Does a History of Non-Vertebral Fracture Identify Women Without Osteoporosis for Treatment?

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BACKGROUND: Postmenopausal women with a prior fracture have an increased risk for future fracture. Whether a history of non-vertebral fracture defines a group of women with low bone mass but without osteoporosis for whom alendronate would prevent new non-vertebral fracture is not known.

SUBJECTS AND METHODS: Secondary analysis of data from the Fracture Intervention Trial (FIT). Of 2,785 postmenopausal women with a T-score at the femoral neck between -1 and -2.5 and without prevalent radiographic vertebral deformity, 880 (31.6%) reported experiencing a fracture after 45 years of age. Women were randomized to placebo or alendronate (5 mg/day years for the first 2 years and 10 mg/day thereafter) and were followed for an average of 4.2±0.5 years. Incident non-vertebral fractures were confirmed by x-rays and radiology reports.

RESULTS: In the placebo arm, a self-report of prior fracture identified women with a 1.5-fold (hazard ratio [RH] 1.46, 95% C.I. 1.04–2.04) increased risk for incident non-vertebral fracture. However, there was no evidence that the effect of alendronate differed across subgroups of women with (RH 1.26 for alendronate vs placebo, 95% C.I. 0.89–1.79) and without prior fracture (RH 1.02 for alendronate vs placebo, 95% C.I. 0.76–1.38; *P*=0.37 for interaction).

CONCLUSION: Assessing a clinical risk factor, prior non-vertebral fracture, did not identify women with low bone mass for whom alendronate reduced future non-vertebral fracture risk.

KEY WORDS: fracture; women; osteoporosis.

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INTRODUCTION

An estimated 18% of women over 50 years of age have osteoporosis (a T-score at or below -2.5), and another 50% have a femoral neck T-score between -1 and -2.5,¹ whereas postmenopausal women with osteoporosis have a higher relative risk of fracture, the majority of fractures occur in women without osteoporosis.^{2–6} This is because there is a lower prevalence of osteoporosis compared to normal and low bone mass in the population. In addition, clinical risks, like prior fracture, falls, low body mass, family history, and poor vision increase risk beyond bone mineral density (BMD) measurements.^{7–10} Professional societies therefore recommend pharmacologic therapy for some postmenopausal women with low BMD and risks but without osteoporosis.^{11,12} With the availability of screening by dual x-ray absorptiometry (DXA), many women without osteoporosis will be identified for treatment.

Presence of vertebral deformity identifies women at greater risk of all fracture types¹³ and can identify women with femoral neck T-scores above -2.5 for treatment. In women with a radiographic vertebral deformity and femoral neck T-scores above -2.5, alendronate therapy reduces the risk of all clinical fractures.¹⁴ In the absence of vertebral deformity, there was a trend for alendronate to protect against clinical vertebral fractures in women with a femoral neck T-score above -2.5,¹⁵ but not reduce the risk of incident non-vertebral fracture.¹⁶ The cost-effectiveness of bisphosphonate therapy among women with a T-score above -2.5 at the femoral neck and without prevalent vertebral deformity may be critically dependent on the non-vertebral fracture reduction efficacy of bisphosphonates.^{17,18} It is, therefore, important to identify subsets of women without osteoporosis that would have reduced non-vertebral fracture incidence with treatment.

Risedronate did not reduce non-vertebral fractures in women chosen for skeletal and nonskeletal risk factors—like

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smoking and propensity for falls—when osteoporosis was not an enrollment criteria.¹⁹ We hypothesized that the risk factor of prior fracture^{7,20,21} would identify a subset of women without osteoporosis that would benefit from antiresorptive therapy. This risk factor can be obtained from a brief history and is a strong predictor of future fracture. In a large cohort of women with a T-score between -1 and -2.5 , measured by peripheral device, a history of fracture elevated 1-year fracture risk to that of women with a T-score ≤ -2.5 .²² We analyzed data from the clinical fracture arm of the fracture intervention trial (FIT) to confirm that in placebo patients without osteoporosis, prior non-vertebral fracture increased the risk of incident non-vertebral fracture. We then examined whether the effect of alendronate on non-vertebral fracture risk in women with low BMD but without osteoporosis differed across categories defined by the presence or absence of prior fracture.

