Long-Term Oral Bisphosphonate Therapy and Fractures in Older Women: The Women's Health Initiative

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OBJECTIVES: To examine the association between long-term bisphosphonate use and fracture in older women at high risk of fracture.

DESIGN: Retrospective cohort.

SETTING: Women's Health Initiative.

PARTICIPANTS: Older women who reported at least 2 years of bisphosphonate use in 2008–09 (N = 5,120).

MEASUREMENTS: Exposure data were from a current medications inventory. Outcomes (hip, clinical vertebral, wrist or forearm, any clinical fracture) were ascertained annually. Using multivariate Cox proportional hazards models, the association between duration of bisphosphonate use (3–5, 6–9, 10–13 years) and fracture was estimated, using 2 years as the referent group.

RESULTS: On average participants were 80 years old and were followed for 3.7 ± 1.2 years. There were 127 hip, 159 wrist or forearm, 235 clinical vertebral, and 1,313 clinical fractures. In multivariate-adjusted analysis, 10 to 13 years of bisphosphonate use was associated with higher risk of any clinical fracture than 2 years of use (hazard ratio (HR) = 1.29, 95% confidence interval (CI) = 1.07–1.57). This association persisted in analyses limited to women with a prior fracture (HR = 1.30, 95% CI = 1.01–1.67) and women with no history of cancer (HR = 1.36, 95% CI = 1.10–1.68). The association of 10 to 13 years of use, compared with 2 years of use, was not statistically significant for hip (HR = 1.66, 95% CI = 0.81–3.40), clinical vertebral (HR = 1.65, 95% CI = 0.99–2.76), or wrist fracture (HR = 1.16, 95% CI = 0.67–2.00).

CONCLUSION: In older women at high risk of fracture, 10 to 13 years of bisphosphonate use was associated with higher risk of any clinical fracture than 2 years of use. These results add to concerns about the benefit of very long-term bisphosphonate use. **J Am Geriatr Soc 65:1924–1931, 2017.**

Key words: long-term bisphosphonate use; fracture; pharmacoepidemiology

Osteoporosis is a condition of low bone mineral density (BMD) and deterioration of the bone microarchitecture, which increases susceptibility to fracture. Age is the strongest risk factor for fracture, and one in two women will experience an osteoporotic fracture after age 50.[1,2] Low BMD increases risk of fracture, and by 2020, an estimated 61 million U.S. adults will have low BMD.[2] Bisphosphonates, the most-prescribed osteoporosis medication class,[3,4] increase BMD by inhibiting bone resorption in the bone remodeling process,[5,6] but recent studies have questioned the benefit of long-term bisphosphonate use.[7–9]

A 2011 Cochrane Collaboration review of all randomized controlled trials (RCTs) of alendronate, the most-prescribed bisphosphonate, concluded that 1 to 4 years of therapy may prevent nonvertebral fracture in women with low BMD or a vertebral fracture before treatment but probably does not prevent fractures in women without those risk factors.[8] Furthermore, a 2011 Food and Drug Administration (FDA) review of all long-term RCTs of bisphosphonates, including the Fracture Intervention Trial Long Term Extension (FLEX),[10] found inconclusive evidence that bisphosphonate therapy for longer than 3 to 5 years prevents fracture, regardless of initial BMD.[7,9] The lack of evidence of benefit from long-term bisphosphonate use and evidence of harms, including atypical fracture, led to a 2011 FDA recommendation that individuals be

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routinely evaluated for the appropriateness of continued therapy during long-term use,[8,11–14] but the small size of the RCTs prevented the FDA review from examining long-term bisphosphonate use in high-risk subgroups.[7,9] In particular, the FDA review included only 334 women aged 70 and older who used bisphosphonates for longer than 5 years and lacked data on use for longer than 11 years.[7] Thus, the FDA has called for more research on long-term bisphosphonate use in subgroups.[7]

In 2008–09, more than 17,000 postmenopausal Women's Health Initiative (WHI) participants reported current bisphosphonate use, with a wide range of duration patterns. The objective of the present analysis was to compare long-term bisphosphonate therapy with short-term use in relation to fracture using data from the WHI in older women at high risk of fracture.

METHODS

Study Population

The WHI is a large, longitudinal study of women's health begun in 1993 with the primary aim of developing strategies to reduce incidence of heart disease, cancer, and fractures in postmenopausal women. It includes an observational study (N = 93,676) and RCTs (N = 68,132) evaluating estrogen alone, estrogen plus progestin, dietary modification, and calcium and vitamin D supplementation. After the planned study end date in 2005, re-consent was required for continued follow-up (n = 115,403). In 2008–09, 97,448 participants completed a current medication inventory administered by mailed questionnaire to all active participants. The WHI study design and methods are described elsewhere.[15–18]

