

## Original Investigation

# Fracture Prediction After Discontinuation of 4 to 5 Years of Alendronate Therapy

## The FLEX Study

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**IMPORTANCE** Discontinuation of bisphosphonate therapy after 3 to 5 years is increasingly considered, but methods to monitor fracture risk after discontinuation have not been established.

**OBJECTIVE** To test methods of predicting fracture risk among women who have discontinued alendronate therapy after 4 to 5 years.

**DESIGN, SETTING, AND PARTICIPANTS** The prospective Fracture Intervention Trial Long-term Extension (FLEX) study randomized postmenopausal women aged 61 to 86 years previously treated with 4 to 5 years of alendronate therapy to 5 more years of alendronate or placebo from 1998 through 2003; the present analysis includes only the placebo group. Hip and spine dual-energy x-ray absorptiometry (DXA) were measured when placebo was begun (FLEX baseline) and after 1 to 3 years of follow-up. Two biochemical markers of bone turnover, urinary type 1 collagen cross-linked N-telopeptide (NTX) and serum bone-specific alkaline phosphatase (BAP), were measured at FLEX baseline and after 1 and 3 years.

**MAIN OUTCOMES AND MEASURES** Symptomatic spine and nonspine fractures occurring after the follow-up measurement of DXA or bone turnover.

**RESULTS** During 5 years of placebo, 94 of 437 women (22%) experienced 1 or more symptomatic fractures; 82 had fractures after 1 year. One-year changes in hip DXA, NTX, and BAP were not related to subsequent fracture risk, but older age and lower hip DXA at time of discontinuation were significantly related to increased fracture risk (lowest tertile of baseline femoral neck DXA vs other 2 tertiles relative hazard ratio, 2.17 [95% CI, 1.38-3.41]; total hip DXA relative hazard ratio, 1.87 [95% CI, 1.20-2.92]).

**CONCLUSIONS AND RELEVANCE** Among postmenopausal women who discontinue alendronate therapy after 4 to 5 years, age and hip BMD at discontinuation predict clinical fractures during the subsequent 5 years. Follow-up measurements of DXA 1 year after discontinuation and of BAP or NTX 1 to 2 years after discontinuation are not associated with fracture risk and cannot be recommended.

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**B**isphosphonate use reduces the risk of hip and spine fractures, particularly among individuals with osteoporosis defined by the presence of a vertebral fracture or bone mineral density (BMD) T score less than  $-2.5$ .<sup>1</sup> Recent concerns about recognized adverse reactions (eg, esophagitis) and potential long-term safety issues, such as atypical femoral fractures, osteonecrosis of the jaw, and esophageal cancer—coupled with the possibility that fracture risk reduction may persist for months to years after long-term treatment is stopped—have resulted in heightened interest in interrupting or stopping bisphosphonate therapy after several years of treatment.<sup>2-4</sup>

The best evidence regarding the benefits and risks of discontinuation of bisphosphonate use comes from large trials in which participants who have received bisphosphonate therapy for a prolonged period are rerandomized to either continuation or discontinuation of the bisphosphonate therapy. The Fracture Intervention Trial Long-term Extension (FLEX) trial demonstrated that among older postmenopausal women who had used oral alendronate sodium for 5 years, those randomized to placebo for an additional 5 years had rates of nonspine and morphometric vertebral fractures similar to those randomized to receive an additional 5 years of alendronate therapy.<sup>5</sup> During the 5 years of follow-up in FLEX, the rates of nonspine fractures were similar in women who continued or discontinued daily alendronate therapy (19.0% vs 18.9%), as were the rates of morphometric vertebral fractures (11.3% vs 9.8%), but the rate of clinical (symptomatic) vertebral fracture was significantly lower among those who continued alendronate therapy (5.3% vs 2.4%).<sup>5</sup>

The purpose of this post hoc analysis was to examine the utility of hip and spine dual-energy x-ray absorptiometry (DXA) and bone turnover marker (BTM) measurements at the time of discontinuation and after 1 to 3 years of follow-up for the 5-year prediction of fractures among women who have discontinued alendronate therapy after 4 to 5 years of treatment.

## Methods

### Participants

The design and results of the Fracture Intervention Trial (FIT) and the FLEX trial have been previously reported<sup>5-9</sup> (Figure 1). All women provided written informed consent, and the protocol was approved by the appropriate institutional review boards. In FIT, postmenopausal women aged 55 to 81 years with low femoral neck BMD ( $<0.68$  g/cm<sup>2</sup>, equivalent to a T score of  $-1.6$ ) were eligible to participate. Of 6459 enrolled participants, 2027 women with at least 1 prevalent vertebral deformity were enrolled in the vertebral fracture arm, and 4432 women with no existing vertebral deformity, in the clinical fracture arm. Within each arm, women were randomized to oral alendronate sodium (5 mg/day for 2 years, 10 mg/day thereafter;  $n = 3236$ ) or placebo ( $n = 3223$ ). Mean follow-up was 2.9 years in the vertebral fracture arm and 4.2 years in the clinical fracture arm. Up to 1 year of alendronate therapy (10 mg/day) was provided at no cost to all participants at the end of

FIT, and although adherence was not assessed during this period, 78% of FLEX participants stated that they were taking alendronate at the time of randomization.