METHODS

Participants

FIT was a randomized double-blind placebo-controlled trial conducted from 1992 until 1997 at 11 clinical sites in the United States. Enrollees were stratified based on the presence or absence of prevalent vertebral deformity using x-ray morphometry.^{23,24} The current analysis is a post hoc subgroup analysis in the study arm of women without prevalent vertebral deformity at baseline, referred to as FIT II.¹²

Four thousand four hundred and thirty-two women with a BMD at the femoral neck below 0.68 g/cm^2 (QDR-2000, Hologic Inc, Waltham, MA) were enrolled in FIT II. This was thought to correspond to a T-score at least two standard deviations below the mean of young adult women, based upon the manufacturer's reference values. When the BMD was standardized to the National Health and Nutrition Examination Survey reference values, it was found to correspond to a T-score of -1.6 .

Thus, when enrolled in FIT II, a total of 2,785 participants without vertebral deformity had a femoral neck T-score above -2.5 and correspond to the study population of this analysis.

Medication

Participants were randomized to receive alendronate or placebo for up to 54 months. The dosage of alendronate was 5 mg/day for the first 2 years, but was increased to 10 mg/day at the second annual visit after results from other trials suggested greater BMD effect of the 10 mg/day dose. Study drug adherence was based on pill counts ($\geq 70\%$) and therapy record ($\geq 75\%$). Participants with dietary calcium less than 1,000 mg/day were instructed to take a daily supplement containing 500 mg elemental calcium and 250 IU of vitamin D.

Baseline Measures

Data were collected regarding clinical variables that may affect fracture risk. Dietary calcium intake was estimated by a dairy intake questionnaire. Participants were asked to rate their general health as poor, fair good, very good, and excellent reported postmenopausal use of estrogen ever, current smoking, and a history of a fall in the past 12 months. If participants

reported a fracture after the age of 45 years, they were asked about timing and location, but not circumstances, of the non-vertebral fracture.

Outcomes

The primary outcome was incident non-vertebral fracture diagnosed by a physician. Written reports of radiographs or other supporting material was used for confirmation. A pathologic fracture was a fracture associated with a malignancy of the bone. Severe trauma included motor vehicle accidents and assaults. Moderate trauma included collision with an object during normal activities (i.e., hitting hand on the door), or with a twisting injury (turned ankle). Minimal trauma fractures were those that occurred with bending, coughing, sneezing, or turning in bed. Falls were categorized as same height fall, change in height (stepping from a curb), and fall from a height (falls off a chair or a porch). Excluded from the primary outcome were pathologic fractures and fractures from severe trauma.

Statistical Analysis

T-test and chi-square analyses were used to compare baseline characteristics in between the alendronate and placebo group within categories of women with and without prior fracture. Within the cohort of placebo patients, Cox proportional hazards models were used to determine the association between prior fracture and incident non-vertebral fracture. Cox proportional hazard models were used to determine the effect of alendronate versus placebo on risk of incident non-vertebral fracture stratified by the presence or absence of self-report of prior fracture at baseline. Only the time to first fracture was considered for analysis. The effect of removing fractures likely associated with trauma (face, skull, fingers,

Table 1. Baseline Characteristics in Women without Osteoporosis at the Femoral Neck by Fracture History Since Age 45

