

Bisphosphonate Use and the Risk of Subtrochanteric or Femoral Shaft Fractures in Older Women

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OSTEOPOROSIS IS ASSOCIATED with significant morbidity and mortality.^{1,2} Approximately 50% of women older than 50 years will sustain an osteoporosis-related fracture during their lifetime, and 1 of 5 patients with an osteoporosis-related fracture will die within 12 months.³⁻⁵ Although randomized trials have shown that treatment with bisphosphonates reduces the risk of osteoporotic fractures,⁶⁻⁸ concerns have recently emerged that bisphosphonate-related suppression of bone remodeling may adversely influence bone strength.⁹

An increasing number of case reports describe women who develop fractures involving the subtrochanteric or shaft region of the femur in the setting of long-term bisphosphonate therapy, generally after minimal trauma.¹⁰ Fractures at these sites are often described as atypical because of their location and characteristic radiographic appearance.^{9,10} The US Food

Context Osteoporosis is associated with significant morbidity and mortality. Oral bisphosphonates have become a mainstay of treatment, but concerns have emerged that long-term use of these drugs may suppress bone remodeling, leading to unusual fractures.

Objective To determine whether prolonged bisphosphonate therapy is associated with an increased risk of subtrochanteric or femoral shaft fracture.

Design, Setting, and Patients A population-based, nested case-control study to explore the association between bisphosphonate use and fractures in a cohort of women aged 68 years or older from Ontario, Canada, who initiated therapy with an oral bisphosphonate between April 1, 2002, and March 31, 2008. Cases were those hospitalized with a subtrochanteric or femoral shaft fracture and were matched to up to 5 controls with no such fracture. Study participants were followed up until March 31, 2009.

Main Outcome Measures The primary analysis examined the association between hospitalization for a subtrochanteric or femoral shaft fracture and duration of bisphosphonate exposure. To test the specificity of the findings, the association between bisphosphonate use and fractures of the femoral neck or intertrochanteric region, which are characteristic of osteoporotic fractures, was also examined.

Results We identified 716 women who sustained a subtrochanteric or femoral shaft fracture following initiation of bisphosphonate therapy and 9723 women who sustained a typical osteoporotic fracture of the intertrochanteric region or femoral neck. Compared with transient bisphosphonate use, treatment for 5 years or longer was associated with an increased risk of subtrochanteric or femoral shaft fracture (adjusted odds ratio, 2.74; 95% confidence interval, 1.25-6.02). A reduced risk of typical osteoporotic fractures occurred among women with more than 5 years of bisphosphonate therapy (adjusted odds ratio, 0.76; 95% confidence interval, 0.63-0.93). Among 52 595 women with at least 5 years of bisphosphonate therapy, a subtrochanteric or femoral shaft fracture occurred in 71 (0.13%) during the subsequent year and 117 (0.22%) within 2 years.

Conclusion Among older women, treatment with a bisphosphonate for more than 5 years was associated with an increased risk of subtrochanteric or femoral shaft fractures; however, the absolute risk of these fractures is low.

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and Drug Administration¹¹ recently announced its intent to actively monitor instances of bisphosphonate-induced atypical fracture, and the American Society for Bone and Mineral Research⁹ has released a task force report regarding the case definition, epidemiology, and need for additional research on these fractures.

Case reports and conflicting findings from small observational studies^{10,12-14} have left clinicians and patients uncertain about whether bisphosphonates increase the risk of subtrochanteric or femoral shaft fractures. We explored the association between long-term bisphosphonate use and subtrochanteric or femoral shaft fractures in a large population of postmenopausal women.

METHODS

Setting and Design

We conducted a population-based, nested case-control study examining the association between bisphosphonate use and fractures in a cohort of Ontario women aged 68 years or older who commenced treatment with a bisphosphonate between April 1, 2002, and March 31, 2008. These patients have universal access to hospital care, physicians' services, and prescription drugs. This project was approved by the Research Ethics Board of Sunnybrook Health Sciences Centre, Toronto, Canada. The analysis was performed at the Institute for Clinical Evaluative Sciences, which has statutory authority to conduct health services research without consent using anonymized administrative data.

