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

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Abstract

BACKGROUND/OBJECTIVES—A Food and Drug Administration review found inconclusive evidence that long-term bisphosphonate therapy prevents fractures and called for research among high-risk subgroups. This study examines the association of long-term bisphosphonate use with fracture among older women with high fracture risk.

DESIGN—Retrospective cohort.

SETTING—Women's Health Initiative.

PARTICIPANTS—Older women who reported at least two years of bisphosphonate use in 2008–9 (n=5,120).

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

RESULTS—On average participants were 80 years old and followed for 3.7 (SD: 1.2) years. There were 127 hip, 159 wrist/forearm, 235 clinical vertebral, and 1,313 clinical fractures. In

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multivariate-adjusted analysis, 10–13 years of bisphosphonate use, compared with two years of use, was associated with higher risk of any clinical fracture (HR: 1.29 [95% 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 10–13 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 [0.99–2.76]), or wrist fracture (HR: 1.16 [0.67–2.00]).

CONCLUSIONS—Among older women with high fracture risk, 10–13 years of bisphosphonate use was associated with higher risk of any clinical fracture compared with two years of use. These results add to concerns about the benefit of very long-term bisphosphonate use.

Keywords

Long-term bisphosphonate use; fracture; pharmacoepidemiology

INTRODUCTION

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] However, recent studies question 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 one to four years of therapy may prevent non-vertebral fracture in women with low BMD (T-score < −2.5 SD) or a vertebral fracture prior to treatment, but probably does not prevent fractures among 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) Trial,[10] found inconclusive evidence that bisphosphonate therapy beyond three to five 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 patients be routinely evaluated for the appropriateness of continued therapy during long-term use.[8,11–14] However, 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 over the age of 70 years who used bisphosphonates beyond five years and lacked data on use beyond 11 years.[7] Thus, the FDA has called for more research on long-term bisphosphonate use in subgroups.[7]

In 2008–9, over 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 examine long-term bisphosphonate therapy, compared with short-

term use, in relationship to fracture using data from the WHI, among older women with high fracture risk.

METHODS

Study Population

The WHI is a large, longitudinal study of women's health begun in 1993 with primary aims to develop strategies that 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 2008–9, 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 two years or more at the 2008–9 medication inventory, had follow-up data thereafter, and had a 5-year hip fracture risk of 1.5% or greater, we analyzed the association of longer duration of use (3–5, 6–9, 10–13 years) with incident site-specific fracture (hip, wrist/forearm, and clinical vertebral) and with any clinical fracture, using shorter duration of use (2 years) as the referent group. We limited the study to women who reported at least two years of bisphosphonate use to include women with persistent medication use. We chose two years as the referent group because this duration of use has been associated with lower fracture risk.[7] Guidelines recommend bisphosphonates as the preferred treatment for women with a high fracture risk (10-year hip fracture risk ≥ 3%) based on the Fracture Risk Assessment Tool (FRAX) score.[19–21] To select a high-risk study sample, we identified women with a predicted 5-year risk of hip fracture of 1.5% or greater, which is comparable to the FRAX definition of high fracture risk, 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 years, parental hip fracture, smoking, corticosteroid use, race/ethnicity, self-reported health, self-reported physical activity, and treated diabetes).[22] To reduce confounding from other medications that affect bone metabolism, we excluded 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 five years before the 2008–9 medication inventory (n=260). Further, we excluded women who discontinued and resumed bisphosphonate use prior to the medication inventory (n=1,000). After exclusions, there were 5,120 women included in the present analysis.

Exposure Ascertainment

Women self-reported duration of bisphosphonate use on the mailed 2008–9 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, etc.), and provided the duration of use (< 1 month, 1–12 months, and 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 shots 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 among participants, the predicted risk of hip fracture within five 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 among 10,418 WHI participants for whom both measures were available.[25] Body mass index (BMI [kg/m^2]) was collected at clinical exams at years 0, 3, 6, and 9 for RCT participants and at years 0 and 3 for observational study participants. History of other medications was collected at years 0, 3, 6, and 9 for RCT participants and at years 0, 3, and 4–8 for observational participants. Cancer diagnosis was self-reported and then, confirmed by medical record review.[17] Physical function score was calculated from the RAND 36-Item Health Survey, with higher numbers indicating better physical function.[26] Recreational physical activity was assessed by 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 2008–9 medication inventory.