In the subset of current oral bisphosphonate users who reported use for 2 years or more at the 2008–09 medication inventory, had follow-up data thereafter, and had a 5-year hip fracture risk of 1.5% or greater, the association between longer duration of use (3–5, 6–9, 10–13 years) and incident site-specific fracture (hip, wrist or forearm, clinical vertebral) and with any clinical fracture was analyzed, using shorter duration of use (2 years) as the reference group. The study was limited to women who reported at least 2 years of bisphosphonate use to include women with persistent medication use. Two years was chosen as the reference group because this duration of use has been associated with lower fracture risk.[7] Guidelines recommend bisphosphonates as the preferred treatment for women at high risk of fracture (10-year hip fracture risk ≥3%) based on Fracture Risk Assessment Tool (FRAX) score.[19–21] To select a high-risk study sample, women with a predicted 5-year risk of hip fracture of 1.5% or greater, which is comparable with the FRAX definition of high fracture risk, were identified using a risk prediction algorithm developed and validated in the WHI that includes 11 clinical factors (age, weight, height, history of fracture after age 54, parental hip fracture, smoking, corticosteroid use, race and ethnicity, self-reported health, self-reported physical activity, treated diabetes mellitus).[22] To reduce confounding from other medications that affect bone metabolism, women who ever reported use of calcitonin, selective estrogen reuptake modulators, parathyroid hormone, or aromatase inhibitors (n = 1,801) and women who reported estrogen use within 5 years before the 2008–09 medication inventory (n = 260) were excluded. Women who discontinued and resumed bisphosphonate use before the medication inventory were also excluded (n = 1,000). After exclusions, 5,120 women were included in the present analysis.

Exposure Ascertainment

Women self-reported duration of bisphosphonate use on the mailed 2008–09 medication inventory form, which instructed participants to gather all current medication prescriptions and to use information from the prescription labels.[23] Participants wrote the drug name, strength, and type (e.g., capsule, inhaler) and duration of use (<1 month, 1–12 months, number of years).

Covariates

Covariates were selected a priori based on literature review to include factors associated with bisphosphonate use or fracture risk. Participants self-reported age, race, education level, fracture, physical function, general health rating (excellent, very good, good, fair, poor),[24] severe memory impairment (Alzheimer's disease or dementia), recreational physical activity, diabetes mellitus treated with injections or medication, glucocorticoid use (≥3 months), parental hip fracture, Parkinson's disease diagnosis, alcohol use (≥3 servings/day), calcium supplement use, smoking status, and rheumatoid arthritis diagnosis. To adjust for potential differences in BMD between participants, the predicted risk of hip fracture within 5 years was calculated from an 11-item algorithm developed and validated in the WHI.[22] The 5-year hip fracture risk score was significantly correlated with BMD in 10,418 WHI participants for whom both measures were available.[25] Body mass index (BMI (kg/m^2)) was calculated at clinical examinations at Years 0, 3, 6, and 9 for RCT participants and Years 0 and 3 for observational study participants. Information on other medications was collected at Years 0, 3, 6, and 9 for RCT participants and Years 0, 3, and 4 to 8 for observational study participants. Cancer diagnosis was self-reported and then confirmed according to medical record review.[17] Physical function score was calculated from the RAND 36-Item Health Survey, with higher scores indicating better physical function.[26] Recreational physical activity was assessed according to self-report on a validated study questionnaire[27] and categorized in metabolic equivalent hours per week.[28] This analysis used the most-recent values and measures collected at or before the 2008–09 medication inventory.

Outcome Ascertainment

Outcomes of interest for this analysis were incident hip, clinical vertebral, and wrist or forearm fracture and incident clinical fracture at any site. Outcomes were ascertained according to self-report on annual forms that asked women to report the first lifetime occurrence of site-specific fractures.[17] The specific date of hip and femur fractures was collected according to self-report for all participants throughout follow-up and adjudicated according to

medical record review for all participants through 2010, for all participants in the hormone therapy RCT, and for African-American and Hispanic participants after 2010 (20% of participants). For other fractures, the fracture date was recorded as the completion date of the annual form. The WHI definition of clinical fracture excludes fractures of the finger, toe, jaw, nose, face, skull, rib, sternum, and cervical spine.

Statistical Analysis

Descriptive Analysis

The 5,120 bisphosphonate users included in the fracture analysis were grouped according to duration of use (2, 3–5, 6–9, 10–13 years) and compared using analysis of variance and the chi-square test.

Statistical Analysis of Fracture Incidence

Participants contributed follow-up time from the date of the 2008–09 medication inventory until the occurrence of fracture, death, loss to follow-up, or end of study follow-up in 2013–14.[12] The fracture incidence per 1,000 person-years was calculated for each outcome type during follow-up. Association between duration of bisphosphonate use and fracture was estimated using multivariate Cox proportional hazards survival models that compared 3 to 5, 6 to 9, and 10 to 13 years of bisphosphonate use with 2 years of use (reference group). There was one model for each site-specific fracture type (hip, wrist or forearm, clinical vertebral fracture) and one model for any clinical fracture. Models for site-specific incident fracture excluded women who reported an incident fracture for that site before the start of follow-up (n = 271 for hip, n = 1,177 for wrist or forearm, n = 361 for clinical vertebral fracture). The models were adjusted a priori for age, race, education level, BMI, physical function, general health rating, severe memory impairment diagnosis, recreational physical activity, treated diabetes mellitus, glucocorticoid use, 5-year hip fracture risk score, estrogen use within 6 to 10 years before medication inventory, calcium supplement use, parental hip fracture, Parkinson's disease diagnosis, alcohol use, smoking status, cancer diagnosis, and rheumatoid arthritis diagnosis. All models were stratified according to history of fracture after age 54. Subjects with missing covariate data were excluded from multivariate models (n = 150; 2.9% of subjects). All statistical tests were two-tailed ($\alpha = 0.05$) and performed in Stata version 13 (Stata Corp., College Station, TX).