Data Sources

We identified medication use using the Ontario Public Drug Program database, which contains comprehensive, high-quality data on publicly funded medications dispensed to Ontarians aged 65 years or older.¹⁵ Hospitalizations were identified using the Canadian Institute for Health Information (CIHI) Discharge Abstract Database, which provides detailed diagnostic and procedural information regarding hospital admissions.¹⁶ We used the Ontario

Health Insurance Plan database to identify physician service claims. Women with a history of malignancy (breast, bone, colorectal, lung, myeloma, thyroid, renal cell, and melanoma) were identified from the Ontario Cancer Registry, a comprehensive population-based tumor registry that contains pathology reports, hospital discharge abstracts, and death certificates of Ontarians with a diagnosis of cancer. Demographic information was obtained from the Registered Persons Database, which contains a single, unique record for all Ontario residents ever issued a health card. Socioeconomic status was estimated for each patient by linking the home postal code to Statistics Canada population census data to obtain the median neighborhood household-income quintile.¹⁷ These databases were linked in an anonymous fashion using unique encrypted health card numbers and are regularly used to explore drug safety issues.¹⁸⁻²¹

Study Population

Our study population consisted of women aged 68 years or older who commenced treatment with an oral bisphosphonate (alendronate, risedronate, or etidronate). Because Ontario residents are eligible for public prescription benefits upon turning 65 years, we were able to examine the first 3 years of prescription records to establish a study population of patients newly treated with a bisphosphonate. The date of the first prescription for bisphosphonate therapy served as the cohort entry date, and switching between eligible bisphosphonates was permitted. We excluded women with any history of cancer in the preceding 10 years, conditions that may be associated with altered bone integrity such as osteomalacia, osteopetrosis, hyperparathyroidism, hypercalcemia, epilepsy, celiac disease, Paget disease, renal osteodystrophy, or gastric bypass in the preceding 5 years and women treated with raloxifene, calcitonin, sodium fluoride, clodronate, pamidronate, or zoledronic acid in the preceding year. Women in the cohort were

followed up until the first subtrochanteric or femoral shaft fracture, death, or the end of the study period (March 31, 2009).

Within the group of women commencing treatment with a bisphosphonate, we defined cases as those hospitalized with a subtrochanteric or femoral shaft fracture between April 1, 2003, and March 31, 2009 using *International Statistical Classification of Diseases, 10th Revision (ICD-10)* codes S72.2 and S72.3, respectively. The date of hospitalization served as the index date, and only the first hospitalization for such a fracture was considered if patients experienced multiple fractures during the study period. We excluded fractures resulting from trauma, motor vehicle collisions, and falls from a height (*ICD-10* codes V01-6, V9, V43-5, and V47). We also excluded fractures coded as subtrochanteric or femoral shaft fractures in the CIHI database that were treated exclusively with hip replacement surgery.

For each case, we selected up to 5 controls from the cohort not hospitalized with a subtrochanteric or femoral shaft fracture. Controls were matched to cases on age (± 1 year) and cohort entry period (calendar year and quarter).^{22,23} The index date for controls was set to equal the index date of the case with which they were matched.

Exposure Assessment

The duration of bisphosphonate exposure was assessed by examining prescriptions for oral alendronate, risedronate, or etidronate dispensed from the start of therapy to the index date. The duration of each prescription was determined from the mandatory "days supply" field of the prescription record. For each case and control, total bisphosphonate exposure was determined by calculating the cumulative total days of therapy for all bisphosphonate prescriptions received.

From the cumulative bisphosphonate exposure values, we categorized participants according to their total duration of treatment as long-term users (≥ 5 years of therapy), intermediate us-

ers (3-5 years of therapy), and short-term users (100 days to 3 years). These exposure groups were compared with a reference group of transient (<100 days in total) users.