Outcome Ascertainment

Outcomes of interest for this analysis were incident hip, clinical vertebral, and wrist/forearm fracture, and incident clinical fracture at any site. Outcomes were ascertained by self-report on annual forms, which asked women to report the first lifetime occurrence for site-specific fractures.[17] The specific date of hip and femur fractures was collected by self-report for all participants throughout follow-up and, also adjudicated by medical record review for all participants through 2010, and 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—We described the 5,120 bisphosphonate users included in the fracture analysis grouped by duration of use (2, 3–5, 6–9, and 10–13 years) and compared groups using ANOVA and the chi-square test.

Statistical Analysis of Fracture Incidence—Participants contributed follow-up time from the date of the 2008–9 medication inventory until the occurrence of fracture, death, loss-to-follow-up, or end of study follow-up in 2013–14.[12] We presented the fracture incidence per 1,000 person-years 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 3–5, 6–9, and 10–13 years of bisphosphonate use with two years of use (reference group). There was one model for each site-specific fracture type (hip, wrist/forearm, and 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 prior to the start of follow-up (n=271 for hip, n=1,177 for wrist/forearm, and n=361 for clinical vertebral fracture). The models were adjusted *a priori* for age (years), 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 6–10 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 by a history of fracture after age 54 years. Subjects with missing covariate data were excluded from multivariate models (n=150; 2.9% of subjects). All statistical tests were two-tailed (α=0.05) and performed in Stata version 13.

Additional Analyses—To create a more homogeneous study sample, we performed a sensitivity analysis limited to women with a history of fracture after age 54 (n=2,779). Because some cancers and cancer treatments increase fracture risk,[29] we conducted a sensitivity analyses limited to women with no history of cancer before the medication inventory (n=4,369). To examine the association of each additional year of bisphosphonate use with fracture, we modeled bisphosphonate use as a continuous variable (years of use) and presented the results 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 in the primary analysis and were stratified by 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 2008–9 medication inventory form are described in Supplementary Table S1. Among the 5,120 women in the analysis, 642 (13%) had used bisphosphonates for two years, 1,746 (34%) for 3–5 years (average 4.1 years [SD: 0.9]), 1,031 (20%) for 6–9 years (average 7.3 years [SD: 1.0]), and 1,701 (33%) for 10–13 years (average 11.1 years [SD: 1.4]; Table 1). For all groups, the average age was approximately 80 years and 97% were over 70 years of age. Having a college degree or higher educational attainment was more common and estrogen use within the 6–10 years before the 2008–9 medication inventory was least common among women with longer duration of bisphosphonate use. Among women with 6–9 or 10–13 years of bisphosphonate use, on average, BMI was lower and diabetes was less common, and physical function score, recreational physical activity, and general health were higher than among women with 2 or 3–5 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 (SD: 1.2) years. During follow-up, there were 127 hip fractures, 159 wrist/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 10–13 years of bisphosphonate use group for all fracture outcome types except for clinical vertebral fracture. Women with two years of bisphosphonate use had the lowest unadjusted fracture rate for all fracture outcome types except for wrist/forearm fracture.

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

In sensitivity analyses limited to women with a history of fracture after age 54 and limited to women with no history of cancer, 10–13 years of bisphosphonate use remained associated with higher risk of any clinical fracture (HR: 1.30 [95% CI: 1.01–1.67]; Table 3 and HR: 1.36 [95% CI: 1.10–1.68]; Table 4). In the additional analysis that modeled bisphosphonate exposure as a continuous variable, a 5-year increase in bisphosphonate use was associated with a 15% higher risk of any clinical fracture (95% CI: 1.07–1.25), a 33% higher risk of hip fracture (95% CI: 1.03–1.72), and a 21% higher risk of clinical vertebral fracture (95% CI: 1.00–1.47).