Eligibility in FLEX was limited to women assigned to alendronate during FIT who completed a total of at least 3 years of treatment during the trial plus the subsequent open-label period. Women whose total hip BMD at FLEX baseline was less than 0.515 g/cm<sup>2</sup> (T score,  $<-3.5$ )<sup>10</sup> or whose total hip BMD was less than at FIT baseline were ineligible. Of the 3236 women enrolled in FIT and assigned to alendronate treatment, 2857 surviving women were contacted regarding participation in FLEX. Of these, a total of 1099 women (39%) were enrolled in FLEX. Compared with women who were eligible but did not participate in FLEX, randomized participants were slightly younger and less likely to have a fracture during FIT but had similar hip BMD.<sup>5,9</sup>

### Treatment Allocation in FLEX

At FLEX baseline, participants were randomly assigned to receive alendronate sodium, 5 or 10 mg/d ( $n = 662$  [60%]), or placebo ( $n = 437$  [40%]) for 5 years. Each participant was also offered a daily supplement containing 500 mg calcium and 250 IU vitamin D<sub>3</sub>. The present analyses are limited to women who received placebo in FLEX.

### DXA Measurements

Bone mineral density was measured at the total hip and its subregions and the posterior-anterior lumbar spine in all participants at FLEX baseline using DXA with the same Hologic QDR 2000 densitometers that were used for FIT (Hologic Inc). Hip DXA was repeated annually; spine DXA was repeated at the 36-month visit only. Quality control measures were the same as those used in FIT and have been outlined in detail elsewhere.<sup>8</sup>

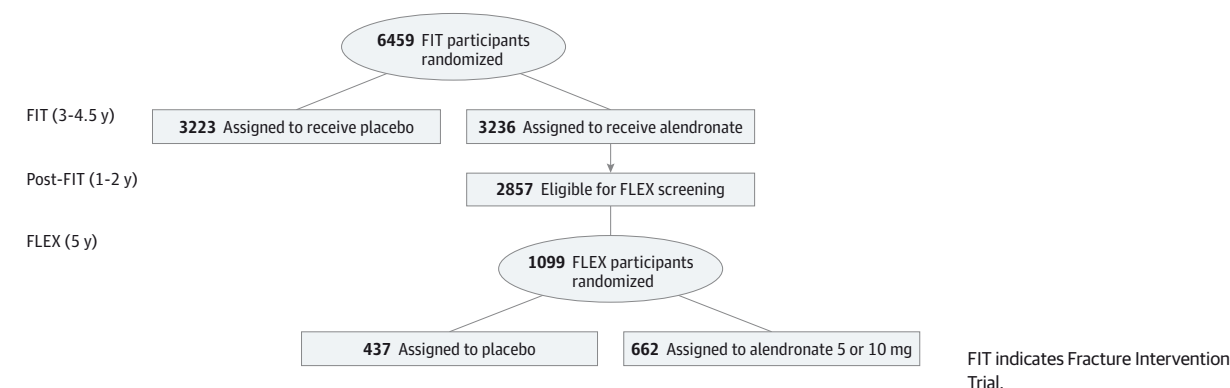
The FLEX investigators were notified without revelation of treatment assignment if any participant experienced excessive bone loss ( $n = 54$ ), defined as a decrease from the FLEX baseline visit of 8% or more in total hip BMD over the first year with an additional 2% decrease added for each subsequent year of follow-up, or 3 or more confirmed incident fractures (including hip or vertebral fractures). The clinical investigator then provided this information to the participant and counseled her on the risks and benefits of continued participation in the trial. In addition, if any follow-up total hip BMD in FLEX was at least 5% less than the participant's total hip BMD at the FIT baseline examination ( $n = 16$ ), discontinuation of study medication was mandatory.

### Bone Turnover Measurements

Measurement of biochemical markers was performed in all FLEX participants at the baseline, 12-month, and 36-month visits in a central laboratory (Mayo Central Laboratories for Clinical Trials, Rochester, Minnesota). Fasting serum samples were analyzed for bone-specific alkaline phosphatase (BAP), an indicator of bone formation, using a commercially available assay (Ostase, Hybritech Inc).<sup>11</sup>

Fasting morning urine samples, preferably second void, were analyzed for urinary type 1 collagen cross-linked N-telopeptide (NTX), a biochemical marker of bone resorp-

Figure 1. Design of Fracture Intervention Trial Long-term Extension (FLEX) Trial



tion, using a commercially available assay (Osteomark, Ostex International Inc).<sup>12</sup> All NTX results are adjusted for urine creatinine concentration.