Validation of ICD-10 Codes for Subtrochanteric and Femoral Shaft Fractures

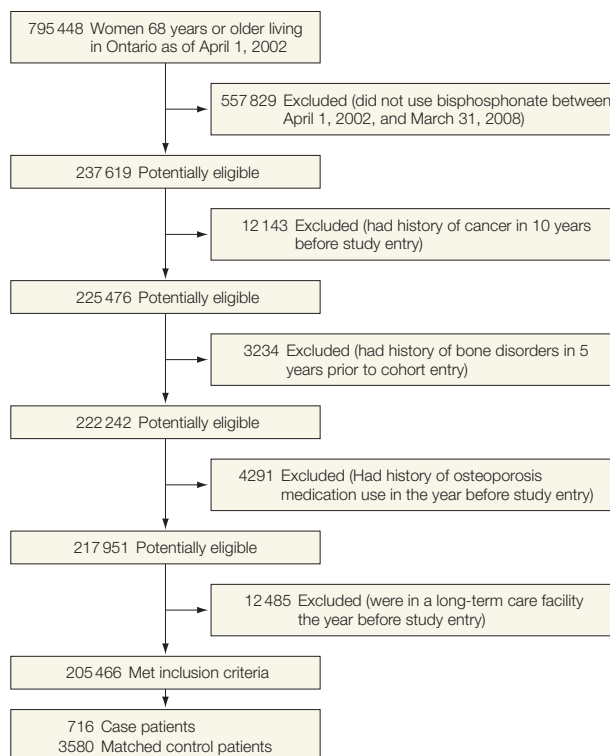
The ICD-10 codes for subtrochanteric and femoral shaft fractures have not been previously validated. We performed a separate validation study to determine the positive predictive value and sensitivity of the diagnostic codes for these fractures. The details of this validation exercise are outlined in eAppendix 1 (available at <http://www.jama.com>). In brief, we compared electronic medical records, operative notes, radiology reports, and discharge letters with administrative data for 2077 individuals with femur fractures admitted to 4 independent hospitals.

Statistical Analysis

Primary Analysis. The primary analysis examined the association between hospitalization for a subtrochanteric or femoral shaft fracture and cumulative duration of bisphosphonate use for more than 5 years. To explore the association with lower cumulative doses, we also examined bisphosphonate durations of 3 to 5 years, and 100 days to 3 years. Women who initiated bisphosphonates but did not continue beyond 100 days (transient use) served as the reference group for all analyses.

We used conditional logistic regression to estimate the odds ratios (ORs) and 95 percent confidence intervals (CIs) for the association between long-term bisphosphonate exposure and subtrochanteric or femoral shaft fractures. We adjusted for multiple other factors that might influence fracture risk.²⁴ The full list of covariates in the multivariable model is given in eAppendix 2. Drugs and diseases were grouped according to indication or mechanism of action to avoid overfitting the model. All analyses were performed using SAS version

Figure. Selection of Study Population



9.2 (SAS Institute Inc, Cary, North Carolina) using a 2-sided type 1 error rate of .05 as the threshold for statistical significance.

Secondary Analyses. We tested the specificity of our design and analysis by replicating the analysis to explore the association between bisphosphonate use and typical osteoporotic femoral neck or intertrochanteric hip fractures, comparing the resulting ORs with the results from the bisphosphonate randomized trials. We reasoned that extended use of these drugs should be associated with a lower risk of such fractures, as demonstrated by randomized controlled trials.^{25,26} For this analysis, we used the ICD-10 codes for femoral neck fracture (S72.0) and intertrochanteric fracture (S72.1).^{27,28}

Case-control studies do not readily yield estimates of excess risk. We therefore estimated the attributable fraction among exposed women, defined as the fraction of exposed cases that might

have been avoided had the exposure not occurred, using the formula $AF_e = (OR-1)/OR$.²⁹⁻³¹ We also estimated the population attributable fraction, defined as the fraction of all cases (exposed and unexposed) that might have been avoided if the exposure had not occurred. This was calculated as population attributable fraction = $(OR-1)/OR \times (\text{proportion of cases exposed to risk factor})$. Finally, to estimate the incidence of subtrochanteric or femoral shaft fractures among women with at least 5 years of bisphosphonate use, we created a cohort of these women and followed them up for 2 additional years to identify all such fractures.

