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Authors
Black, Dennis M
Geiger, Erik J
Eastell, Richard
et al.

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Atypical Femur Fracture Risk versus Fragility Fracture Prevention with Bisphosphonates

Dennis M. Black, Ph.D.,

Erik J. Geiger, M.D.,

Richard Eastell, M.D.,

Eric Vittinghoff, Ph.D.,

Bonnie H. Li, M.S.,

Denison S. Ryan, M.P.H.,

Richard M. Dell, M.D.,

Annette L. Adams, Ph.D.

Departments of Epidemiology and Biostatistics (D.M.B., E.V.) and Orthopedic Surgery (E.J.G.), University of California, San Francisco, San Francisco, the Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena (D.M.B., B.H.L., D.S.R., A.L.A.), and the Department of Orthopedics, Kaiser Permanente Southern California, Downey (R.M.D.) — all in California; and the Department of Oncology and Metabolism, University of Sheffield, Sheffield, United Kingdom (R.E.).

Abstract

BACKGROUND—Bisphosphonates are effective in reducing hip and osteoporotic fractures. However, concerns about atypical femur fractures have contributed to substantially decreased bisphosphonate use, and the incidence of hip fractures may be increasing. Important uncertainties remain regarding the association between atypical femur fractures and bisphosphonates and other risk factors.

METHODS—We studied women 50 years of age or older who were receiving bisphosphonates and who were enrolled in the Kaiser Permanente Southern California health care system; women were followed from January 1, 2007, to November 30, 2017. The primary outcome was atypical femur fracture. Data on risk factors, including bisphosphonate use, were obtained from electronic health records. Fractures were radiographically adjudicated. Multivariable Cox models were used. The risk–benefit profile was modeled for 1 to 10 years of bisphosphonate use to compare associated atypical fractures with other fractures prevented.

RESULTS—Among 196,129 women, 277 atypical femur fractures occurred. After multivariable adjustment, the risk of atypical fracture increased with longer duration of bisphosphonate use: the hazard ratio as compared with less than 3 months increased from 8.86 (95% confidence interval

Address reprint requests to Dr. Black at the Department of Epidemiology and Biostatistics, University of California, San Francisco, 550 16th St., Box 0560, San Francisco, CA 94143, or at dennis.black@ucsf.edu.

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[CI], 2.79 to 28.20) for 3 years to less than 5 years to 43.51 (95% CI, 13.70 to 138.15) for 8 years or more. Other risk factors included race (hazard ratio for Asians vs. Whites, 4.84; 95% CI, 3.57 to 6.56), height, weight, and glucocorticoid use. Bisphosphonate discontinuation was associated with a rapid decrease in the risk of atypical fracture. Decreases in the risk of osteoporotic and hip fractures during 1 to 10 years of bisphosphonate use far outweighed the increased risk of atypical fracture among Whites but less so among Asians. After 3 years, 149 hip fractures were prevented and 2 bisphosphonate-associated atypical fractures occurred in Whites, as compared with 91 and 8, respectively, in Asians.

CONCLUSIONS—The risk of atypical femur fracture increased with longer duration of bisphosphonate use and rapidly decreased after bisphosphonate discontinuation. Asians had a higher risk than Whites. The absolute risk of atypical femur fracture remained very low as compared with reductions in the risk of hip and other fractures with bisphosphonate treatment. (Funded by Kaiser Permanente and others.)

Osteoporosis, A Bone Disease Characterized by bone loss and microarchitectural deterioration, is one of the most disabling consequences of aging. As the population ages, the incidence and associated costs of osteoporotic fractures will rise dramatically.[1,2] These fractures lead to substantial disability and many deaths, so the identification and treatment of the persons at highest risk are important to prevent fractures and their consequences.