### Fracture Outcomes

During FLEX follow-up, participants were queried about potential clinical fractures (nonspine and symptomatic vertebral fractures) every 3 months; self-reported fractures were confirmed by radiology or surgical reports. Fractures of the skull and those due to cancer or excessive trauma were excluded. If a vertebral fracture was diagnosed by a participant's physician, usually following reported back pain, the spine radiograph used to diagnose the fracture was requested and compared with the radiograph obtained at FLEX baseline using semiquantitative grading.<sup>13</sup>

### Statistical Analyses

These analyses are limited to women randomized to placebo in FLEX to mimic the clinical circumstance in which women discontinue alendronate therapy after 4 to 5 years. The primary outcome for this analysis was incident clinical fracture, defined as either a new nonspine fracture or a new clinical vertebral fracture during FLEX follow-up. Because acute fracture may affect both BMD and BTM measurements,<sup>14</sup> we did not include clinical fractures occurring before the follow-up measurement of BMD or BTM in our primary analyses. The BTM levels were not normally distributed and are reported as geometric means (means after log transformation). The relationships between baseline BMD or BTM measurements and subsequent clinical fractures were analyzed with age-adjusted Cox models using fractures that occurred after the first year of follow-up. Analyses relating change in BMD or BTM to fracture outcomes were further adjusted for BMD or BTM levels at FLEX baseline, respectively, and for the presence or absence of an existing vertebral fracture. Cox model results are reported as relative hazard ratios (RHRs) and 95% confidence intervals. Secondary analyses examined 2-year changes in hip BMD and 3-year changes in BTM and hip and spine BMD using similar methods that excluded incident fractures occurring before the follow-up BTM or BMD measurement. Post hoc power calculations were not performed. All analyses were performed without knowledge of an individual's fracture status using SAS, version 9.1.

## Results

### Baseline Characteristics and Fracture Outcomes in the FLEX Placebo Group

Of the 437 FIT participants (150 with existing vertebral fracture) randomized to receive placebo in FLEX, 94 (22%) experienced 1 or more clinical fractures during follow-up. Twelve women experienced clinical fracture before the first year when follow-up BMD and BTM measurements were repeated, and these fractures were excluded from the primary analysis. Women in the FLEX placebo group who experienced fracture after the first year of follow-up were older than those who did not (mean age, 76.2 vs 73.1 years;  $P < .001$ ); however, BMI, duration of prior alendronate therapy, prevalence of vertebral fractures at FLEX baseline, and prevalence of confirmed nonspine fractures during FIT were similar (Table 1). Both femoral neck and total hip BMD were significantly lower at baseline among women who subsequently experienced fracture, but spine BMD and baseline BTM levels did not significantly differ among women who did and did not experience fracture (Table 1).

### Changes in BMD and BTM Levels After Discontinuation of Alendronate Therapy

As previously reported,<sup>5</sup> mean hip BMD decreased and BTMs increased in the FLEX placebo group (eFigure 1 and eFigure 2 in Supplement) to a greater extent than in those randomized to continue alendronate therapy, but there were no significant differences 1 year after discontinuation of alendronate therapy among those with and without clinical fracture during follow-up (Table 2).

### BMD, BTMs, and Fracture Outcomes After Discontinuation of Alendronate Therapy

Examining fracture outcomes after the first year of FLEX follow-up by tertile of baseline BMD at the time of discontinuation revealed that those in the lowest tertile of femoral neck or total hip BMD were more likely to experience fracture than those in higher tertiles (Figure 2A). After adjustment for age (Table 3), the risk of fracture during FLEX in the lowest tertile of baseline total hip BMD was 87% higher compared with that in the other 2 tertiles (RHR, 1.87 [95% CI, 1.20-2.92]). Results were similar for femoral neck BMD. In separate analyses, base-

**Table 1. Characteristics of Women Who Discontinue Alendronate (Fracture Intervention Trial Long-term Extension [FLEX] Placebo Group) by Fracture Status After the First Year of FLEX Follow-up**

Variable	Fracture After FLEX Year 1		P Value
	No (n = 355) <sup>a</sup>	Yes (n = 82)	
Age, mean (SD), y	73.1 (5.7)	76.2 (6.1)	<.001
BMI, mean (SD)	25.9 (4.2)	25.4 (4.6)	.34
Prior alendronate therapy, mean (SD), y	5.0 (0.8)	4.9 (0.6)	.27
Clinical fracture during FIT, %			
≥1	9	12	.43
1	8	10	...
>1	0.6	2	...
Prevalent vertebral fracture at FLEX baseline, %	33	40	.18
Total hip BMD at FLEX baseline, mean (SD), g/cm <sup>2</sup>	0.73 (0.09)	0.68 (0.08)	<.001
Total hip T score <-2.5, %	20	38	.30
Femoral neck BMD at FLEX baseline, mean (SD), g/cm <sup>2</sup>	0.62 (0.07)	0.58 (0.07)	<.001
Femoral neck T score <-2.5, %	26	48	.33
Spine BMD at FLEX baseline, mean (SD), g/cm <sup>2</sup>	0.91 (0.14)	0.88 (0.14)	.08
Spine T score <-2.5, %	22	29	.75
NTX/Cr at FLEX baseline, geometric mean (SD), nmol/mmol	19.7 (13.2)	19.4 (11.8)	.86
BAP at FLEX baseline, geometric mean (SD), ng/mL	9.0 (3.4)	9.5 (3.7)	.15

Abbreviations: BAP, bone-specific alkaline phosphatase; BMD, bone mineral density; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ellipses, comparison not made; FIT, Fracture Intervention Trial; NTX/Cr, type 1 collagen cross-linked N-telopeptide to creatinine concentration ratio.