DISCUSSION

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

Our findings support previous studies that found no significant benefit for overall fracture risk during long-term bisphosphonate use, compared with shorter duration of use.[7,10,30–35] The 2011 FDA review of long-term bisphosphonate RCTs found similar fracture rates during short-term and long-term bisphosphonate use among women over age 70.[7] Post-hoc FLEX Trial analysis found a benefit for clinical vertebral fractures, but no benefit for non-vertebral fractures during 10 years of alendronate use, compared with discontinuing after 5

years.[10] An RCT of risedronate found no association between 6–7 years of bisphosphonate use and fracture risk, compared with 1–2 years of use.[34] Wang et al found no benefit for overall fracture risk comparing up to eight years of use with less than five years of exposure.[30]

Observational study findings are mixed for the association of hip fracture with long-term bisphosphonate use, compared with shorter exposure.[33,35,36] Our study and studies by Erviti and Pazianas found no hip fracture benefit with longer bisphosphonate exposure while a study by Abrahamsen found a benefit for 10 or more years of use.[33,35,36] The inclusion of patients who had not used bisphosphonates long enough to achieve benefit may explain Abrahamsen's findings. These studies required only one bisphosphonate prescription for study inclusion.[33,35,36] However, Pazianas additionally excluded patients with a femoral fracture within three months of the initial prescription and Erviti used a test for trend to examine longer exposure.[33,35] Participants in the Abrahamsen study with less than one year of exposure had the highest fracture incidence, but when Abrahamsen switched the referent group to three to less than five exposure years, 10 or more years of exposure was not beneficial.[36] Our study selected participants who had used bisphosphonates long enough to achieve benefit by specifically requiring two years of bisphosphonate use.

The contrast between our findings and the FLEX Trial finding of benefit for clinical vertebral fracture risk also deserves consideration.[10] Bisphosphonate efficacy may differ in the population we examined compared with the FLEX Trial 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 for 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 our findings including over-suppression of the bone remodeling process that 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 3–5 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 among older women with high fracture risk.

Although our analysis adjusted for many participant characteristics associated with fracture, long-term bisphosphonate users may have had other risk factors not accounted for in our analysis, such as lower BMD at initiation of bisphosphonate treatment. However, to minimize confounding by unmeasured characteristics such as BMD, we restricted our analysis 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]

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

There were several additional limitations. Not all fractures were confirmed by medical record review. However, 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 2008–9 medication inventory found near perfect agreement of self-report with pharmacy records for four chronically used medications, including bisphosphonates.[47] Our study lacked information about bisphosphonate persistence during the follow-up. Additionally, our findings are not generalizable to comparing long-term use with never initiating bisphosphonates, because our referent group was short-term use.

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

Among older women with high fracture risk, 10–13 years of bisphosphonate use was associated with higher risk of any clinical fracture compared with two years of use; while 3–5 and 6–9 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Conflict of Interest

AZL serves on Scientific Advisory Boards for Amgen and Sermonix, and served as a one-time consultant for Pfizer in the past 12 months. RTC is a consultant for Novartis, Amgen, Genentech, and Novo Nordisk and RTC serves on the speakers Bureau for Novartis and Genentech. All other authors state they have no conflicts of interest.

Author Contributions

Conception or design, acquisition of data, and data analysis: AZL, DMB, MGK, RLD, SAAB, and SRH. Drafted manuscript: RLD. Supervision: AZL, DMB, SAAB. Administrative, technical, or material support: RTC. Critical manuscript revision of manuscript for important intellectual content and interpretation of data: All authors.

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The grants R25CA092408 and 2T32HL007034-41 had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. The WHI Program had no role in the design and conduct of the study; analysis and interpretation of the data, the preparation of the manuscript, or the decision to submit the manuscript for publication. The WHI program had a role in data collection and management. Review and approval of the manuscript was carried out by committees composed of WHI investigators and NHLBI representatives.