Since their introduction in the 1990s, bisphosphonates have been the mainstay of osteoporosis treatment.[3] Bisphosphonates inhibit osteoclast-mediated resorption and remodeling of bone. Many large, randomized, controlled trials have established the efficacy of bisphosphonates, showing their ability to increase bone mineral density and decrease the risk of hip and vertebral fractures by as much as 40 to 70%.[4,5]

Case reports of unusual fragility fractures in the subtrochanteric region and along the femoral diaphysis in bisphosphonate-treated patients first appeared approximately 15 years ago,[6,7] followed by larger studies of these fractures (now known as atypical femur fractures) (Fig. S1 in the Supplementary Appendix, available with full text of this article at NEJM.org) and their relation to bisphosphonates.[8] Concerns and publicity about atypical fractures have led to substantial declines in bisphosphonate use, despite their established efficacy and favorable risk–benefit profile.[9,10] However, substantial uncertainty and controversy remain regarding the magnitude of the association between bisphosphonates and atypical femur fractures.[11,12] Some studies have shown minimal risk,[13] whereas others have indicated a clear association, particularly with prolonged use.[14,15]

By analyzing a large, prospective cohort of women through direct radiographic adjudication and rigorous multivariate methods, the present study addresses several key gaps in the evidence[8,12] regarding atypical femur fractures, including their relation to bisphosphonate use, race or ethnic group, and other risk factors. We hypothesized that the risk of atypical fracture would be related to the duration of bisphosphonate use but would be attenuated after adjustment for multiple clinical variables.

METHODS

STUDY DESIGN

This study was conducted within Kaiser Permanente Southern California, an integrated health care system with more than 4.6 million racially, ethnically, and socioeconomically diverse members broadly representative of the Southern California population.[16] Eligible cohort members were women 50 years of age or older followed from January 1, 2007, to November 30, 2017, with at least 12 months of continuous enrollment before cohort entry (with gaps of ≤92 days allowed). The date of cohort entry was either January 1, 2007, or later, once entry criteria were met. The present analysis was limited to women who had received at least one prescription for oral or intravenous bisphosphonate for osteoporosis.

OUTCOMES

The primary outcome was atypical femur fracture. Potential cases of atypical fracture were selected with the use of International Classification of Diseases (ICD) diagnosis codes (Table S1) for subtrochanteric femoral-shaft fractures, excluding cases with ICD E-codes (which describe the cause of injury) for high-energy trauma within 3 days before or after the date of fracture. Radiographic images were independently adjudicated by two reviewers (who were unaware of the type or duration of bisphosphonate treatment and clinical risk factors) using the 2014 American Society for Bone and Mineral Research case definition of atypical femur fracture.[8] Reviewers discussed adjudication discrepancies until consensus was reached. Hip fractures, identified with the use of ICD codes, were secondary outcomes (Table S1).

BISPHOSPHONATE USE AND OTHER RISK FACTORS

Data on potential risk factors that were gathered from electronic health records included age, patient-reported race or ethnic group, glucocorticoid use, height, weight, and smoking status. Previous fracture was identified by means of ICD and Current Procedural Terminology codes. We calculated all covariable values at the time of cohort entry, looking cumulatively back to membership initiation; all values (except for race or ethnic group and height) were updated annually after entry. The cumulative duration of bisphosphonate treatment and the time since last treatment were determined from pharmacy records, and cumulative exposure was calculated and updated annually. Measurements of bone mineral density that were performed by means of dual-energy x-ray absorptiometry (restricted to within 2 years before or after treatment initiation) were available in a subgroup of 102,467 women of the 196,129 who had received bisphosphonates.

STATISTICAL ANALYSIS

Follow-up time was divided into 1-year intervals. Fracture incidence rates were calculated per 10,000 person-years and tabulated according to age, race or ethnic group, duration of bisphosphonate use, and time since bisphosphonate discontinuation.

Cox proportional-hazards models were used to estimate univariate hazard ratios and 95% confidence intervals for the association between each potential risk factor and atypical femur fractures. Multivariable Cox models that included all risk factors with a P value of less than

0.2 in unadjusted models were used to compare categories of duration of bisphosphonate use (reference, <3 months). Secondary multivariate modeling that also included bone mineral density was performed in the subgroup of women with data on pretreatment bone mineral density (measured within 2 years before treatment initiation). A sensitivity analysis was performed in the entire cohort (1,097,530 women) not limited to the 196,129 women who had ever used bisphosphonates.

To compare the risks and benefits of bisphosphonates with respect to fracture risk, we modeled the number of associated atypical fractures as compared with other fractures prevented according to varying years of bisphosphonate treatment in a hypothetical cohort of 10,000 women. Calculations were performed within three groups with respect to race or ethnic group (Whites, Asians, and Hispanics). Black women had only two atypical femur fractures and were not included in this calculation. Methods are summarized here, with additional details in the Supplementary Appendix (Methods section and Table S2).