<sup>a</sup> Includes 12 women with clinical fractures before first year of follow-up.

**Table 2. Hip Bone Mineral Density (BMD) and Bone Turnover Marker (BTM) Levels Among Women Who Discontinue Alendronate Therapy by Fracture Status After the First Year of FLEX Follow-up**

Variable	Fracture After FLEX Year 1	
	No (n = 355)	Yes (n = 82) <sup>a</sup>
BMD, mean (95% CI)		
Femoral neck		
Baseline, g/cm <sup>2</sup>	0.62 (0.61 to 0.63)	0.58 (0.57 to 0.60)
After 1 year, g/cm <sup>2</sup>	0.61 (0.61 to 0.62)	0.58 (0.56 to 0.59)
1-year change, %	-0.71 (-1.12 to -0.29)	-1.05 (-1.91 to -0.18)
Total hip		
Baseline, g/cm <sup>2</sup>	0.73 (0.72 to 0.74)	0.69 (0.67 to 0.71)
After 1 year, g/cm <sup>2</sup>	0.72 (0.71 to 0.73)	0.68 (0.66 to 0.70)
1-year change, %	-1.32 (-1.59 to -1.05)	-1.49 (-2.06 to -0.92)
BTM, geometric mean (95% CI)		
NTX/Cr		
Baseline, nmol/mmol	19.7 (18.7 to 20.9)	19.1 (17.0 to 21.5)
After 1 year, nmol/mmol	24.1 (22.9 to 25.3)	24.7 (22.2 to 27.4)
1-year change, %	22.0 (15.5 to 28.9)	29.1 (15.1 to 44.7)
BAP		
Baseline, ng/mL	9.0 (8.7 to 9.3)	9.4 (8.7 to 10.2)
After 1 year, ng/mL	10.5 (10.1 to 11.0)	11.0 (10.2 to 12.0)
1-year change, %	17.1 (13.4 to 20.8)	17.2 (9.7 to 25.1)

Abbreviations: BAP, bone-specific alkaline phosphatase; FLEX, Fracture Intervention Trial Long-term Extension; NTX/Cr, type 1 collagen cross-linked N-telopeptide to creatinine concentration ratio.

<sup>a</sup> Any nonspine or clinical vertebral fracture occurring after the 1-year visit.

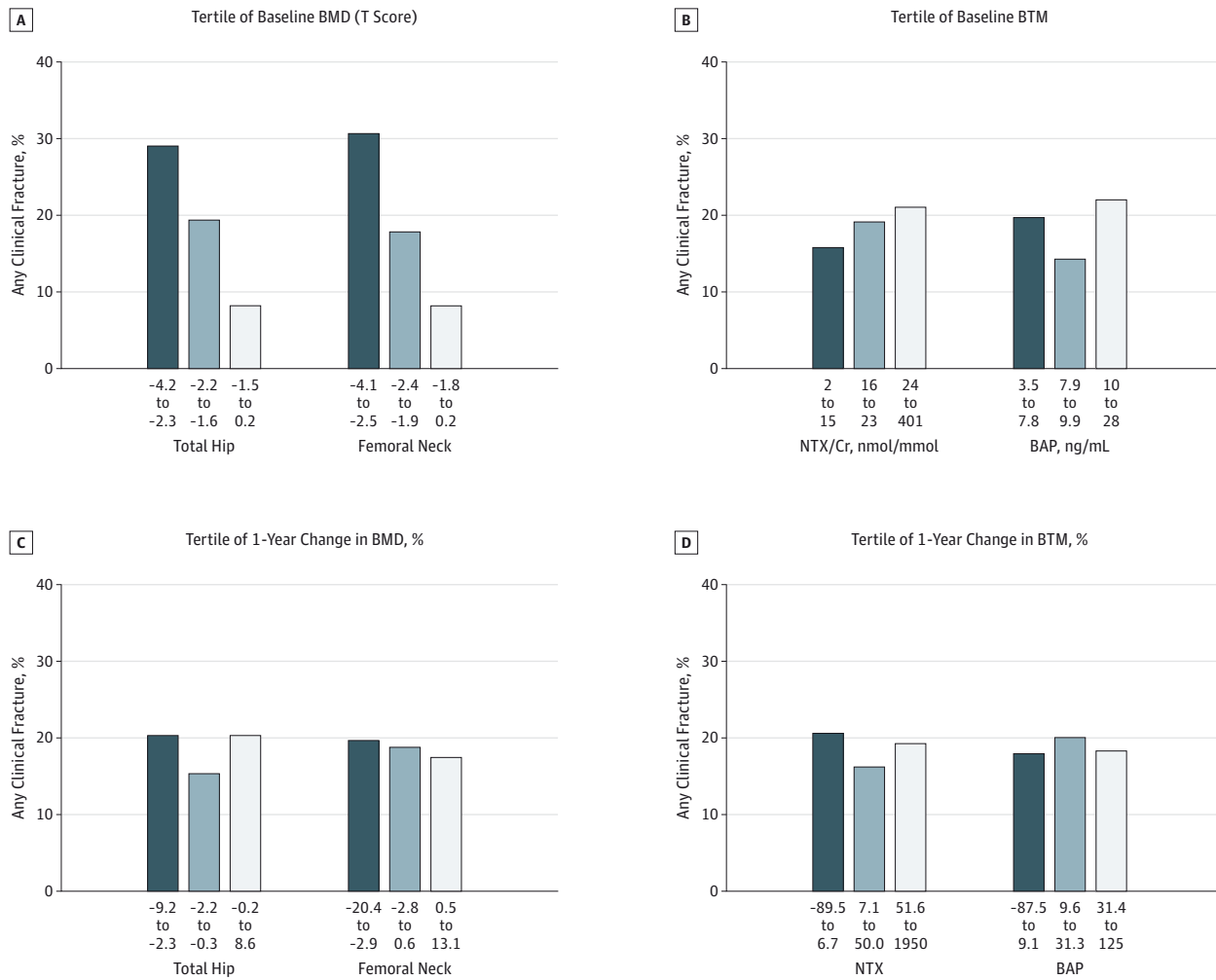
line levels of NTX and BAP were not associated with fracture outcomes in the FLEX placebo group (Figure 2B and Table 3). Older age was independently associated with a greater risk of fracture (RHR, 1.54 [95% CI, 1.26-1.85] per 5-year increase) after discontinuation of alendronate therapy (Table 3).