RESULTS

Over the 7-year study period, we identified 205 466 women aged 68 years or older treated with a bisphosphonate who met our inclusion criteria. Within this group, we identified 716 women (0.35%) who sustained a subtrochanteric or femoral shaft fracture following initiation of

bisphosphonate therapy, including 411 women with a subtrochanteric fracture and 305 women with a femoral shaft fracture. The FIGURE details the cohort selection steps. These cases were matched to 3580 controls of the same age and time of cohort entry. The baseline characteristics of the cases and controls are shown in TABLE 1. The median age of

cases was 83 years (interquartile range, 79-88 years), and they were followed up for a median of 4.0 years (range, 2.6-5.4) from the start of bisphosphonate therapy.

In the validation study, the ICD-10 codes for subtrochanteric or femoral shaft fracture had a positive predictive value of 90% (95% CI,

88%-92%) and a sensitivity of 81% (95% CI, 78%-84%). This analysis is reported in more detail in eAppendix 1 (available at <http://www.jama.com>).

In the primary analysis, use of bisphosphonates for 5 years or longer was associated with an increased risk of hospitalization for subtrochanteric or femoral shaft fracture compared with transient use of bisphosphonates (adjusted odds ratio, 2.74; 95% CI, 1.25-6.02; TABLE 2). Shorter durations of bisphosphonate use were not associated with a statistically significant increase in the risk of subtrochanteric or femoral shaft fracture (Table 2).

In the secondary analysis examining the risk of typical osteoporotic fractures, we identified 9723 women with fractures of the femoral neck or intertrochanteric region during bisphosphonate therapy. As expected, we found that extended bisphosphonate use (≥ 5 years) was associated with a reduced risk of fracture compared with transient use (adjusted OR, 0.76; 95% CI, 0.63-0.93). Women with intermediate bisphosphonate use (3-5 years) demonstrated a similarly low risk with the upper CI limit just crossing unity (adjusted OR, 0.86; 95% CI, 0.73-1.00; TABLE 3), while a shorter duration of bisphosphonate use (100 days to 3 years) was associated with a nonsignificant reduction in the risk of such fractures (adjusted OR, 0.93; 95% CI, 0.81-1.07).

The attributable fraction of the exposed women was 64%, suggesting that more than half of subtrochanteric or femoral shaft fractures among women taking bisphosphonates for greater than 5 years were attributable to extended bisphosphonate use. The population attributable fraction was 11%, suggesting that approximately 1 of every 10 subtrochanteric or femoral shaft fractures cases in the population might be prevented if no patient received more than 5 years of exposure.

We estimated the absolute risk of subtrochanteric or femoral shaft fracture following long-term bisphosphonate use