To estimate the number of atypical femur fractures associated with various durations of current bisphosphonate use, we used a Poisson model with each woman contributing records for each follow-up year. Then, with the use of the Poisson model coefficients, adjusted incidence rates of atypical fractures were calculated for women who had never used bisphosphonates and current users with 1 to 10 cumulative years of bisphosphonate use. In a final step, the cumulative risk difference between a current user and a woman who had never used bisphosphonates was rescaled to estimate the number of bisphosphonate-associated cases in a population of 10,000 women.

The numbers of hip and all clinical fractures (nonvertebral plus clinical vertebral) prevented were calculated by estimating the cumulative incidence of each in an untreated cohort from the Study of Osteoporotic Fractures, a cohort of 9704 White women studied before the introduction of bisphosphonates.[17,18] This analysis was limited to women 65 years of age or older who did not use hormone-replacement therapy and who had a bone mineral density T score of less than −2.5 at the total hip or a history of hip or vertebral fracture. The annual rates among untreated women were then adjusted for Asians and Hispanics with the use of national U.S. data.[19–22] The rates among treated women were then estimated by applying data on the reduction in the risk of fractures with alendronate from a recent meta-analysis (see the Methods section in the Supplementary Appendix).[5] The difference between the annual rates (treated minus untreated women) was rescaled to 10,000 to give cumulative fracture numbers prevented for each year.

RESULTS

PATIENT CHARACTERISTICS

The total cohort included 1,097,530 women, and the analytic cohort included 196,129 women (17.9%) who used bisphosphonates at any point during the study period. The characteristics of the women in the analytic cohort are shown in Table 1 and Table S3. The distribution with respect to race or ethnic group was as follows: White, 53.3%; Hispanic, 24.0%; Asian, 13.5%; Black, 5.9%; and other or unknown, 3.3%. A total of 59.5% of the women were 65 years of age or older, 16.1% had a maximum cumulative bisphosphonate

exposure of less than 3 months, and 21.9% had a maximum cumulative bisphosphonate exposure of 5 years or more.

INCIDENCE OF ATYPICAL FEMUR FRACTURES AND HIP FRACTURES

Among the 196,129 women, 277 atypical femur fractures occurred (1.74 fractures per 10,000 patient-years) (Table 2, Fig. 1, and Fig. S2), and 9102 hip fractures occurred (58.90 fractures per 10,000 person-years) (Table S4). Women 65 to 74 years of age and 75 to 84 years of age had higher rates of atypical fracture (2.24 and 2.35 per 10,000 person-years, respectively) than those 50 to 64 years of age and those 85 years of age or older (0.83 and 0.99 per 10,000 person-years, respectively) (Table 2), whereas the incidence of hip fractures increased with increasing age. Asian women had higher rates of atypical fracture than White women (5.95 vs. 1.09 per 10,000 person-years) but lower rates of hip fracture (20.41 vs. 81.18 per 10,000 person-years). The incidence of atypical fractures increased as duration of bisphosphonate use increased, from 0.07 per 10,000 person-years among women with less than 3 months of bisphosphonate use to 13.10 per 10,000 person-years among those with 8 years or more of use (Table 2). Rates of atypical fractures decreased with time since bisphosphonate discontinuation (4.50 per 10,000 person-years among current users [including ≤3 months since discontinuation], 1.81 per 10,000 person-years at >3 months to 15 months since discontinuation, and approximately 0.50 per 10,000 person-years at >15 months after discontinuation). Among the women who had never received bisphosphonates (approximately 0.9 million), an additional 29 atypical fractures were identified (0.10 per 10,000 person-years).