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Table 1

Characteristics of 5,120 post-menopausal women with ≥ 1.5% 5-year hip fracture risk categorized by duration of bisphosphonate use at 2008–9 medication inventory

	Years of Bisphosphonate Use at 2008–9 Medication Inventory								
	2 Y (n=642)		3–5 Y (n=1,746)		6–9 Y (n=1,031)		10–13 Y (n=1,701)		
Characteristic	**No. % or Mean ± SD**								**P-Value**
Bisphosphonate use (y)	2.0 ± 0		4.1 ± 0.9		7.3 ± 1.0		11.1 ± 1.4		
Age (y)	79.6 ± 5.1		79.6 ± 5.0		79.4 ± 5.0		79.9± 4.9		0.09
Age > 70 y	617	96.1	1,686	96.6	997	96.7	1,664	97.8	0.07
White race	596	92.8	1,638	93.8	983	95.3	1,609	94.6	0.15
Education									0.01
< High school diploma/GED	24	3.7	51	2.9	21	2.0	36	2.1	
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 or higher	265	41.3	762	43.6	488	47.3	838	49.3	
Prior fracture after age 54 y	344	53.6	947	54.2	542	52.6	946	55.6	0.46
Parental hip fracture	104	16.2	312	17.9	211	20.5	330	19.4	0.13
Rheumatoid arthritis diagnosis	54	8.4	141	8.1	84	8.1	129	7.6	0.90
Glucocorticoid use ≥ 3 months	28	4.4	73	4.2	52	5.0	73	4.3	0.74
Alcohol ≥ 3 servings/day	21	3.3	45	2.6	30	2.9	46	2.7	0.82
Current smoker	32	5.0	83	4.8	45	4.4	61	3.6	0.29
Hip fracture risk score[a]	23.1 ± 2.9		23.1 ± 2.8		23.0 ± 2.9		23.3 ± 2.9		0.06
BMI (kg/m^2)	26.7 ± 4.8		26.1 ± 5.0		25.3 ± 4.5		25.2 ± 4.5		<0.001
Physical function score	67.4 ± 26.2		70 ± 25.2		72.6 ± 23.7		71.8 ± 23.8		<0.001

	Years of Bisphosphonate Use at 2008–9 Medication Inventory								
	2 Y (n=642)		3–5 Y (n=1,746)		6–9 Y (n=1,031)		10–13 Y (n=1,701)		
Characteristic	**No. % or Mean ± SD**								**P-Value**
Recreational physical activity[b]	12.0 ± 13.6		12.6 ± 12.3		14.0 ± 13.8		13.5 ± 13.2		0.003
General health rating									0.002
Fair or poor	851	13.2	188	10.8	89	8.6	144	8.5	
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	73	11.4	163	9.3	83	8.1	132	7.8	0.03
Severe memory impairment	16	2.5	53	3.0	16	1.6	36	2.1	0.08
Estrogen used 6–10 y before	324	50.5	874	50.1	510	49.5	757	44.5	0.003
Current calcium supplement use	587	91.4	1,638	93.8	957	92.8	1,585	93.2	0.32
Cancer diagnosis	92	14.3	258	14.8	141	13.7	260	15.3	0.71
Parkinson’s disease diagnosis	4	0.6	18	1.0	11	1.1	16	0.9	0.80

Abbreviations: BMI, body mass index; GED, General Education Development; SD, standard deviation.

[a]Risk score for hip fracture within 5 years calculated from an 11-item algorithm where a score of 23 equals a risk probability of 3.5%;

[b]Recreational physical activity was categorized in metabolic equivalent-hours per week.