Additional Analyses

To create a more-homogeneous study sample, a sensitivity analysis was performed limited to women with a history of fracture after age 54 (n = 2,779). Because some cancers and cancer treatments increase fracture risk,[29] a sensitivity analyses was conducted limited to women with no history of cancer before the medication inventory (n = 4,369). To examine the association between each additional year of bisphosphonate use and fracture, bisphosphonate use was modeled as a continuous variable (years of use) and the results presented as the predicted hazard ratio associated with a 5-year increase in duration of bisphosphonate use, which is equivalent to the interquartile range of duration of bisphosphonate use. All additional analyses were adjusted for the same covariates as the primary analysis and stratified according to history of fracture, except for the analysis limited to women with a history of fracture.

RESULTS

Descriptive Characteristics

Characteristics of all 97,448 women who completed the 2008–09 medication inventory form are described in Table S1. Of the 5,120 women in the analysis, 642 (13%) had used bisphosphonates for 2 years, 1,746 (34%) for 3 to 5 years (average 4.1 ± 0.9 years), 1,031 (20%) for 6 to 9 years (average 7.3 ± 1.0 years), and 1,701 (33%) for 10 to 13 years (average 11.1 ± 1.4 years) (Table 1). The average age of all the groups was approximately 80 years, and 97% were aged 70 and older. Having a college degree or higher educational attainment was more common and estrogen use within the 6 to 10 years before the 2008–09 medication inventory was least common in women with longer duration of bisphosphonate use. In women with 6 to 9 or 10 to 13 years of bisphosphonate use, on average, BMI was lower; diabetes mellitus was less common; and physical function score, recreational physical activity, and general health were higher than in women with 2 or 3 to 5 years of use. Other characteristics, including history of fracture after age 54, did not significantly differ between groups.

Fracture Outcomes

Women in the fracture analysis were followed for an average of 3.7 ± 1.2 years. During follow-up, there were 127 hip fractures, 159 wrist or forearm fractures, 235 clinical vertebral fractures, and 1,313 clinical fractures (Table 2). The unadjusted fracture rate per 1,000 person-years was highest for the group with 10 to 13 years of bisphosphonate use for all fracture outcome types except clinical vertebral fracture. Women with 2 years of bisphosphonate use had the lowest unadjusted fracture rate for all fracture outcome types except for wrist or forearm fracture.

In the primary multivariate-adjusted survival analysis, 10 to 13 years of bisphosphonate use was associated with higher risk of any clinical fracture than 2 years of use (hazard ratio (HR) = 1.29, 95% confidence interval (CI) = 1.07–1.57). Although the associations for 10 to 13 years were not statistically significant for any site-specific fracture, the risk was greater for hip (HR = 1.66, 95% CI = 0.81–3.40) and clinical vertebral fracture (HR = 1.65, 95% CI = 0.99–2.76). There was no significant association between 3 to 5 or 6 to 9 years of bisphosphonate use and fracture outcomes.

In sensitivity analyses limited to women with a history of fracture after age 54 (HR = 1.30, 95% CI = 1.01–1.67; Table 3) and to women with no history of cancer (HR = 1.36, 95% CI = 1.10–1.68; Table 4), 10 to 13 years of bisphosphonate use remained associated with greater risk of any clinical fracture. In the additional

Table 1. Characteristics of 5,120 Postmenopausal Women with a 5-Year Risk of Hip Fracture of 1.5% or Greater Categorized According to Duration of Bisphosphonate Use at 2008–09 Medication Inventory