RISK FACTORS FOR ATYPICAL FEMUR FRACTURES

Unadjusted and multivariate-adjusted relationships of bisphosphonate use to atypical femur fracture are shown in Table 3. For duration of bisphosphonate use, the unadjusted hazard ratios as compared with less than 3 months ranged from 33.76 (95% confidence interval [CI], 12.07 to 94.48) for 3 years to less than 5 years to 179.51 (95% CI, 64.64 to 498.52) for 8 years or more. After adjustment, the hazard ratios were attenuated but remained significant (the confidence intervals did not include 1.0) beyond 3 years of bisphosphonate use, increasing from 8.86 (95% CI, 2.79 to 28.20) for 3 years to less than 5 years to 43.51 (95% CI, 13.70 to 138.15) for 8 years or more (Table 3). The adjusted hazard ratios were significant for race (hazard ratio for Asian vs. White, 4.84; 95% CI, 3.57 to 6.56), decreasing height (hazard ratio per 5-cm decrement, 1.28; 95% CI, 1.15 to 1.43), increasing weight (hazard ratio per 5-kg increment, 1.15; 95% CI, 1.11 to 1.19), age (hazard ratio for 65 to 74 years vs. >85 years, 2.76; 95% CI, 1.62 to 4.72), and glucocorticoid use for 1 year or more (hazard ratio vs. no glucocorticoid use, 2.28; 95% CI, 1.52 to 3.43). Time since bisphosphonate discontinuation was associated with a 48% reduction in the risk of atypical femur fracture at more than 3 months to 15 months (hazard ratio vs. ≤3 months, 0.52; 95% CI, 0.37 to 0.72) and an approximately 74 to 79% reduction in risk in subsequent years (Table 3 and Fig. S3).

The sensitivity multivariate analysis in the entire cohort showed similar results to the primary analysis (Table S5). In multivariate analysis of the subgroup with data on pretreatment bone mineral density at the total hip (102,467 women [52.2%]), bone mineral

density was not significantly associated with the risk of atypical femur fracture, and results for other variables did not substantially change.

RISK–BENEFIT ANALYSIS FOR BISPHOSPHONATES

The number of osteoporotic and hip fractures prevented, as compared with the number of bisphosphonate-associated atypical femur fractures that occurred, in 10,000 treated women with osteoporosis as a function of duration of bisphosphonate use is shown according to race or ethnic group in Figure 2. Among Whites, the number of fractures prevented for each fracture type far outweighed bisphosphonate-associated atypical fractures at all time points. For example, after 3 years, there were 2 bisphosphonate-associated atypical fractures as compared with 149 hip fractures prevented and 541 clinical fractures prevented. After 5 years, the respective numbers were 8, 286, and 859. Among Asians, the balance was still toward greater prevention of hip and clinical fractures than occurrence of atypical fractures, but less so than in Whites. At 3 years, there were 8 bisphosphonate-associated atypical fractures as compared with 91 hip fractures prevented and 330 clinical fractures prevented. At 5 years, the respective numbers in Asians were 38, 174, and 524. However, by 10 years among Asians, the number of bisphosphonate-associated atypical fractures was only slightly less than the number of hip fractures prevented. The risk–benefit balance was intermediate in Hispanics.

DISCUSSION

Our results support previous studies showing that the absolute risk of atypical femur fracture is very low as compared with the greater number of fractures that are effectively prevented by bisphosphonates. Our findings show that covariate adjustment attenuated, but did not eliminate, the relation between longer duration of bisphosphonate use (as shown by others)[14,15] and higher risk of atypical femur fracture. These results in a diverse cohort contribute to existing but limited evidence about the risks and benefits of treatment in individual patients or populations, using multivariate models with time-dependent variables to identify independent risk factors, including duration of bisphosphonate use, for radiographically adjudicated atypical femur fracture.

In addition to the duration of bisphosphonate treatment, we identified several other noteworthy risk factors for atypical femur fracture, including Asian ancestry, shorter height, higher weight, and glucocorticoid use for 1 year or more. Although older age, previous fractures, and lower bone mineral density are key risk factors for hip and other osteoporotic fractures, they did not substantially increase the risk of atypical fracture. In fact, the oldest women in our cohort, who are at highest risk for hip and other fractures, were at lowest risk for atypical fracture. These risk relationships can be used to individualize clinical decisions about bisphosphonate therapy on the basis of unique combinations of patient characteristics and could provide the basis of a risk calculator.

The increased risk of atypical femur fracture that we observed among North American women of Asian ancestry is consistent with other observations. An earlier Kaiser Permanente Southern California case-series study showed that 49% of 142 atypical femur fractures occurred in Asian patients, who comprised only 10% of the study population.[14]

Other studies in California and Australia have shown that the risk of atypical fracture is 5 to 6 times as high among Asian women as among women of other races or ethnic groups, after adjustment for age and bisphosphonate exposure but with limited adjustment for other risk factors.[23–25]

In our study, adjustment for multiple risk factors did not attenuate the higher risk of atypical fracture (by a factor of 5) among Asians than among Whites. Reasons for the observed increased risk are probably multifactorial and include increased lateral tensile forces on bowed Asian femora, greater medication adherence in this population, and genetic differences in drug metabolism and bone turnover. Several studies have suggested that the degree of femoral bowing could be related to the occurrence of atypical femur fractures[26,27] and may account for the difference in fracture location observed between women in Singapore and those in Sweden.[28] At this early stage, further research into the cause of the increased risk among women of Asian ancestry is warranted. Whether the increase applies only to Asians living outside of Asia is uncertain. Differences in lifestyle, such as diet and physical activity within and outside of Asia, might also contribute to differences and deserve future research.