Table 1. Baseline Characteristics of Cases and Controls^a

	Cases (n = 716)	Controls (n = 3580)
Age, median (IQR), y	83 (79-88)	83 (79-87)
Socioeconomic income quintile, No. (%)		
1 (lowest)	187 (26.1)	783 (21.9)
2	140 (19.6)	768 (21.5)
3	149 (20.8)	665 (18.6)
4	117 (16.3)	637 (17.8)
5	118 (16.5)	688 (19.2)
Previous osteoporotic fracture in preceding 5 y, No. (%) ^b	500 (69.8)	861 (24.1)
Previous fall in preceding 5 y, No. (%)	480 (67.0)	197 (5.5)
No. of unique drugs prescribed in preceding y, median (IQR)	10 (6-14)	8 (5-12)
No. of family physician visits in preceding y, median (IQR)	11 (5-19)	7 (3-12)
Bone mineral density test, preceding 5 y, No. (%)	239 (33.4)	1330 (37.2)
Medical conditions, preceding 5 y, No. (%)		
Depression	35 (4.9)	73 (2.0)
Arthritis	110 (15.4)	284 (7.9)
Diabetes	83 (11.6)	201 (5.6)
Hypertension	287 (40.1)	652 (18.2)
Hyperthyroidism	<6	<6
Parkinson disease	9 (1.3)	28 (0.8)
Dementia	104 (14.5)	140 (3.9)
Congestive heart failure	92 (12.9)	170 (4.8)
Syncope	27 (3.8)	100 (2.8)
Asthma, COPD, emphysema	62 (8.7)	194 (5.4)
Stroke or transient ischemic attack	42 (5.9)	106 (3.0)
Drug therapy, preceding y, No. (%)		
Antidepressants	309 (43.2)	1062 (29.7)
Anticonvulsants	22 (3.1)	98 (2.7)
Antipsychotics	97 (13.6)	228 (6.4)
Benzodiazepines	302 (42.2)	1260 (35.2)
β -Adrenergic antagonists	255 (35.6)	1082 (30.2)
Estrogen	31 (4.3)	165 (4.6)
Opioid analgesics	457 (63.8)	1656 (46.3)
Thyroid replacement therapy	190 (26.5)	805 (22.5)
Calcium channel blockers	278 (38.8)	1345 (37.6)
Diuretics	367 (51.3)	1781 (49.8)
Oral glucose lowering drugs	71 (9.9)	359 (10.0)
Proton pump inhibitors	325 (45.4)	1272 (35.5)
Statins	252 (35.2)	1428 (39.9)
Glucocorticoids	92 (12.9)	427 (11.9)
Warfarin	121 (16.9)	377 (10.5)
Nitrates	20 (2.8)	138 (3.9)

Abbreviations: COPD, chronic obstructive pulmonary disease; IQR, interquartile range.

^a Cells ≤ 5 are suppressed.

^b Previous osteoporotic fracture includes fractures of vertebrae, wrist, hand, forearm, humerus, clavicle, ankle, pelvis, hip.

from 52 595 women in our cohort with at least 5 years of bisphosphonate therapy. Among these women, a subtrochanteric or femoral shaft fracture occurred in 71 women (0.13%) during the subsequent year and 117 (0.22%) within 2 years.

COMMENT

In this population-based study, we found that long-term bisphosphonate treatment was associated with an increased risk of subtrochanteric or femoral shaft fracture in older women. The increase in risk of subtrochanteric or femoral shaft fracture was apparent with 5 or more years of cumulative bisphosphonate drug exposure. These findings contrast with a recently published analysis of 3 bisphosphonate trials that found no association between bisphosphonate use and the risk of subtrochanteric or femoral shaft fractures.^{32,33} However, that analysis included a minority of women who received more than 3 to 4 years of bisphosphonate treatment and analyzed only 284 hip or femur fracture events across the 3 studies, which resulted in low statistical power to detect associations involving rare events.

Our study represents the largest assessment of the issue published to date.^{12,14,32} Additionally, our validation study documented that the fracture codes we used were associated with good sensitivity and positive predictive value. This allowed us to study a large population-based cohort of women and accurately identify subtrochanteric and femoral shaft fractures.

We also found that, as expected, extended bisphosphonate therapy was associated with a reduced risk of typical osteoporotic fractures. This result provides an independent validation of our primary findings because it is consistent with evidence from randomized trials of bisphosphonate therapy, for which adjusted OR estimates of 0.60 to 0.74 were reported for alendronate and risedronate, respectively.^{6,7}

Some limitations of our study merit emphasis. Our study outcome was defined by fracture site (subtrochanteric or femoral shaft) and absence of trauma.