Characteristic	Years of Bisphosphonate Use at 2008–09 Medication Inventory				*P*-Value
	2, n = 642	3–5, n = 1,746	6–9, n = 1,031	10–13, n = 1,701	
Bisphosphonate use, years, mean ± SD	2.0 ± 0	4.1 ± 0.9	7.3 ± 1.0	11.1 ± 1.4	
Age, mean ± SD	79.6 ± 5.1	79.6 ± 5.0	79.4 ± 5.0	79.9 ± 4.9	.09
Aged ≥70, n (%)	617 (96.1)	1,686 (96.6)	997 (96.7)	1,664 (97.8)	.07
White, n (%)	596 (92.8)	1,638 (93.8)	983 (95.3)	1,609 (94.6)	.15
Education, n (%)					
< High school diploma/GED	24 (3.7)	51 (2.9)	21 (2.0)	36 (2.1)	.01
High school diploma/GED	109 (17.0)	199 (11.4)	163 (15.8)	263 (15.5)	
School after high school	240 (37.4)	630 (36.1)	355 (34.4)	555 (32.6)	
≥College degree	265 (41.3)	762 (43.6)	488 (47.3)	838 (49.3)	
Prior fracture after age 54 year, n (%)	344 (53.6)	947 (54.2)	542 (52.6)	946 (55.6)	.46
Parental hip fracture, n (%)	104 (16.2)	312 (17.9)	211 (2.5)	330 (19.4)	.13
Rheumatoid arthritis diagnosis, n (%)	54 (8.4)	141 (8.1)	84 (8.1)	129 (7.6)	.90
Glucocorticoid use for ≥3 months, n (%)	28 (4.4)	73 (4.2)	52 (5.0)	73 (4.3)	.74
Alcohol ≥3 servings/d, n (%)	21 (3.3)	45 (2.6)	30 (2.9)	46 (2.7)	.82
Current smoker, n (%)	32 (5.0)	83 (4.8)	45 (4.4)	61 (3.6)	.29
Hip fracture risk score, mean ± SD[a]	23.1 ± 2.9	23.1 ± 2.8	23.0 ± 2.9	23.3 ± 2.9	.06
Body mass index, kg/m^2, mean ± SD	26.7 ± 4.8	26.1 ± 5.0	25.3 ± 4.5	25.2 ± 4.5	<.001
Physical function score, mean ± SD	67.4 ± 26.2	70 ± 25.2	72.6 ± 23.7	71.8 ± 23.8	<.001
Recreational physical activity, metabolic equivalent h/wk, mean ± SD	12.0 ± 13.6	12.6 ± 12.3	14.0 ± 13.8	13.5 ± 13.2	.003
General health rating, n (%)					
Fair or poor	851 (13.2)	188 (10.8)	89 (8.6)	144 (8.5)	.002
Good	255 (39.7)	735 (42.1)	372 (36.1)	622 (36.6)	
Very good or excellent	302 (47.0)	823 (47.1)	570 (55.3)	935 (55.0)	
Treated diabetes mellitus, n (%)	73 (11.4)	163 (9.3)	83 (8.1)	132 (7.8)	.03
Severe memory impairment, n (%)	16 (2.5)	53 (3.0)	16 (1.6)	36 (2.1)	.08
Estrogen use 6–10 year before, n (%)	324 (50.5)	874 (50.1)	510 (49.5)	757 (44.5)	.003
Current calcium supplement use, n (%)	587 (91.4)	1,638 (93.8)	957 (92.8)	1,585 (93.2)	.32
Cancer diagnosis, n (%)	92 (14.3)	258 (14.8)	141 (13.7)	260 (15.3)	.71
Parkinson's disease diagnosis, n (%)	4 (0.6)	18 (1.0)	11 (1.1)	16 (0.9)	.80

[a] Risk score for hip fracture within 5 years calculated from an 11-item algorithm; a score of 23 equals a risk probability of 3.5%.
GED = general education development; SD = standard deviation.

analysis that modeled bisphosphonate exposure as a continuous variable, a 5-year increase in bisphosphonate use was associated with 15% greater risk of any clinical fracture (95% CI = 1.07–1.25), 33% greater risk of hip fracture (95% CI = 1.03–1.72), and 21% greater risk of clinical vertebral fracture (95% CI = 1.00–1.47; Table 5).

DISCUSSION

This study examined the association between fracture risk and bisphosphonate use in more high-risk, older, female long-term bisphosphonate users than any previous study and included 1,701 women who had used bisphosphonates for 10 or more years. The multivariate-adjusted analysis found that 10 to 13 years of bisphosphonate use was associated with greater risk of any clinical fracture than 2 years of use. This association remained significant in sensitivity analyses limited to women with a history of fracture and to women without a history of cancer. The associations for 10 to 13 years of use were not significant for site-specific fractures, but the risk was greater for hip and clinical vertebral fracture. In additional analyses modeling bisphosphonate exposure as a continuous variable, longer exposure was associated with greater risk of any clinical fracture, hip fracture, and clinical vertebral fracture.

These findings support previous studies that did not find significantly lower overall fracture risk during long-term bisphosphonate use than with shorter duration of use.[7,10,30–35] The 2011 FDA review of long-term bisphosphonate RCTs found similar fracture rates during short- and long-term bisphosphonate use in women aged 70 and older.[7] Post hoc FLEX analysis found fewer clinical vertebral fractures but not fewer nonvertebral fractures with 10 years of alendronate use than with discontinuing after 5 years.[10] An RCT of risedronate found no difference in association between 6 and 7 years of bisphosphonate use and fracture risk from 1 to 2 years of use.[34] Another study found no lower overall fracture risk with 8 years of use than with less than 5 years of exposure.[30]

Observational study findings are mixed for the association between hip fracture and long-term bisphosphonate use.[33,35,36] The current study and two of those studies found no hip fracture benefit with longer bisphosphonate exposure, whereas the third study found a benefit for 10 or more years of use.[33,35,36] The inclusion of individuals who had not used bisphosphonates long enough to achieve benefit may explain the third study's findings. These

Table 2. Fracture Incidence in 5,120 Postmenopausal Women with a 5-Year Risk of Hip Fracture of 1.5% or Greater and Risk of Fracture According to Duration of Bisphosphonate Use at 2008–09 Medication Inventory

