to be clinically important for individual patient care.

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