Characteristic	With Prior Fracture (n=880)	No Prior Fracture (n=1905)	p value
Age, years, mean (SD)	67.4 (6.0)	66.0 (6.1)	<.001
<65, n (%)	278 (32)	774 (41)	
65–74, n (%)	487 (55)	954 (50)	
75–80, n (%)	115 (13)	177 (9)	
Femoral neck BMD, mean (SD)	0.63 (0.03)	0.63 (0.03)	
Femoral neck T-score, mean (SD)	−2.0 (0.3)	−2.0 (0.3)	.08
−1 to −2, n (%)	402 (46)	956 (50)	
−2 to −2.5, n (%)	478 (54)	949 (50)	
Lumbar spine T-score*, mean (SD)	−1.9 (1.1)	−1.8 (1.2)	.02
Above −1, n (%)	149 (17)	413 (22)	
−1 to −2, n (%)	295 (34)	575 (31)	
−2 to −2.5, n (%)	164 (19)	338 (18)	
Below −2.5, n (%)	257 (30)	550 (29)	
≥ 1 falls within the last year, n (%)	297 (34)	441 (23)	<.001
Weight, kg, mean (SD)	67.6 (10.9)	66.1 (10.8)	<.001
Current smoker, n (%)	78 (9)	177 (9)	.70

*29 women without prior fracture and 15 with prior fracture did not have an interpretable DXA of the lumbar spine
BMD bone mineral density

and toes) from baseline and incident fracture categories was determined. Finally, the effect of limiting the definition of prior fracture to those of the wrist, hip and ribs was determined. These are considered traditional osteoporotic fractures; therefore, pharmacologic therapy would be expected to have the most impact on these fractures.

RESULTS

Baseline Characteristics

Baseline characteristics of the 2,785 women with low BMD but without osteoporosis by prior fracture status are shown in Table 1. Compared to the 1,905 women without prior fracture, the 880 women (31.6%) with a prior fracture were older, heavier, more likely to have fallen, and had a lower lumbar spine T-score ($P < .05$ for all comparisons, Table 1). Prior fractures occurred 8.26 (range 0 to 32) years before the baseline exam. They were: wrist (26.4%); ankle, heel and foot (24.7%); face, fingers, toes, and skull (14.6%); arm and shoulder (10.5%); legs (8.3%); rib (7.2%); hip and pelvis (2.8%); and hand (2.6%). Other fractures made up less than 1% each.

As anticipated, given the randomized trial design, baseline characteristics were similar between treatment groups (Table 2), except that among women without prior fracture, past estrogen use was more frequent in women assigned to alendronate. After randomization, women were followed for 4.2 ± 0.5 years. Adherence to treatment did not differ between those assigned to placebo versus alendronate for those with ($P = .35$) and without ($P = .83$) prior fracture.

Fracture Outcomes

A history of prior fracture was associated with an increased risk of incident non-vertebral fracture in the placebo group (hazard ratio [RH] 1.46, 95% C.I. 1.04–2.04). Among the 880

women reporting prior fracture, 127 women (14.4%) had 153 incident non-vertebral fractures. Among 1,905 women without prior fracture, there were 174 women with 194 incident non-vertebral fractures (9.1%). Types and mechanism of incident fracture were similar between the women with and without prior fracture.

Among all 2,785 women in FIT II with low BMD but not osteoporosis, we did not detect a difference in risk of incident non-vertebral fracture in the alendronate versus the placebo arm (Table 3). There was no reduction in risk among women with or without prior fracture, nor was there an interaction between presence and absence of prior fracture and treatment assignment for the risk of incident non-vertebral fracture ($P = .37$). Among women with prior fracture, the results were not altered with exclusion of baseline or incident fractures of the face, fingers, toes, or skull (1.22, 95% CI 0.83–1.81) and when the definition of self-reported prior fractures was limited to the wrist, hip, and ribs ($N = 366$ women; RH 1.41, 95% CI 0.80–2.50, $P = .54$ for interaction).

DISCUSSION

In the clinical fracture arm of FIT, self-report of fracture after the age of 45 years identified women without osteoporosis with a 50% increased risk for future non-vertebral fracture. Prior fracture is a powerful predictor of future fracture, can be quickly identified in the practice setting, and could be used in the acute fracture setting to target postmenopausal women for osteoporosis therapy. However, prior fracture did not identify women without osteoporosis that had a reduced risk of non-vertebral fracture with 4 years of alendronate therapy. A potential explanation for our finding is that antiresorptives exert their action on bone density, turnover, and quality, but presumably have no impact on other risks for fractures, like fall risk or low body mass.