Although we validated the diagnostic codes for these fractures against radiological reports, we could not ascertain the specific radiological features listed in the recent American Society of Bone and Mineral Research (ASBMR) Task Force Report on Atypical Femoral Fractures.⁹ Standard radiological reports do not typically comment on the radiological pattern associated with atypical fractures, and no consensus regarding the characteristic radiological features existed until late 2010.⁹ However, our study outcome represents 2 of the 4 major features of atypia proposed by the task force,⁹ and the fact that we observed these fractures to occur more often among long-term bisphosphonate users is clinically important, independent of radiographic appearance.

As with all epidemiological studies, residual confounding is a potential limitation. However, we took several steps to minimize the potential for residual confounding. First, by restricting the

cohort to women who had been prescribed bisphosphonate therapy, all women in the study were presumed to have osteoporosis and an increased risk of fracture, thereby making cases and controls more comparable. Second, we matched cases to controls on age and period of cohort entry and adjusted for many potentially confounding variables in our multivariable model. Perhaps most importantly, our analysis of the relationship between typical osteoporotic hip fractures and bisphosphonate use revealed a strong protective association, consistent with evidence from clinical trials. Post hoc examination of the transient (nonadherent) bisphosphonate reference group in our study revealed that these patients tended to be sicker than their adherent (long-term bisphosphonate users) counterparts, and this may have contributed to the differences between the adjusted and unadjusted OR estimates.

We used administrative data and did not have information on lifestyle behav-

Table 2. Risk of Subtrochanteric or Femoral Shaft Fractures Among Women Taking Bisphosphonate Therapy

	Duration of Bisphosphonate Therapy			
	Transient, <100 days	Short-term Use, 100 days to 3 years	Intermediate Use, 3 to 5 Years	Long-Term Use, ≥5 Years
No. (%) of patients				
Case (n = 716)	42 (5.9)	349 (48.7)	204 (28.5)	121 (16.9)
Control (n = 3580)	218 (6.1)	1832 (51.2)	1070 (29.9)	460 (12.9)
Odds Ratio (95% CI)				
Crude	1.0 [Reference]	1.00 (0.70-1.43)	1.08 (0.73-1.59)	1.74 (1.11-2.73)
Adjusted ^a	1.0 [Reference]	0.90 (0.48-1.68)	1.59 (0.80-3.15)	2.74 (1.25-6.02)

Abbreviation: CI, confidence interval.

^aThe full list of covariates for the adjusted model are given in eAppendix 2 (available at <http://www.jama.com>).

Table 3. Risk of Femoral Neck or Intertrochanteric Hip Fractures Among Women Taking Bisphosphonate Therapy

	Duration of Bisphosphonate Therapy			
	Transient, <100 days	Short-term Use, 100 days to 3 years	Intermediate Use, 3 to 5 Years	Long-Term Use, ≥5 Years
No. (%) of patients				
Case (n = 9723)	817 (8.4)	5587 (57.5)	2438 (25.1)	881 (9.1)
Control (n = 48 564)	3434 (7.1)	27 086 (55.8)	13 148 (27.1)	4896 (10.1)
Odds Ratio (95% CI)				
Crude	1.0 [Reference]	0.87 (0.80-0.94)	0.72 (0.65-0.79)	0.65 (0.58-0.74)
Adjusted ^a	1.0 [Reference]	0.93 (0.81-1.07)	0.86 (0.73-1.00)	0.76 (0.63-0.93)

Abbreviation: CI, confidence interval.