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Table 2

Among 5,120 postmenopausal women with a 5-year risk of hip fracture ≥ 1.5%, fracture incidence, hazard ratio, and 95% confidence interval of hip, clinical vertebral, wrist/forearm, and any clinical fracture by duration of bisphosphonate use at 2008–9 medication inventory

		Fractures		
Duration of Bisphosphonate Use	**Subjects (No.)**	**No.[a]**	**Incidence per 1,000 Person-years**	**Adjusted HR (95% CI)[b]**
		Hip Fracture		
2 y	607	11	6.5	1.00
3–5 y	1,607	38	8.0	1.12 (0.53–2.34)
6–9 y	987	20	7.0	1.26 (0.56–2.81)
10–13 y	1,648	58	12.2	1.66 (0.81–3.40)
		Wrist/Forearm Fracture		
2 y	502	20	14.5	1.00
3–5 y	1,374	53	13.9	0.96 (0.55–1.66)
6–9 y	787	29	12.8	0.96 (0.53–1.75)
10–13 y	1,280	57	15.6	1.16 (0.67–2.00)
		Clinical Vertebral Fracture		
2 y	590	21	12.8	1.00
3–5 y	1,621	77	17.0	1.23 (0.73–2.06)
6–9 y	977	53	18.8	1.37 (0.80–2.37)
10–13 y	1,571	84	18.7	1.65 (0.99–2.76)
		Any Clinical Fracture		
2 y	642	141	86.1	1.00
3–5 y	1,746	419	92.1	1.04 (0.85–1.26)
6–9 y	1,031	254	92.2	1.04 (0.84–1.29)
10–13 y	1,701	499	112.2	1.29 (1.07–1.57)

Abbreviations: CI, confidence interval; HR, hazard ratio.

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

[b] 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, BMI, physical function score, general health rating, recreational physical activity, treated diabetes mellitus, severe memory impairment, glucocorticoid use ≥ 3 months, risk of hip fracture within 5 years calculated by WHI 11-item fracture risk algorithm, calcium supplement use, estrogen use during 6–10 years prior to medication inventory, parental hip fracture, smoking status, Parkinson's disease diagnosis, alcohol ≥ 3 servings/day, rheumatoid arthritis diagnosis, and cancer diagnosis and stratified by history of fracture after age 54.

Table 3

Among 2,779 postmenopausal women with a history of fracture after age 54 before the 2008–9 medication inventory and a 5-year risk of hip fracture ≥ 1.5%, fracture incidence, hazard ratio, and 95% confidence interval of hip, clinical vertebral, wrist/forearm, and any clinical fracture by duration of bisphosphonate use at 2008–9 medication inventory

		Fractures		
Duration of Bisphosphonate Use	**Subjects (No.)**	**No.[a]**	**Incidence per 1,000 Person-years**	**Adjusted HR (95% CI)[b]**
		Hip Fracture		
2 y	309	8	9.2	1.00
3–5 y	871	23	9.4	0.65 (0.27–1.54)
6–9 y	498	11	7.5	0.64 (0.24–1.67)
10–13 y	893	32	12.4	0.88 (0.39–2.03)
		Wrist/Forearm Fracture		
2 y	213	14	23.6	1.00
3–5 y	624	26	15.5	0.72 (0.35–1.49)
6–9 y	341	14	14.2	0.72 (0.33–1.60)
10–13 y	575	32	19.6	0.99 (0.49–1.98)
		Clinical Vertebral Fracture		
2 y	292	13	16.0	1.00
3–5 y	822	50	22.1	1.22 (0.62–2.41)
6–9 y	488	35	24.9	1.62 (0.81–3.24)
10–13 y	816	47	20.3	1.47 (0.75–2.87)
		Any Clinical Fracture		
2 y	344	84	96.1	1.00
3–5 y	947	256	106.8	1.10 (0.85–1.43)
6–9 y	542	155	108.3	1.12 (0.85–1.47)
10–13 y	946	300	122.4	1.30 (1.01–1.67)

Abbreviations: CI, confidence interval; HR, hazard ratio.

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

[b] 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, BMI, physical function score, general health rating, recreational physical activity, treated diabetes mellitus, severe memory impairment, glucocorticoid use ≥ 3 months, risk of hip fracture within 5 years calculated by WHI 11-item fracture risk algorithm, calcium supplement use, estrogen use during 6–10 years prior to medication inventory, parental hip fracture, smoking status, Parkinson's disease diagnosis, alcohol ≥ 3 servings/day, rheumatoid arthritis diagnosis, and cancer diagnosis.