Table 2. Characteristics of Participants According to Fracture History Status and Treatment Assignment

Characteristic	Fracture History					
	With Prior Nonvertebral Fracture			No Prior Nonvertebral Fracture		
	Placebo (n=442)	ALN (n=438)	p value	Placebo (n=954)	ALN (n=951)	p value
Age, yrs, mean (SD)	67.4 (6.0)	67.5 (6.0)	.74	66.1 (6.0)	65.9 (6.1)	.51
<65, n (%)	141 (32)	137 (31)		391 (41)	383 (40)	
65–74, n (%)	243 (55)	244 (56)		467 (49)	487 (51)	
75–80, n (%)	58 (13)	57 (13)		96 (10)	81 (9)	
FN BMD, g/cm ² , mean (SD)	0.63 (0.03)	0.63 (0.03)	.08	0.63 (0.03)	0.63 (0.03)	.69
FN T-score, mean (SD)	−2.0 (0.3)	−2.0 (0.3)	.08	−2.0 (0.3)	−2.0 (0.3)	.69
−1 to −2, n (%)	215 (49)	187 (43)		478 (50)	478 (50)	
−2 to −2.5, n (%)	227 (51)	251 (57)		476 (50)	473 (50)	
LS T-score, mean (SD)	−1.9 (1.1)	−1.9 (1.1)	.44	−1.8 (1.2)	−1.8 (1.1)	.59
Above −1, n (%)	81 (19)	68 (16)		207 (22)	206 (22)	
−1 to −2, n (%)	146 (34)	149 (35)		285 (30)	290 (31)	
−2 to −2.5, n (%)	80 (18)	84 (20)		167 (18)	171 (18)	
Below −2.5, n (%)	128 (29)	129 (30)		281 (30)	269 (29)	
≥1 falls in past year, n (%)	139 (32)	158 (37)	.13	219 (23)	222 (24)	.83
Perceived health status < very good, n (%)	149 (34)	139 (32)	.53	299 (31)	273 (29)	.21
Weight, kg, mean (SD)	67.6 (11.1)	67.6 (10.8)	.98	65.9 (10.8)	66.2 (10.9)	.47
Height, cm, mean (SD)	161 (6)	162 (6)	.27	161 (6)	161 (6)	.41
Current smoker, n (%)	43 (10)	35 (8)	.38	91 (10)	86 (9)	.69
Ca intake, mg, mean (SD)	664 (407)	679 (413)	.59	667 (414)	631 (403)	.06
Prior HRT, n (%)	158 (36)	149 (34)	.54	295 (31)	336 (36)	.04

Abbreviations: ALN alendronate, FN femoral neck, BMD bone mineral density, LS lumbar spine, Ca calcium, HRT hormone replacement therapy

Table 3. Incidence of and Hazard Ratios for Non-vertebral Fracture by Treatment Group and Risk Subgroup

	Placebo, n (%) (N=1,396)	ALN, n (%) (N=1,389)	Hazard Ratio (95% CI)	P value for Interaction
All Participants (N=2785)	143 (10)	158 (11)	1.12 (0.89–1.40)	–
Prior fracture since age 45				
No (N=1,905)	86 (9)	88 (9)	1.02 (0.76–1.38)	
Yes (N=880)	57 (13)	70 (16)	1.26 (0.89–1.79)	0.37