Duration of Bisphosphonate Use, Years	Subjects, n	Fractures		Adjusted Hazard Ratio (95% Confidence Interval)
		N[a]	Incidence per 1,000 Person-Years	
	Hip fracture			
2	607	11	6.5	1.00
3–5	1,607	38	8.0	1.12 (0.53–2.34)
6–9	987	20	7.0	1.26 (0.56–2.81)
10–13	1,648	58	12.2	1.66 (0.81–3.40)
	Wrist or forearm fracture			
2	502	20	14.5	1.00
3–5	1,374	53	13.9	0.96 (0.55–1.66)
6–9	787	29	12.8	0.96 (0.53–1.75)
10–13	1,280	57	15.6	1.16 (0.67–2.00)
	Clinical vertebral fracture			
2	590	21	12.8	1.00
3–5	1,621	77	17.0	1.23 (0.73–2.06)
6–9	977	53	18.8	1.37 (0.80–2.37)
10–13	1,571	84	18.7	1.65 (0.99–2.76)
	Any clinical fracture			
2	642	141	86.1	1.00
3–5	1,746	419	92.1	1.04 (0.85–1.26)
6–9	1,031	254	92.2	1.04 (0.84–1.29)
10–13	1,701	499	112.2	1.29 (1.07–1.57)

Follow-up period is from completion date of medication inventory to end of study in 2013–14. Estimates are from Cox proportional hazards models adjusted for age, race, education level, body mass index, physical function score, general health rating, recreational physical activity, treated diabetes mellitus, severe memory impairment, glucocorticoid use for ≥3 months, risk of hip fracture within 5 years calculated using Women's Health Initiative 11-item fracture risk algorithm, calcium supplement use, estrogen use during the 6–10 years before medication inventory, parental hip fracture, smoking status, Parkinson's disease diagnosis, ≥3 servings per day of alcohol, rheumatoid arthritis diagnosis, and cancer diagnosis, stratified according to history of fracture after age 54.

[a] Number of fractures during all follow-up years.

Table 3. Fracture Incidence in 2,779 Postmenopausal Women with a History of Fracture After Age 54 and Before the 2008–9 Medication Inventory and a 5-Year Risk of Hip Fracture of 1.5% or Greater and Risk of Fracture According to Duration of Bisphosphonate Use at 2008–09 Medication Inventory

Duration of Bisphosphonate Use, Years	Subjects, n	Fractures		Adjusted Hazard Ratio (95% Confidence Interval)
		N[a]	Incidence per 1,000 Person-Years	
	Hip fracture			
2	309	8	9.2	1.00
3–5	871	23	9.4	0.65 (0.27–1.54)
6–9	498	11	7.5	0.64 (0.24–1.67)
10–13	893	32	12.4	0.88 (0.39–2.03)
	Wrist or forearm fracture			
2	213	14	23.6	1.00
3–5	624	26	15.5	0.72 (0.35–1.49)
6–9	341	14	14.2	0.72 (0.33–1.60)
10–13	575	32	19.6	0.99 (0.49–1.98)
	Clinical vertebral fracture			
2	292	13	16.0	1.00
3–5	822	50	22.1	1.22 (0.62–2.41)
6–9	488	35	24.9	1.62 (0.81–3.24)
10–13	816	47	20.3	1.47 (0.75–2.87)
	Any clinical fracture			
2	344	84	96.1	1.00
3–5	947	256	106.8	1.10 (0.85–1.43)
6–9	542	155	108.3	1.12 (0.85–1.47)
10–13	946	300	122.4	1.30 (1.01–1.67)

Follow-up period is from completion date of medication inventory to end of study in 2013–14. Estimates are from Cox proportional hazards models adjusted for age, race, education level, body mass index, physical function score, general health rating, recreational physical activity, treated diabetes mellitus, severe memory impairment, glucocorticoid use for ≥3 months, risk of hip fracture within 5 years calculated using Women's Health Initiative 11-item fracture risk algorithm, calcium supplement use, estrogen use during 6–10 years before medication inventory, parental hip fracture, smoking status, Parkinson's disease diagnosis, ≥3 servings per day of alcohol, rheumatoid arthritis diagnosis, and cancer diagnosis.

[a] Number of fractures during all follow-up years.

studies required only one bisphosphonate prescription for study inclusion,[33,35,36] although one of the studies also excluded individuals with a femoral fracture within 3 months of the initial prescription, and another used a test for trend to examine longer exposure.[33,35] Participants in one study with less than 1 year of exposure had the highest fracture incidence, but when the reference group was switched to 3 to 5 years of exposure, 10 or more years of exposure was not beneficial.[36] The current study selected participants who had used bisphosphonates long enough to achieve benefit by specifically requiring 2 years of bisphosphonate use.