^aThe full list of covariates for the adjusted model are given in eAppendix 2 (available at <http://www.jama.com>).

iors such as exercise, diet, smoking status, weight, use of over-the-counter therapies such as vitamin D or calcium, family history of osteoporosis, bone mineral density values, radiographs, hip geometry, height, body mass index, or biochemical markers of bone turnover. We also relied on prescription data to determine duration of bisphosphonate exposure, and some degree of exposure misclassification may therefore have occurred in our analysis. However, because we examined prescription refill behavior over an extended period, this lessens the likelihood of exposure misclassification among long-term bisphosphonate users, in whom the strongest association was seen. We represented long-term drug exposure with a simple metric determined by calculating each patient's cumulative duration of therapy, a straightforward and easily understood measure. We were only able to follow up women for up to 7 years because reliable subtrochanteric or femoral shaft fracture codes were not available in our databases until 2002, when the *ICD-10* system was implemented. We also could not study women younger than 68 years of age, so the generalizability of our findings to younger women is unknown. Finally, because our database did not contain information about which femur was fractured, we were not able to examine the frequency of bilateral femoral fractures.

The proportion of subtrochanteric or femoral shaft fractures attributable to long-term bisphosphonate use was 64%, suggesting that the majority of subtrochanteric or femoral shaft fractures occurring among long-term users were attributable to bisphosphonate use. However, the population attributable fraction for long-term use was only 11%. The large difference between the attributable risk among the exposed and the population attributable risk reflects the relatively low prevalence of long-term bisphosphonate use among the cases in our population.³⁴ Over the study period (2002 to 2008), only a small proportion of our cohort received 5 or more years of bisphospho-

nate treatment, which is another limitation of our study. However, this is also important because it is likely that the prevalence of long-term bisphosphonate exposure will increase over time as more women achieve 5 cumulative years of therapy because these drugs are still relatively new and because sustained adherence to bisphosphonates is actively promoted in the community setting. Consequently, the population attributable fraction may increase as the population of women exposed to long-term bisphosphonates also increases. It is therefore possible that the population attributable fraction estimate yielded by our analysis is an underestimate of the present-day proportion of subtrochanteric or femoral shaft fractures attributable to long-term bisphosphonate use.

Importantly, the results of our study should not deter clinicians and patients from using bisphosphonates in appropriate patients. Our study confirms the known benefits of bisphosphonate treatment for typical osteoporotic fracture, and evidence suggests that bisphosphonate therapies are underused in individuals at high risk of fracture despite their established efficacy.³⁵ We identified 9723 typical hip fractures in our cohort over the study period compared with 716 subtrochanteric or femoral shaft fractures. These numbers are consistent with the clinical observation that typical fractures are far more common than subtrochanteric or femoral shaft fractures, which we found to be uncommon even among women with at least 5 years of bisphosphonate therapy. The estimate of absolute risk of a subtrochanteric or femoral shaft in women surpassing 5 years of bisphosphonate therapy was 0.13% during the subsequent year and 0.22% within 2 years. This observation is consistent with the prevalent clinical impression that such fractures are rare, even among patients with long-term bisphosphonate therapy. Moreover, our analysis does not include osteoporotic fractures at other sites such as the wrist and spine, for which bisphosphonate therapy has also been demonstrated ef-

fective.^{6,7} However, the optimal duration of bisphosphonate therapy has not been established, and the balance of benefits and risks of extended bisphosphonate therapy is unclear.^{36,37}

In summary, our findings provide strong evidence that prolonged bisphosphonate therapy is associated with an increased risk of subtrochanteric or femoral shaft fracture, although the absolute risk of these fractures is low. These findings also highlight the need for a thoughtful assessment of individual risk of fracture when considering extended bisphosphonate therapy and that long-term use of these drugs may warrant reconsideration, especially in patients at relatively low risk of fracture. It may be appropriate to consider a drug holiday for selected patients, particularly as the cumulative duration of bisphosphonate therapy surpasses 5 years.^{36,38-43} Additional research is needed to better understand the prognosis of subtrochanteric or femoral shaft fractures among frail older adults, identify the specific subgroups of long-term users at the highest risk for these adverse effects, and explore whether interruptions in therapy reduce the risk of subtrochanteric or femoral shaft fractures over the long term.

Author Contributions: Dr Park-Wyllie and Ms Gunraj had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Online-Only Materials: eAppendixes 1 and 2 are available online at <http://www.jama.com>.

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