ALN alendronate

Most other trials of prescription medication enrolled women with a T-score above -2.5 only if they had a prevalent vertebral deformity,^{25–28} and so cannot address whether subsets of women without either vertebral deformity or osteoporosis should receive treatment. The Women's Health Initiative (WHI) demonstrated that estrogen plus progestin reduced hip and all fractures in women for whom osteoporosis was not an enrollment criteria. However, within the subset of women with a BMD measurement, there was the suggestion that the benefits were most pronounced in women with T-score below -2.5 . Similar to our findings, prior fracture did not identify women in WHI that would derive greater fracture reduction from hormone replacement.²⁹ In trials of raloxifene and risendronate, a significant number of women were enrolled that did not have osteoporosis or BMD measurement; our results parallel the findings from these studies. Among women with coronary heart disease risks, in whom BMD was unknown, raloxifene did not decrease the risk of non-vertebral fracture.³⁰ In the HIP trial, women age 80 years and older were chosen for non-skeletal risks for fracture. A substantial proportion had vertebral deformity on spine films or osteoporosis by DXA, but not all women were screened at enrollment.¹⁹ Risk factors obtainable by history alone did not define women for whom risendronate prevented hip and other non-vertebral fracture. The authors hypothesized that the majority of these women had a femoral neck T-score above -2.5 . Finally, the importance of a femoral neck BMD cut point was underscored in a post hoc analysis of the ibandronate trial, in which prevalent vertebral deformity was an enrollment criterion. Ibandronate reduced the risk of non-vertebral fracture only at T-scores below -3 .²⁷

Given that the majority of fractures occur in women without osteoporosis, it is a public health imperative to prevent fractures in this group; given the large size of population at risk, these interventions may need to be targeted. Zoledronic acid prevented non-vertebral fracture and reduced mortality in men and women enrolled after hip fracture. An unreported number had baseline vertebral deformity, but the majority had a femoral neck T-score greater than -2.5 .³¹ It is unclear why our study finding were different from this study; possible explanations include the greater potency of zoledronic acid; or the likely high prevalence of undiagnosed prevalent vertebral fracture associated with incident hip fracture.³² Finally, the measurement of bone turnover is an effective and possibly cost-effective tool to identify women without osteoporosis for treatment with alendronate. This approach is ideal as biomarker measurement can be performed in the outpatient setting.^{33,34}

This study has limitations. The power for this analysis was only approximately 30%; however, the lower limits of the confidence interval (0.89) indicate that it is unlikely that alendronate reduces the risk of non-vertebral fracture by even

10% in women without osteoporosis but with prior non-vertebral fracture. Although history of fracture after the age of 45 years was obtained by self-report and not validated, self-report has previously been demonstrated to be accurate. Specificity is above 80% for self-report of fracture,^{35–37} with underreporting rare.³⁷ Our primary outcome, non-vertebral fracture, was heterogeneous, but our results were unchanged in the analysis that focused on fragility fractures. The dose of alendronate was only 5 mg/day for the first 2 years of the trial, which is not the current recommended dose. Finally, although our hypothesis was specified before the analysis, this is a subgroup analysis of a clinical trial. A randomized controlled trial designed to determine the effect of treatment including alendronate in postmenopausal women without osteoporosis is best positioned to definitely address our question. Given the lower absolute risk of fracture in these women, such a trial is unlikely to be conducted because of time and resource constraints.

In conclusion, alendronate therapy does not appear to reduce the risk of non-vertebral fracture in the absence of osteoporosis or a vertebral deformity, even among women with prior fracture.

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Members of the Fracture Intervention Trial Research Group are listed in reference 23.

Authors' contributions: Conception: KMR, SRC; Design: KMR, SRC, DCB, SS; analysis and interpretation: LP, KMR, SRC, DCB, KE; manuscript preparation: KMR, LP, SS, SRC, DCB, AF, JS, KE, AVS SRC

Sponsor role: Drafts of the manuscript were reviewed, and changes to the manuscript were recommended by all coauthors and staff at Merck. The final version of this manuscript was reviewed by all coauthors and the Fracture Intervention Trial Steering Committee; Merck Investigators constituted a minority of the steering committee. Merck Research Laboratories funded the original FIT study.

Lisa Palermo had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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