The contrast between the current findings and the FLEX finding of benefit for clinical vertebral fracture risk also deserves consideration.[10] Bisphosphonate efficacy in the population examined may differ from that in FLEX participants, who were younger.[10] RCTs are unlikely to provide the information needed about fractures during very long-term bisphosphonate use.[37] Given the limited evidence of fracture risk reduction, guidelines recommending up to 10 years of bisphosphonate treatment should be reconsidered in light of observational study data, particularly for elderly women.[19]

Biological changes in bone during long-term bisphosphonate use may explain the current study findings, including oversuppression of the bone remodeling process, which may damage bone.[38–41] Suppression of bone remodeling inhibits resorption of damaged bone, which may increase bone heterogeneity and thereby increase bone brittleness.[42] Reviews by the FDA and American Society of Bone and Mineral Research concur that bisphosphonate use beyond

Table 4. Fracture Incidence in 4,369 Postmenopausal Women with No History of Cancer and a 5-Year Risk of Hip Fracture of 1.5% or Greater and Risk of Fracture According to Duration of Bisphosphonate Use at 2008–09 Medication Inventory

Duration of Bisphosphonate Use, Years	Subjects, n	Fractures		Adjusted Hazard Ratio (95% Confidence Interval)
		N[a]	Incidence per 1,000 Person-Years	
	Hip fracture			
2	519	9	6.2	1.00
3–5	1,424	30	7.4	1.26 (0.54–2.92)
6–9	850	19	7.7	1.60 (0.66–3.90)
10–13	1,398	50	12.3	2.06 (0.93–4.58)
	Wrist or forearm fracture			
2	432	16	13.5	1.00
3–5	1,170	46	14.0	1.00 (0.54–1.85)
6–9	680	25	12.8	1.13 (0.58–2.20)
10–13	1,092	49	15.6	1.28 (0.69–2.37)
	Clinical vertebral fracture			
2	507	18	12.8	1.00
3–5	1,375	61	15.7	1.27 (0.71–2.28)
6–9	846	44	17.9	1.53 (0.84–2.78)
10–13	1,336	65	16.9	1.68 (0.95–2.98)
	Any clinical fracture			
2	550	120	85.1	1.00
3–5	1,488	351	89.3	1.08 (0.87–1.34)
6–9	890	222	93.2	1.12 (0.89–1.41)
10–13	1,441	416	110.0	1.36 (1.10–1.68)

Follow-up period is from completion date of medication inventory to end of study in 2013–14. Estimates are from Cox proportional hazards models adjusted for age, race, education level, body mass index, physical function score, general health rating, recreational physical activity, treated diabetes mellitus, severe memory impairment, glucocorticoid use for ≥3 months, risk of hip fracture within 5 years calculated using Women's Health Initiative 11-item fracture risk algorithm, calcium supplement use, estrogen use during the 6–10 years before medication inventory, parental hip fracture, smoking status, Parkinson's disease diagnosis, ≥3 servings per day of alcohol, rheumatoid arthritis diagnosis, and cancer diagnosis, stratified according to history of fracture after age 54.

[a] Number of fractures during all follow-up years.

3 to 5 years increases risk of rare atypical femur fractures, with the rates of atypical fractures increasing from 1.78/100,000 during 2 years of use to 113/100,000 during 8 to 9.9 years of use.[7,43,44] Suppression of bone remodeling for 10 or more years may increase overall risk of fracture in older women with high fracture risk.

Although the analysis adjusted for many participant characteristics associated with fracture, long-term bisphosphonate users may have had other risk factors not accounted for in the current analysis, such as lower BMD at initiation of bisphosphonate treatment. To minimize confounding by unmeasured characteristics such as BMD, the analysis was restricted to bisphosphonate users with a 5-year hip fracture risk of 1.5% or greater using the WHI fracture risk algorithm and adjusted for 5-year hip fracture risk score, which significantly correlates with BMD and fracture risk.[22,25]

Table 5. Fracture Incidence in 5,120 Postmenopausal Women with a 5-Year Risk of Hip Fracture of 1.5% or Greater and Risk of Fracture Associated with 5-Year Increase in Bisphosphonate Use

Bisphosphonate Use (5-Year Increase)	Subjects, n	Fractures		Adjusted Hazard Ratio (95% Confidence Interval)
		N[a]	Incidence per 1,000 Person-Years	
Hip fracture	4,912	127	9.0	1.33 (1.03–1.72)
Wrist or forearm fracture	3,943	159	14.3	1.14 (0.90–1.44)
Clinical vertebral fracture	4,759	235	17.4	1.21 (1.00–1.47)
Any clinical fracture	5,120	1,313	98.0	1.15 (1.07–1.25)

Five years is equivalent to the interquartile range. Follow-up period is from completion date of medication inventory to end of study in 2013–14. Estimates are from Cox proportional hazards models adjusted for age, race, education level, body mass index, physical function score, general health rating, recreational physical activity, treated diabetes mellitus, severe memory impairment, glucocorticoid use for ≥3 months, risk of hip fracture within 5 years calculated using Women's Health Initiative 11-item fracture risk algorithm, calcium supplement use, estrogen use during the 6–10 years before medication inventory, parental hip fracture, smoking status, Parkinson's disease diagnosis, ≥3 servings per day of alcohol, rheumatoid arthritis diagnosis, and cancer diagnosis, stratified according to history of fracture after age 54.

[a] Number of fractures during all follow-up years.

The finding that hip and vertebral fracture risk appeared to be high, whereas wrist or forearm fracture risk was not, also warrants more investigation. The unique etiology of site-specific incident fracture may explain differences according to fracture site. Incident wrist or forearm fracture, for instance, occurs at an earlier age on average than hip or clinical vertebral fracture.[45] The current analysis examined only incident site-specific fracture; before the start of follow-up, a greater percentage of women in this analysis had had an incident wrist or forearm fracture than had had a hip or clinical vertebral fracture. Thus, more women were excluded from the site-specific analysis for wrist or forearm fracture.