The incidence of hip and other osteoporotic fractures is lower among Asians and other non-Whites than among Whites.[19,20] This difference between ethnic groups affects the risk–benefit balance of bisphosphonate treatment in these populations and could directly affect decisions regarding treatment initiation and duration.

We found that discontinuing bisphosphonates was associated with a rapid decline in the risk of atypical femur fracture, a finding consistent with that in another report.[15] Although this favors drug holidays, the effect of discontinuation on other osteoporotic fractures must also be considered. Two recent studies showed no more than a minimal increase in the risk of hip or other fractures after bisphosphonate discontinuation,[29,30] which suggests that risk of atypical fracture considered together with risk of hip and other fractures could inform more effective therapy.

Our study has important strengths, including its large and diverse population, rigorous radiographic adjudication of atypical femur fracture, and prospective, multivariate statistical analysis. Yet, it has some potential limitations. First, alendronate accounted for the vast majority of treatment exposure, so our inferences cannot be extended to other medications or formulations, including other bisphosphonates or denosumab. Second, our assessment of covariates, including bisphosphonate exposure, is limited to the Kaiser Permanente membership period; therefore, we may have underestimated cumulative bisphosphonate exposure for those with shorter membership periods before cohort entry. Third, our risk–benefit comparison is based on numbers of fractures only. A more complete comparison would consider costs plus associated morbidity and mortality. Mortality after atypical femur fracture is lower than after hip fracture, although data are limited.[31] Our modeling of fracture reductions from treatment for 1 to 5 years has a strong evidence base from randomized clinical trials, but beyond 5 years, the evidence base is more limited. For approximately 16% of ICD-identified femoral-shaft fractures, radiographs could not be obtained or were inadequate for adjudication, which resulted in a possible underestimate of

the true incidence of atypical fractures. Fourth, there were only two atypical femur fractures in Blacks, which prevents inference in this population.