One-year changes in BMD were not associated with the risk of clinical fracture after discontinuing alendronate therapy. The risk of fracture after the first year of follow-up did not differ across tertiles of 1-year change in femoral neck (P for trend = .81)

or total hip BMD (P for trend = .96) (Figure 2C). The age- and baseline BMD-adjusted risk of fracture after the first year of follow-up among those in the tertile with the greatest total hip bone loss (1-year change in BMD, -2.3% to -9.2%) did not differ from those in the other 2 tertiles (RHR, 1.06 [95% CI, 0.67-1.68]) (Table 4). Results were similar for 1-year change in femoral neck BMD.

One-year changes in BTMs were not associated with risk of fracture after discontinuation of alendronate therapy. The risk of fracture after 1 year of follow-up did not differ across

Figure 2. Proportion of Women With Any Clinical Fracture After Discontinuation of Alendronate Therapy



A, By tertile of hip bone mineral density (BMD) at Fracture Intervention Trial Long-term Extension (FLEX) baseline. *P* for trend < .001 for total hip BMD and for femoral neck BMD. B, By tertile of bone turnover marker at FLEX baseline. *P* for trend = .18 for urinary type 1 collagen cross-linked N-telopeptide to creatinine concentration ratio (NTX/Cr) and .40 for serum bone-specific alkaline

phosphatase (BAP). C, By tertile of 1-year percent change in hip BMD. *P* for trend = .96 for total hip BMD and .81 for femoral neck BMD. D, By tertile of 1-year percent change in bone turnover marker. *P* for trend = .91 for NTX/Cr and .70 for BAP.

tertiles of 1-year change in NTX (*P* for trend = .91) or BAP (*P* for trend = .70) (Figure 2D). The age- and baseline NTX-adjusted risk of fracture after the first year of follow-up among those in the tertile with the greatest increase in NTX (1-year increase in NTX, >51.6%) did not differ from those in the other 2 tertiles (RHR, 1.14 [95% CI, 0.70-1.86]) (Table 4). Results were similar for 1-year change in BAP.

### Additional Analyses

We further classified 1-year changes in BMD and BTMs on the basis of published estimates of the “least significant change,” which represent the smallest difference in paired measurements that is unlikely to be due to chance (*P* < .05).<sup>15</sup> Women with 3% or greater 1-year loss of femoral neck (29% of women) or total hip BMD (21% of women) did not have a statistically significant increase in fractures after the first year of fol-

low-up (Table 4). Similarly, fracture risk after the first year of follow-up was similar among women with a 30% or greater 1-year increase in NTX (45% of women) or BAP (37% of women) compared with those with smaller increases in BTM (Table 4).

Similarly, most associations between 2- or 3-year changes in BMD and fracture risk were not statistically significant, although there were fewer fractures after the second (*n* = 70) and third (*n* = 57) annual visits included in the analysis (Table 4). The risk of fracture was elevated among those with greater total hip bone loss after 2 or 3 years of follow-up, but after adjustment for age and baseline BMD, only 2-year total hip bone loss greater than 3% was significantly associated with fracture risk (RHR, 1.68 [95% CI, 1.05-2.72]). Neither 2- or 3-year change in femoral neck BMD nor 3-year change in spine BMD was associated with fracture risk.

Three-year changes in BTMs after discontinuation of alendronate therapy were not associated with fracture risk (Table 4). For example, after adjustment for age and baseline NTX, the risk of fracture among women in the highest tertile of 3-year change in NTX (>56% increase) did not differ significantly from those in the other 2 tertiles with smaller increases in NTX (RHR, 1.02 [95% CI, 0.55-1.91]).