There were several additional limitations. Not all fractures were confirmed according to medical record review, although a validity study found good to excellent validity of self-reported fracture in the WHI.[46] Medication use was self-reported, but a validity study of the 2008–09 medication inventory found near-perfect agreement between self-report and pharmacy records for four chronically used medications, including bisphosphonates.[47] The current study lacked information about bisphosphonate persistence during follow-up. Additionally, the findings are not generalizable to comparing long-term use with never initiating bisphosphonates, because the reference group was short-term use.

There are several strengths of this analysis. The large sample included older long-term bisphosphonate users (mean age 80) and women with up to 13 years of use.

Although the study lacked BMD data, the analysis adjusted for 5-year hip fracture risk score, which is correlated with BMD.[22,25] Additionally, the analysis adjusted for many participant characteristics predictive of fracture risk, and characteristics were similar across exposure groups.

CONCLUSIONS

In older women with high fracture risk, 10 to 13 years of bisphosphonate use was associated with higher risk of any clinical fracture than 2 years of use; 3 to 5 and 6 to 9 years of use were not associated with fracture risk. Longer exposure was associated with site-specific fracture risk when bisphosphonate exposure was modeled as a continuous variable but not when it was modeled as a categorical variable. These findings add to concerns about the safety of long-term bisphosphonate use. Confirmatory studies are needed to inform guidelines for the optimal duration of bisphosphonate use.

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REFERENCES

1. Barrett-Connor E, Siris ES, Wehren LE et al. Osteoporosis and fracture risk in women of different ethnic groups. J Bone Miner Res 2005;20:185–194.
2. Becker DJ, Kilgore ML, Morrisey MA. The societal burden of osteoporosis. Curr Rheumatol Rep 2010;12:186–191.
3. 2010 Top 200 Generic Drugs by Total Prescriptions [on-line]. Available at http://drugtopics.modernmedicine.com/drugtopics/data/articlestandard//drugtopics/252011/727243/article.pdf Accessed July 1, 2014.
4. 2010 Top 200 Branded Drugs by Total Prescriptions [on-line]. Available at http://drugtopics.modernmedicine.com/drugtopics/data/articlestandard//drugtopics/252011/727256/article.pdf Accessed July 1, 2014.
5. Fleisch H. Bisphosphonates: Mechanisms of action. Endocr Rev 1998;19:80–100.
6. Rodan GA, Fleisch HA. Bisphosphonates: Mechanisms of action. J Clin Invest 1996;97:2692–2696.
7. Background Document for Meeting of Advisory Committee for Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committee. Division of Reproductive and Urologic Products, Office of New Drugs Division of Pharmacovigilance II, Office of Surveillance and Epidemiology Division of Epidemiology, Office of Surveillance and Epidemiology Center for Drug Evaluation and Research Food and Drug Administration; September 9, 2011.
8. Wells GA, Cranney A, Peterson J et al. Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev 2008; doi: 10.1002/14651858.CD001155.pub2.
9. Whitaker M, Guo J, Kehoe T et al. Bisphosphonates for osteoporosis—Where do we go from here? N Engl J Med 2012;366:2048–2051.
10. Schwartz AV, Bauer DC, Cummings SR et al. Efficacy of continued alendronate for fractures in women with and without prevalent vertebral fracture: The FLEX trial. J Bone Miner Res 2010;25:976–982.
11. Czerwinski E. Atypical subtrochanteric fractures after long-term bisphosphonate therapy. Endokrynol Pol 2011;62(Suppl 2):42–45.
12. Froelich K, Radeloff A, Kohler C et al. Bisphosphonate-induced osteonecrosis of the external ear canal: A retrospective study. Eur Arch Otorhinolaryngol 2011;268:1219–1225.
13. Park-Wyllie LY, Mamdani MM, Juurlink DN et al. Bisphosphonate use and the risk of subtrochanteric or femoral shaft fractures in older women. JAMA 2011;305:783–789.
14. Vescovi P, Nammour S. Bisphosphonate-related osteonecrosis of the jaw (BRONJ) therapy. A critical review. Minerva Stomatol 2010;59:181–203, 204–13.
15. Design of the Women's Health Initiative clinical trial and observational study. The Women's Health Initiative Study Group. Control Clin Trials 1998;19:61–109.