We found that the risk of atypical femur fracture increased significantly with longer duration of bisphosphonate treatment — particularly beyond 5 years of use — even after multivariate adjustment in this diverse cohort of bisphosphonate-treated patients. It is important that the absolute risk of atypical femur fracture remained small as compared with risks of other osteoporotic fractures, most obviously in Whites, although the risk–benefit balance appeared less favorable for Asian women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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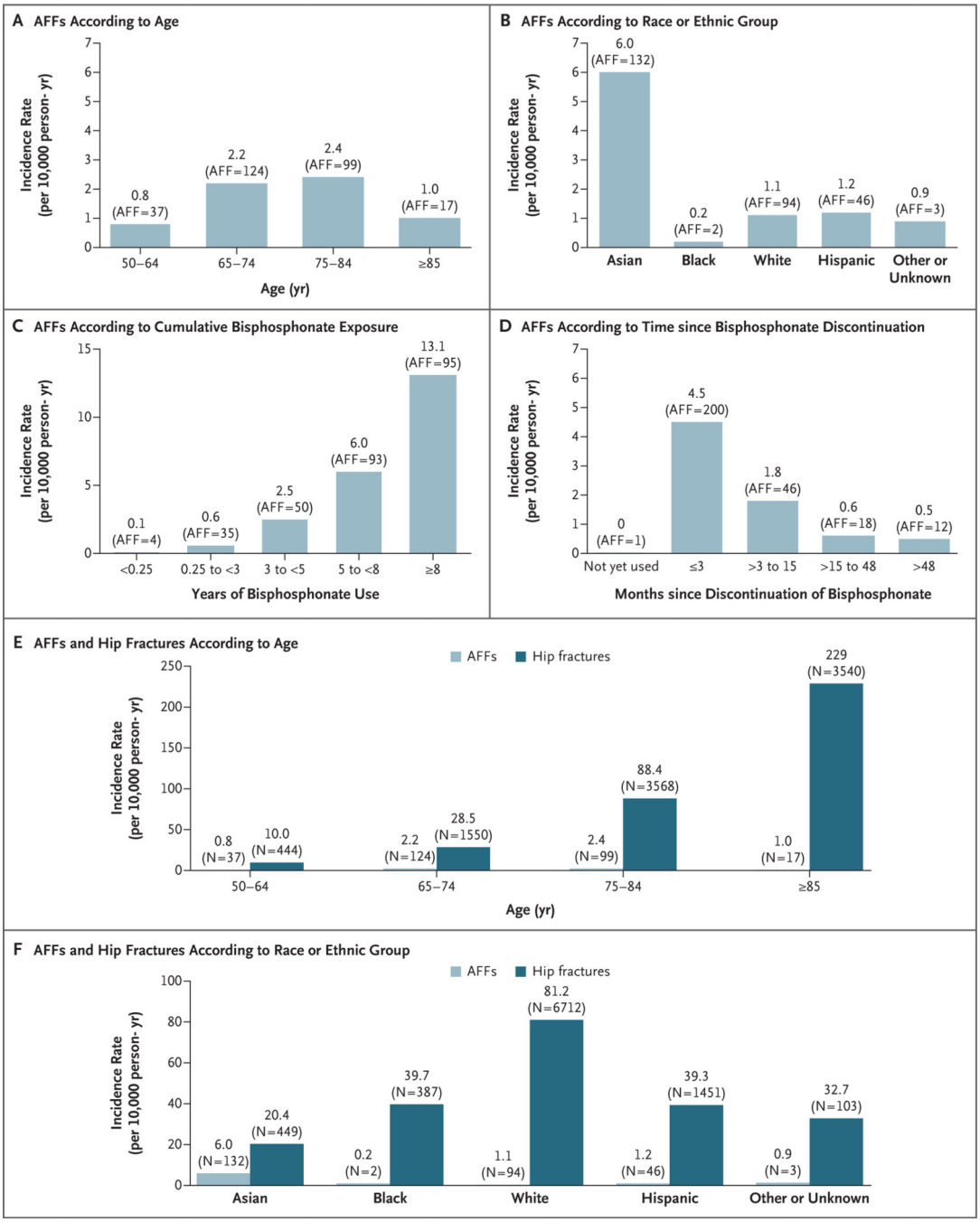

Figure 1. Incidence Rate of Atypical Femur Fractures (AFFs) and Hip Fractures, According to Categories of Risk Factors.