Additional analyses were performed to assess the impact of duration of alendronate therapy, the presence of a vertebral fracture, and self-reported alendronate use at FLEX baseline, but the results were similar. For example, the total duration of alendronate therapy was not associated with bone loss or fracture risk, and fracture analyses that were further adjusted for duration of alendronate use or prevalent vertebral fractures gave similar results (data not shown). Similarly, results were qualitatively similar in analyses limited to the 78% of FLEX participants who reported alendronate use at FLEX baseline (data not shown).

Last, although we excluded fractures that occurred before the follow-up BMD or BTM measurement in our primary analyses, results were qualitatively similar when all non-spine and clinical vertebral fractures were analyzed. We did not plan separate analyses of the relationships between change in BMD or BTM and clinical vertebral fractures because of the small number (n = 23), but qualitatively the results were similar to those observed with nonspine fractures (data not shown).

## Discussion

Bisphosphonates are highly effective antifracture treatments, particularly in patients with osteoporosis.<sup>1</sup> Recently, on the basis of randomized trials that reported fracture end points after discontinuation of long-term bisphosphonate use<sup>5,16</sup> and a US Food and Drug Administration Advisory Committee meeting about the benefits and risks of long-term bisphosphonate

use for the treatment and prevention of osteoporosis,<sup>17</sup> clinicians and patients are increasingly considering temporary or permanent discontinuation after 3 to 5 years of treatment.<sup>2,18</sup> After discontinuation of bisphosphonate use, some experts recommend yearly measurements of BMD or BTMs, or both, to help identify those individuals in need of additional antifracture treatment.<sup>2,19-21</sup> In this post hoc analysis of FLEX participants randomized to placebo after receiving 5 years of oral alendronate therapy, we found that older age and lower hip BMD

**Table 3. FLEX Baseline Bone Mineral Density (BMD), Bone Turnover Markers (BTMs), and Other Characteristics and Age-Adjusted Risk of Fracture Among Women Who Discontinued Alendronate Therapy**

Variables Measured at FLEX Baseline <sup>a</sup>	Risk of Fracture, Relative Hazard Ratio (95% CI) <sup>b</sup>
Demographic and clinical characteristics	
Age, per 5-y increase, y	1.54 (1.26-1.85) <sup>c</sup>
BMI, per SD increase	1.10 (0.87-1.38)
Vertebral fracture	1.11 (0.71-1.75)
Previous nonspine fracture	1.24 (0.64-2.40)
BMD, lowest tertile vs other 2, T score	
Total hip	1.87 (1.20-2.92) <sup>c</sup>
Femoral neck	2.17 (1.38-3.41) <sup>c</sup>
BTMs, highest tertile vs other 2	
NTX/Cr, nmol/mmol	1.33 (0.84-2.10)
BAP, ng/mL	1.39 (0.89-2.17)

Abbreviations: BAP, bone-specific alkaline phosphatase; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); FLEX, Fracture Intervention Trial Long-term Extension; NTX/Cr, type 1 collagen cross-linked N-telopeptide to creatinine concentration ratio.

<sup>a</sup> With the exception of age, each variable was examined in a separate age-adjusted model.

<sup>b</sup> Any nonspine or clinical vertebral fracture occurring after the 1-year visit.

<sup>c</sup> Statistically significant association.

**Table 4. Change in Bone Mineral Density (BMD) or Bone Turnover Markers (BTMs) and Subsequent Age-Adjusted Risk of Clinical Fracture After Discontinuation of Alendronate Therapy<sup>a</sup>**

Variable	Risk of Fracture, Relative Hazard Ratio (95% CI)		
	1-Year Change	2-Year Change	3-Year Change
<b>BMD</b>			
Tertile with greatest decrease vs other 2			
Femoral neck	0.98 (0.61-1.56)	1.51 (0.93-2.44)	1.32 (0.77-2.28)
Total hip	1.07 (0.68-1.69)	1.56 (0.97-2.52)	1.68 (0.98-2.86)
Spine	NA	NA	1.11 (0.63-1.97)
≥3% decrease			
Femoral neck	1.12 (0.70-1.80)	1.45 (0.90-2.35)	1.39 (0.81-2.36)
Total hip	1.36 (0.83-2.23)	1.68 (1.05-2.72) <sup>b</sup>	1.63 (0.95-2.27)
Spine	NA	NA	0.77 (0.36-1.64)
<b>BTMs</b>			
Tertile with greatest increase vs other 2			
NTX/Cr	1.14 (0.70-1.86)	NA	1.02 (0.55-1.91)
BAP	1.03 (0.63-1.67)	NA	0.79 (0.41-1.50)
≥30% increase			
NTX/Cr	1.24 (0.77-1.99)	NA	1.26 (0.69-2.32)
BAP	0.94 (0.58-1.52)	NA	0.83 (0.44-1.57)

Abbreviations: BAP, bone-specific alkaline phosphatase; BMD, bone mineral density; NA, not available; NTX/Cr, type 1 collagen cross-linked N-telopeptide to creatinine concentration ratio; RHR, relative hazard ratio.

<sup>a</sup> Any nonspine or clinical vertebral fracture occurring after the 1-year (n = 82 fractures), 2-year (n = 70 fractures), or 3-year (n = 57 fractures) visits.