16. Anderson GL, Manson J, Wallace R et al. Implementation of the Women's Health Initiative study design. Ann Epidemiol 2003;13(9 Suppl):S5–S17.
17. Curb JD, McTiernan A, Heckbert SR et al. Outcomes ascertainment and adjudication methods in the Women's Health Initiative. Ann Epidemiol 2003;13(9 Suppl):S122–S128.
18. Rossouw JE, Anderson GL, Prentice RL et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321–333.
19. Adler RA, El-Hajj Fuleihan G, Bauer DC et al. Managing osteoporosis in patients on long-term bisphosphonate treatment: Report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res 2016;31:1910.
20. Cosman F, de Beur SJ, LeBoff MS et al. Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int 2014;25:2359–2381.
21. Kanis JA, McCloskey E, Johansson H et al. FRAX((R)) with and without bone mineral density. Calcif Tissue Int 2012;90:1–13.
22. Robbins J, Aragaki AK, Kooperberg C et al. Factors associated with 5-year risk of hip fracture in postmenopausal women. JAMA 2007;298:2389–2398.
23. Women's Health Initiative Forms. F153 v151 Medication and Supplement Inventory [on-line]. Available at https://www.whi.org/researchers/studydoc/SitePages/Forms.aspx Accessed July 14, 2015.
24. Ware JE Jr, Gandek B. Overview of the SF-36 Health Survey and the International Quality of Life Assessment (IQOLA) Project. J Clin Epidemiol 1998;51:903–912.
25. Chlebowski RT, Chen Z, Cauley JA et al. Oral bisphosphonate use and breast cancer incidence in postmenopausal women. J Clin Oncol 2010;28:3582–3590.
26. Hays RD, Sherbourne CD, Mazel RM. The RAND 36-Item Health Survey 1.0. Health Econ 1993;2:217–227.
27. Wolf AM, Hunter DJ, Colditz GA et al. Reproducibility and validity of a self-administered physical activity questionnaire. Int J Epidemiol 1994;23:991–999.
28. Ainsworth BE, Haskell WL, Whitt MC et al. Compendium of physical activities: An update of activity codes and MET intensities. Med Sci Sports Exerc 2000;32(9 Suppl):S498–S504.
29. Gralow JR, Biermann JS, Farooki A et al. NCCN Task Force Report: Bone health in cancer care. J Natl Compr Canc Netw 2009;7 (Suppl 3):S1–S32; quiz S33–S35.
30. Wang CC, Lu HT, Dusetzina SB et al. The association between long-term bisphosphonate use and the risk of fracture among women aged 50 or older with osteoporosis. J Womens Health 2016;25:738–746.
31. Drieling RL, LaCroix AZ, Beresford SA et al. Long-term oral bisphosphonate use in relation to fracture risk in postmenopausal women with breast cancer: Findings from the Women's Health Initiative. Menopause 2016;23:1168–1175.
32. Meijer WM, Penning-van Beest FJ, Olson M et al. Relationship between duration of compliant bisphosphonate use and the risk of osteoporotic fractures. Curr Med Res Opin 2008;24:3217–3222.
33. Erviti J, Alonso A, Gorricho J et al. Oral bisphosphonates may not decrease hip fracture risk in elderly Spanish women: A nested case-control study. BMJ Open 2013;3:e002084.
34. Mellstrom DD, Sorensen OH, Goemaere S et al. Seven years of treatment with risedronate in women with postmenopausal osteoporosis. Calcif Tissue Int 2004;75:462–468.
35. Pazianas M, Abrahamsen B, Wang Y et al. Incidence of fractures of the femur, including subtrochanteric, up to 8 years since initiation of oral bisphosphonate therapy: A register-based cohort study using the US MarketScan claims databases. Osteoporos Int 2012;23:2873–2884.
36. Abrahamsen B, Eiken P, Prieto-Alhambra D et al. Risk of hip, subtrochanteric, and femoral shaft fractures among mid and long term users of alendronate: Nationwide cohort and nested case-control study. BMJ 2016;353:i3365.
37. Ott SM. Long-term bisphosphonates: Primum non nocere. Menopause 2016;23:1159–1161.
38. Bala Y, Depalle B, Farlay D et al. Bone micromechanical properties are compromised during long-term alendronate therapy independently of mineralization. J Bone Miner Res 2012;27:825–834.
39. Bala Y, Farlay D, Chapurlat RD et al. Modifications of bone material properties in postmenopausal osteoporotic women long-term treated with alendronate. Eur J Endocrinol 2011;165:647–655.
40. Benhamou CL. Effects of osteoporosis medications on bone quality. Joint Bone Spine 2007;74:39–47.
41. Turner CH. Biomechanics of bone: Determinants of skeletal fragility and bone quality. Osteoporos Int 2002;13:97–104.
42. Boskey AL. Bone composition: Relationship to bone fragility and antiosteoporotic drug effects. Bonekey Rep 2013;2:447.
43. Dell RM, Adams AL, Greene DF et al. Incidence of atypical nontraumatic diaphyseal fractures of the femur. J Bone Miner Res 2012;27:2544–2550.
44. Shane E, Burr D, Abrahamsen B et al. Atypical subtrochanteric and diaphyseal femoral fractures: Second report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res 2014;29:1–23.
45. Johnell O, Kanis J. Epidemiology of osteoporotic fractures. Osteoporos Int 2005;16(Suppl 2):S3–S7.
46. Chen Z, Kooperberg C, Pettinger MB et al. Validity of self-report for fractures among a multiethnic cohort of postmenopausal women: Results from the Women's Health Initiative observational study and clinical trials. Menopause 2004;11:264–274.
47. Drieling R, LaCroix A, Beresford S et al. Validity of self-reported medication use compared with pharmacy records in a cohort of older Women: Findings from the Women's Health Initiative. Am J Epidemiol 2016;184:233–8.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Characteristics of 97,448 postmenopausal women categorized by bisphosphonate use at 2008–09 medication inventory and by 5-year hip fracture risk.

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