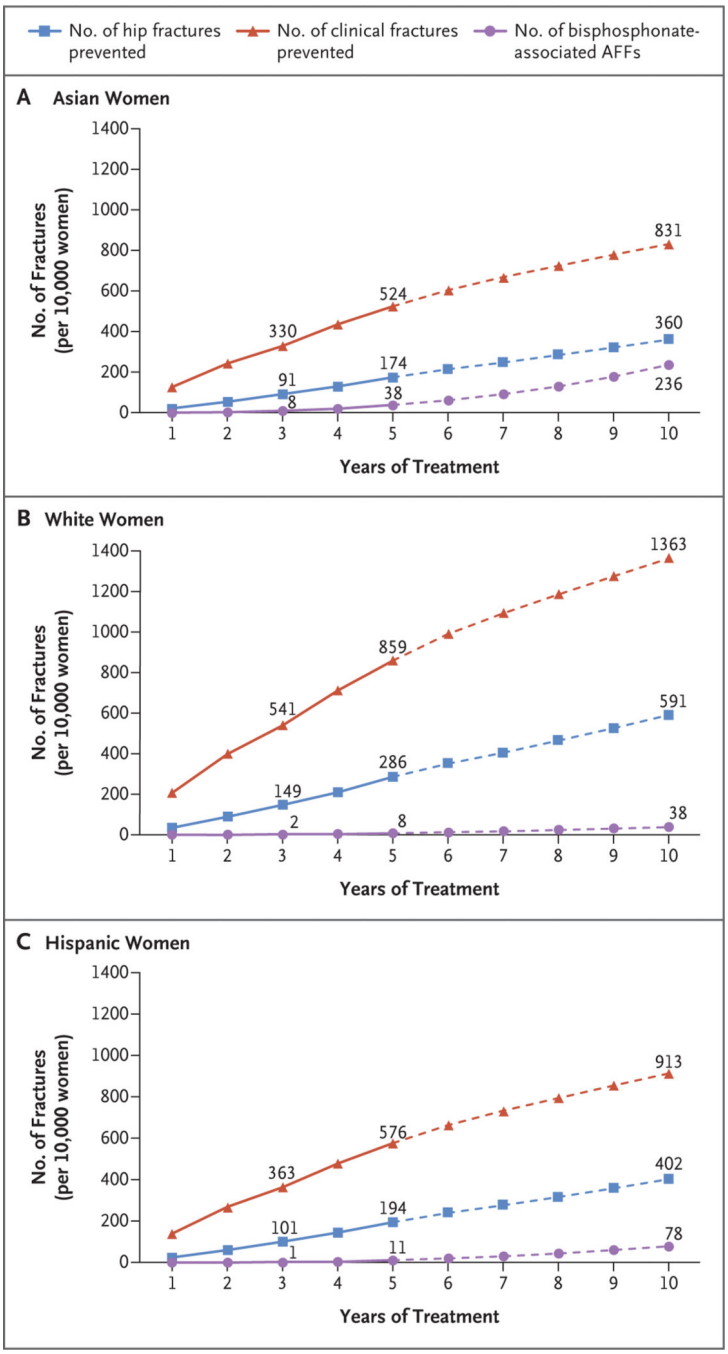

Figure 2. Hip and Clinical Fractures Prevented as Compared with AFFs Associated with Bisphosphonate Use.

Shown are numbers of fractures as a function of years of bisphosphonate treatment, according to race or ethnic group. Solid lines for years 1 through 5 indicate a stronger evidence base for reductions in the risk of hip and clinical fractures with bisphosphonate treatment in the first 5 years of treatment than for risk reductions after 5 years. (See the Methods section in the Supplementary Appendix.)

Table 1.

Characteristics at Baseline and during Follow-up of 196,129 Women with Any Bisphosphonate Use.[*]

Characteristic	Value
At baseline[†]	
Age at baseline — no. (%)	
50–64 yr	79,369 (40.5)
65–74 yr	63,900 (32.6)
75–84 yr	40,567 (20.7)
≥85 yr	12,293 (6.3)
Race or ethnic group — no. (%)[‡]	
Asian	26,431 (13.5)
Black	11,570 (5.9)
White	104,515 (53.3)
Hispanic	47,119 (24.0)
Other or unknown	6,494 (3.3)
Previous bisphosphonate exposure — no. (%)	
<0.25 yr	110,193 (56.2)
0.25 to <3 yr	69,441 (35.4)
3 to <5 yr	10,753 (5.5)
5 to <8 yr	4,799 (2.4)
≥8 yr	943 (0.5)
Height — cm	159±7
Weight — kg	67±15
During follow-up	
Maximum follow-up — no. (%)	
<3 yr	26,084 (13.3)
3 to <5 yr	19,588 (10.0)
5 to <8 yr	28,037 (14.3)
≥8 yr	122,420 (62.4)
Maximum cumulative bisphosphonate exposure — no. (%)	
<0.25 yr	31,499 (16.1)
0.25 to <3 yr	92,304 (47.1)
3 to <5 yr	29,287 (14.9)
5 to <8 yr	26,146 (13.3)
≥8 yr	16,893 (8.6)
Types of bisphosphonates used — no. (%)	
Both oral bisphosphonates and zoledronic acid	3,485 (1.8)
Oral bisphosphonates only[§]	191,287 (97.5)
Zoledronic acid only	1,357 (0.7)

[*] Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.

[†] Shown are values at the time of cohort entry. Additional baseline characteristics are shown in Table S3 in the Supplementary Appendix.

[‡] Race and ethnic group were reported by the patient.

[§] More than 95% of oral bisphosphonate use was alendronate.

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Table 2.