Table 4

Among 4,369 postmenopausal women with no history of cancer and a 5-year risk of hip fracture ≥ 1.5%, fracture incidence, hazard ratio, and 95% confidence interval of hip, clinical vertebral, wrist/forearm, and any clinical fracture by duration of bisphosphonate use at 2008–9 medication inventory

		Fractures		
Duration of Bisphosphonate Use	**Subjects (No.)**	**No.[a]**	**Incidence per 1,000 Person-years**	**Adjusted HR (95% CI)[b]**
		Hip Fracture		
2 y	519	9	6.2	1.00
3–5 y	1,424	30	7.4	1.26 (0.54–2.92)
6–9 y	850	19	7.7	1.60 (0.66–3.90)
10–13 y	1,398	50	12.3	2.06 (0.93–4.58)
		Wrist/Forearm Fracture		
2 y	432	16	13.5	1.00
3–5 y	1,170	46	14.0	1.00 (0.54–1.85)
6–9 y	680	25	12.8	1.13 (0.58–2.20)
10–13 y	1,092	49	15.6	1.28 (0.69–2.37)
		Clinical Vertebral Fracture		
2 y	507	18	12.8	1.00
3–5 y	1,375	61	15.7	1.27 (0.71–2.28)
6–9 y	846	44	17.9	1.53 (0.84–2.78)
10–13 y	1,336	65	16.9	1.68 (0.95–2.98)
		Any Clinical Fracture		
2 y	550	120	85.1	1.00
3–5 y	1,488	351	89.3	1.08 (0.87–1.34)
6–9 y	890	222	93.2	1.12 (0.89–1.41)
10–13 y	1,441	416	110.0	1.36 (1.10–1.68)

Abbreviations: CI, confidence interval; HR, hazard ratio.

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

[b] 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, BMI, physical function score, general health rating, recreational physical activity, treated diabetes mellitus, severe memory impairment, glucocorticoid use ≥ 3 months, risk of hip fracture within 5 years calculated by WHI 11-item fracture risk algorithm, calcium supplement use, estrogen use during 6–10 years prior to medication inventory, parental hip fracture, smoking status, Parkinson's disease diagnosis, alcohol ≥ 3 servings/day, and rheumatoid arthritis diagnosis and stratified by history of fracture after age 54.

Table 5

Among 5,120 postmenopausal women with a 5-year risk of hip fracture ≥ 1.5%, fracture incidence, hazard ratio, and 95% confidence interval of hip, clinical vertebral, wrist/forearm, and any clinical fracture associated with a 5-year increase in bisphosphonate use[a]

		Fractures		
Exposure	**Subjects (No.)**	**No.[b]**	**Incidence per 1,000 Person-years**	**Adjusted HR (95% CI)[c]**
		Hip Fracture		
Bisphosphonate use (5 year increase)	4,912	127	9.0	1.33 (1.03–1.72)
		Wrist/Forearm Fracture		
Bisphosphonate use (5 year increase)	3,943	159	14.3	1.14 (0.90–1.44)
		Clinical Vertebral Fracture		
Bisphosphonate use (5 year increase)	4,759	235	17.4	1.21 (1.00–1.47)
		Any Clinical Fracture		
Bisphosphonate use (5 year increase)	5,120	1,313	98.0	1.15 (1.07–1.25)

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] 5 years is equivalent to the interquartile range;

[b] Number of fractures during all follow-up years;

[c] 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, BMI, physical function score, general health rating, recreational physical activity, treated diabetes mellitus, severe memory impairment, glucocorticoid use ≥ 3 months, risk of hip fracture within 5 years calculated by WHI 11-item fracture risk algorithm, calcium supplement use, estrogen use during 6–10 years prior to medication inventory, parental hip fracture, smoking status, Parkinson's disease diagnosis, alcohol ≥ 3 servings/day, and rheumatoid arthritis diagnosis and stratified by history of fracture after age 54.