<sup>b</sup> Statistically significant association.

at the time of discontinuation were associated with higher rates of clinical fracture during the next 5 years, but neither 1-year changes in hip DXA nor 1- and 3-year changes in BTM levels were associated with fracture risk. We did observe an increased risk of fracture among those with greater 2- or 3-year hip bone loss, but only 2-year change in total hip BMD was statistically significant. Thus, clinicians and patients contemplating a drug holiday after 5 years of alendronate therapy should be aware that short-term monitoring to detect individuals at higher risk who might resume bisphosphonate therapy, or initiate another therapy, may not add to risk prediction over and above age and BMD measured at the time of discontinuation of therapy.

These results build on and extend previous results from the FLEX study.<sup>5,22</sup> The analyses detailed here are limited to the placebo-treated group in FLEX and were designed to mimic the clinical scenario in which the decision has been made to stop alendronate therapy after 4 to 5 years and begin a drug holiday. Because 22% of FLEX participants experienced fracture during the 5 years following discontinuation of alendronate use, it is important to document the utility of serial monitoring that attempts to detect those at highest risk of fracture after discontinuation. Previous FLEX analyses have found that bone loss after discontinuation of 4 to 5 years of alendronate therapy could not be easily predicted on the basis of clinical risk factors.<sup>23</sup>

Given the mechanism of action of bisphosphonates and well-documented treatment-related effects on bone turnover and BMD,<sup>24</sup> it is somewhat surprising that short-term changes in these individual measurements are not associated with fracture risk after discontinuation of alendronate therapy, particularly BTM measurements, which increased 17% to 25% during the first year after discontinuation of alendronate use. Interestingly, greater individual treatment-related reductions in bone turnover are associated with increased fracture risk among postmenopausal women treated with alendronate,<sup>25</sup> risedronate sodium,<sup>26</sup> and zoledronic acid.<sup>27</sup> Conversely, some<sup>25,28</sup> but not all<sup>29</sup> studies have found that treatment-related changes in BMD are not associated with individual fracture risk.

Although our results were consistent and robust after accounting for numerous potential confounding factors, such as duration of treatment and previous vertebral fractures, several other factors may have contributed to the lack of significant associations between short-term changes in BMD or BTMs and subsequent fracture in this analysis. First, our results only apply to the eligible women who chose to participate in FLEX and may not apply to those who were not eligible or chose not to participate in FLEX. Second, the number of fractures during FLEX follow-up was relatively small, and for some analyses (particularly those examining 2- and 3-year changes in BMD or BTMs) confidence intervals were wide, indicating limited power to detect significant associations. Third, BTM measurements were only assessed once at each visit. Repeated measurements at each visit might have improved BTM precision and allowed identification of women at higher risk of fracture. Last, we examined tertile changes in BMD and BTM, as well as those that approximated the least significant change

for those measurements, and the results for other cut points may have differed. Although an underlying assumption of the least significant change calculation is that no change in the true value of the measurement has occurred, it is frequently used in settings in which changes are likely (eg, changes in BMD or BTMs with antiresorptive therapy).<sup>30</sup>

Although short-term changes in BMD and BTM were not associated with fracture risk in FLEX, older age and lower BMD at the time of discontinuation were associated with the risk of fracture after discontinuation. Thus, although there are no accepted guidelines regarding continuation of bisphosphonate therapy or switching to another therapy, clinicians should be aware that older patients and those with low hip BMD after 5 years of alendronate therapy remain at high risk of fracture. Interestingly, we found that several other factors typically associated with higher fracture risk among untreated populations, such as lower BMI or previous fracture (including prevalent vertebral fracture), were not associated with fracture risk after discontinuation of alendronate therapy. Additional studies are needed to clarify the optimal management of patients who remain at risk of fracture after completing 3 to 5 years of bisphosphonate therapy.

Previous published studies have not examined the utility of serial BMD or BTM monitoring after discontinuation of bisphosphonate use, and these findings need confirmation with other bisphosphonates and in other settings. Additional strengths of this study include careful assessment of alendronate exposure and fracture outcomes, blinding to therapy assignment, and high-quality BMD and BTM measurements with rigorous quality control. Such efforts likely improve the accuracy and precision of BMD and BTM measurements compared with those obtained in clinical practice. Furthermore, to avoid acute and subacute fracture-related changes in BMD and BTM measurements, we excluded women with documented clinical fractures before the follow-up measurement of BMD or BTMs. Our study does have several additional weaknesses; as noted, the modest number of pooled fractures, particularly after the second and third annual visits, resulted in relatively wide confidence intervals and precluded analyses of specific fracture types, and fracture follow-up in FLEX was limited to 5 years. Finally, these results only apply to postmenopausal women treated with alendronate 5 to 10 mg/d for 5 years and not to other populations or to other bisphosphonates.