Incidence of Atypical Femur Fractures among Women with Bisphosphonate Use, According to Risk Factors. *

Risk Factor†	Person-Yr of Follow-up‡	Atypical Femur Fractures	Incidence/10,000 Person-Yr
	number		
Age (yr)			
50–64	447,644	37	0.83
65–74	554,527	124	2.24
75–84	421,490	99	2.35
≥85	171,776	17	0.99
Race or ethnic group§			
Asian	221,979	132	5.95
Black	99,913	2	0.20
White	864,371	94	1.09
Hispanic	377,165	46	1.22
Other or unknown	32,009	3	0.94
Cumulative bisphosphonate exposure (yr)			
<0.25	547,558	4	0.07
0.25 to <3	624,373	35	0.56
3 to <5	196,917	50	2.54
5 to <8	154,098	93	6.04
≥8	72,492	95	13.10
Time since bisphosphonate discontinuation (yr)			
Not yet used	350,410	1	0.03
≤0.25: current user	444,771	200	4.50
>0.25–1.25	254,558	46	1.81
>1.25–4	291,471	18	0.62
>4	254,227	12	0.47
Ever smoked§			
Yes	130,980	10	0.76
No	1,464,458	267	1.82
Previous fracture			

Risk Factor†	Person-Yr of Follow-up‡	Atypical Femur Fractures	Incidence/10,000 Person-Yr
Yes	140,123	31	2.21
No	1,455,314	246	1.69
Body-mass index¶			
<18.5	62,561	4	0.64
18.5 to <25	709,629	129	1.82
25 to <30	503,938	98	1.94
≥30	319,310	46	1.44
Glucocorticoid exposure (yr)			
None	801,944	117	1.46
>0 to <1	715,703	129	1.80
≥1	77,791	31	3.99

*A total of 277 atypical femur fractures were observed during 1,545,462 person-years of follow-up.

†Risk-factor values are time-varying (updated annually) unless otherwise specified.

‡Included are person-years before bisphosphonate initiation.

§Values were fixed at baseline, not time-varying.

¶The body-mass index is the weight in kilograms divided by the square of the height in meters.

Table 3.

Hazard Ratios for Atypical Femur Fracture in a Cohort of Women with Bisphosphonate Use.*

Risk Factor	Hazard Ratio (95% CI)	
	Unadjusted	Multivariate-Adjusted
Age (yr)		
50–64	0.97 (0.55–1.71)	1.59 (0.87–2.91)
65–74	2.36 (1.42–3.92)	2.76 (1.62–4.72)
75–84	2.48 (1.48–4.15)	2.50 (1.47–4.23)
≥85	Reference	Reference
Race or ethnic group		
Asian	5.38 (4.12–7.01)	4.84 (3.57–6.56)
White	Reference	Reference
Other	0.92 (0.65–1.29)	0.99 (0.70–1.42)
Duration of bisphosphonate use (yr)		
0 to <0.25	Reference	Reference
0.25 to <3	7.56 (2.67–21.47)	2.54 (0.79–8.14)
3 to <5	33.76 (12.07–94.48)	8.86 (2.79–28.20)
5 to <8	80.90 (29.22–224.01)	19.88 (6.32–62.49)
≥8	179.51 (64.64–498.52)	43.51 (13.70–138.15)
Time since last bisphosphonate use (yr)		
≤0.25: current user	Reference	Reference
>0.25–1.25	0.38 (0.27–0.52)	0.52 (0.37–0.72)
>1.25–4	0.12 (0.07–0.20)	0.21 (0.13–0.34)
>4	0.08 (0.05–0.15)	0.26 (0.14–0.48)
Not yet used	0.01 (0.00–0.06)	0.09 (0.01–0.83)
Ever smoked		
Yes	0.40 (0.22–0.76)	0.64 (0.34–1.22)
No	Reference	Reference
Height (per 5-cm decrement)	1.39 (1.28–1.52)	1.28 (1.15–1.43)
Weight (per 5-kg increment)	0.94 (0.91–0.98)	1.15 (1.11–1.19)
Any previous fracture		

Risk Factor	Hazard Ratio (95% CI)	
	Unadjusted	Multivariate-Adjusted
Yes	1.27 (0.87–1.84)	1.28 (0.86–1.89)
No	Reference	Reference
Body-mass index (per 1-unit change)†	1.00 (0.98–1.02)	
Glucocorticoid use (yr)		
None	Reference	Reference
>0 to <1	1.16 (0.90–1.49)	1.10 (0.85–1.42)
≥1	2.57 (1.72–3.83)	2.28 (1.52–3.43)

*Any variable with a P value of more than 0.2 in the univariate model was included in the multivariate model. For continuous variables (height and weight), entry to the multivariate model was determined by P value for continuous univariate analysis.

†Height and weight but not body-mass index were included in the multivariate model.