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## Conclusions

We found that after discontinuation of 4 to 5 years of alendronate therapy, 22% of women experience fracture during the subsequent 5 years. Older age and lower hip BMD at the time of discontinuation strongly predict fracture risk after discontinuation, but neither 1-year change in hip BMD nor 1- or 3-year change in NTX or BAP are associated with the risk of fracture after discontinuation. Women with greater total hip bone loss 2 or 3 years after discontinuation may be at increased risk of fracture, but these results need to be confirmed in other studies before routine measurement of BMD after discontinuation

of alendronate therapy can be recommended. Future discontinuation studies should be designed to confirm these findings, test newer BTMs (such as serum procollagen type 1 N propeptide and C-terminal telopeptide of type 1 collagen<sup>30</sup>), and study long-term changes in hip BMD (eg, >5 years) and per-

haps newer imaging modalities. These studies should focus on women whose hip BMD remains low after long-term treatment.<sup>31</sup> In the meantime, short-term monitoring with BMD, BAP, or NTX after discontinuation of 4 to 5 years of alendronate therapy does not appear to improve fracture prediction.

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**Study concept and design:** Bauer, Cummings, Black.  
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**Drafting of the manuscript:** Bauer.

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### Invited Commentary

## Bone Density and Bone Turnover Marker Monitoring After Discontinuation of Alendronate Therapy: An Evidence-Based Decision to Do Less

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**The clinical utility** of medication monitoring has been a controversial issue in osteoporosis management. In the 1998<sup>1</sup> and 2001<sup>2</sup> coverage rules commonly called the “Bone Mass Measurement Act,” the Centers for Medicare & Medicaid Services (CMS) outlined provisions for bone mineral density (BMD) and



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bone turnover marker measurements for Medicare beneficiaries. The CMS covers BMD testing for 5 indications and bone turnover marker testing for 3 indications (**Box**), including monitoring of US Food and Drug Administration-approved osteoporosis drug therapy. The CMS authorizes BMD measurements if at least 23 months have passed since the last measurement, or more frequently “when medically necessary.”<sup>1(p34324)</sup> The CMS also summarized appropriate use of bone turnover markers, assuming documentation of medical necessity: “because of significant specimen to specimen collagen crosslink physiologic variability (15-20%), current recommendations for appropriate utilization include: one or two base-line assays from specified urine collections on separate days; followed by a repeat assay about three months after starting anti-resorptive therapy; followed by a repeat assay in 12 months after the three-month assay; and thereafter not more than annually, unless there is a change in therapy in which circumstance an additional test may be indicated three months after the initiation of new therapy.”<sup>2(p58844)</sup>

Subsequent studies have suggested low utility of BMD<sup>3</sup> and bone turnover marker measurements<sup>4</sup> for monitoring response to treatment in patients receiving alendronate sodium (the most commonly prescribed drug for osteoporosis), but clinical practice guidelines<sup>5</sup> endorse serial testing during drug treatment for osteoporosis. More recently, concern about long-term risks of bisphosphonate treatment have led to proposals to interrupt or stop therapy after several years, and some experts have encouraged consideration of periodic BMD and/or bone turnover marker monitoring during a “drug holiday” after discontinuation of bisphosphonate use.<sup>6</sup> Clinical outcomes data to support this practice were lacking.

In this issue of *JAMA Internal Medicine*, Bauer and colleagues<sup>7</sup> provide clinically useful data from the placebo group of the Fracture Intervention Trial Long-term Extension (FLEX) trial regarding the value of BMD and bone turnover marker measurements after completion of a 5-year course

#### Box. Qualifying Conditions for Bone Monitoring According to the Bone Mass Measurement Act

##### Bone Density Testing<sup>a</sup>

- An estrogen-deficient woman at clinical risk for osteoporosis means a woman who has been determined by the physician (or a qualified nonphysician practitioner) treating her to be estrogen deficient and at clinical risk for osteoporosis, based on her medical history or other findings.
- An individual with vertebral abnormalities as demonstrated by x-ray to be indicative of osteoporosis, low bone mass (osteopenia), or vertebral fracture.
- An individual receiving glucocorticoid (steroid) therapy equivalent to 7.5 mg of prednisone, or greater, per day for more than 3 months, or if the expected duration of such therapy is more than 3 months.
- An individual with primary hyperparathyroidism.
- An individual being monitored to assess the response to or efficacy of an FDA-approved osteoporosis drug therapy.

##### Bone Turnover Markers (Collagen Crosslinks Testing, Especially on Urine Samples)<sup>b</sup>

- Identify individuals with elevated bone resorption, who have osteoporosis in whom response to treatment is being monitored.
- Predict response (as assessed by bone mass measurements) to FDA approved antiresorptive therapy in postmenopausal women.
- Assess response to treatment of patients with osteoporosis, Paget's disease of the bone, or risk for osteoporosis where treatment may include FDA approved antiresorptive agents, anti-estrogens or selective estrogen receptor moderators.

<sup>a</sup> Reproduced from Department of Health and Human Services Health Care Financing Administration, 1998.<sup>1(p34323)</sup>

<sup>b</sup> Reproduced from Centers for Medicare & Medicaid Services, 2001.<sup>2(pp58843-58844)</sup>

of alendronate therapy. The data of Bauer and colleagues<sup>7</sup> suggest that in older women, older age and lower hip BMD at the time of treatment discontinuation predict higher fracture incidence over the subsequent 5 years. In contrast, posttreatment BMD measurements after 1 to 2 years or bone turnover marker levels after 1 or 3 years did not predict fracture incidence. These results have implications for current clinical practice and future clinical trials.