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Risk of Atypical Femoral Fracture during and after Bisphosphonate Use

TO THE EDITOR: Bisphosphonates prevent clinical fractures in women younger than 80 years of age with documented osteoporosis, according to efficacy trials.[1,2] However, adverse events related to these agents may affect all patients, including those in groups in which the benefit of these drugs is less well established. We previously found a strong association between bisphosphonate use and atypical fractures in Swedish women.[3] That study of data from 2008 has now been extended to include the period of 2008 through 2010 to investigate the association of potential adverse events with sex, type of bisphosphonate, and timing of use.

We reviewed radiographs of 5342 women and men (97% of eligible patients) 55 years of age or older, with a femoral shaft fracture, and found 172 patients with an atypical fracture (according to the American Society for Bone and Mineral Research criteria).[4,5] Registry data on medication use since July 2005 and information about coexisting conditions were obtained.[3] Nationwide cohort and case–control analyses were performed as described previously.[3] However, patients receiving bisphosphonates before October 2005 were defined as longtime users and were excluded from the case–control analysis of current use.

In the cohort analysis, the age-adjusted relative risk of an atypical fracture with bisphosphonate use was 55.2 (95% confidence interval [CI], 38.8 to 78.7) among women and 54.1 (95% CI, 15.2 to 192.3) among men. Nevertheless, the absolute risk was three times as high among women as among men; among bisphosphonate users, women as compared with men had a relative risk of 3.1 (95% CI, 1.1 to 8.4). As compared with risedronate users, alendronate users had a relative risk of 1.9 (95% CI, 1.1 to 3.3), which might be related to a higher antiresorptive effect of alendronate with recommended doses. The risk of atypical fracture among women increased progressively with the duration of use, and the relative risk after at least 4 years reached 126.0 (95% CI, 55.1 to 288.1), with an annual absolute risk of 11 fractures (95% CI, 7 to 14) per 10,000 person-years of use.

In the case–control analysis, short-term use conferred an increased risk of atypical fracture (Table 1). The multivariable-adjusted odds ratio with 4 to 5 years of current use was 100 times as high as that with nonuse. For each year since the last use, the risk was 70% less. In the multivariable-adjusted analysis, women as compared with men had a risk of atypical fracture of 3.6 (95% CI, 2.5 to 5.3). Bisphosphonate users also commonly used glucocorticoids and proton-pump inhibitors, but these uses did not modify the risk of atypical fracture.

There is long-lasting skeletal accumulation of bisphosphonate, but ongoing use seems to be the dominant risk factor for these rare fractures. Oral bisphosphonates might do more harm than good if given to patients without an evidence-based indication, and the evidence base for treatment over many years is weak.

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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Table 1. Risk of Atypical Femoral Fracture Associated with Bisphosphonate Use.*

Variable	Patients with Atypical Femoral Fracture	Controls with Ordinary Femoral Fracture	Odds Ratio Adjusted for Age and Sex (95% CI)	Multivariable-Adjusted Odds Ratio (95% CI)†
All participants — no.	172	952		
Bisphosphonate use — no. (%)				
Never	38 (22)	842 (88)	1.0 (reference)	1.0 (reference)
Ever	134 (78)	110 (12)	25.8 (19.8–33.7)	26.3 (18.3–37.8)
Type of bisphosphonate — no.				
Alendronate	120	73	35.6 (28.6–44.3)	35.9 (27.5–46.4)
Risedronate	16	26	11.6 (6.5–20.7)	12.6 (6.1–25.9)
Etidronate	0	13	NA	NA
Ibandronate	2	0	NA	NA
Zoledronate	0	2	NA	NA
Risk of fracture				
Per yr of use	NA	NA	2.6 (2.1–3.2)	2.5 (2.0–3.1)
Per yr since last use	NA	NA	0.31 (0.28–0.36)	0.31 (0.27–0.35)
Use within previous yr — no.	129	79	34.1 (25.5–45.6)	34.5 (23.3–51.2)
Duration of use among current users — no.‡				
<1 yr	1	10	1.3 (0.1–15.9)	1.7 (0.2–18.6)
≥1–2 yr	5	11	8.4 (2.5–28.2)	8.2 (2.5–26.6)
≥2–3 yr	17	11	27.2 (24.8–29.9)	28.7 (25.8–32.0)
≥3–4 yr	12	5	47.1 (22.4–99.0)	39.7 (17.4–90.5)
≥4–5 yr	13	3	80.8 (39.8–164.4)	116.4 (58.0–233.7)
Women — no.	160	774		
Bisphosphonate use — no. (%)				
Never	30 (19)	670 (87)	1.0 (reference)	1.0 (reference)
Ever	130 (81)	104 (13)	26.1 (20.8–32.8)	29.3 (20.8–41.3)
Risk of fracture				
Per yr of use	NA	NA	2.6 (2.2–3.2)	2.6 (2.1–3.3)
Per yr since last use	NA	NA	0.30 (0.28–0.33)	0.29 (0.26–0.32)
Men — no.	12	178		
Bisphosphonate use — no. (%)				
Never	8 (67)	172 (97)	1.0 (reference)	1.0 (reference)
Ever	4 (33)	6 (3)	19.1 (8.0–46.0)	19.0 (9.9–36.6)
Risk of fracture				
Per yr of use	NA	NA	2.1 (1.3–3.3)	2.4 (2.1–2.7)
Per yr since last use	NA	NA	0.37 (0.28–0.50)	0.37 (0.30–0.47)

* NA denotes not applicable.
† Analyses were adjusted for age, sex, glucocorticoid use (yes or no), and Charlson comorbidity index score.
‡ Current use was defined as a first use after October 1, 2005, to ascertain nonuse in the period from July 2005 through September 2005. The national Swedish Prescribed Drug Register, started on July 1, 2005, provides complete national data on persons with exposure to dispensed drugs in the Swedish population, and the drugs are normally dispensed every third month.

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The symposium will be held in Fort Lauderdale, FL, Oct. 3–5. It is presented by Cleveland Clinic Florida in collaboration with the CORE Institute.

Contact Kimberly Schmidt, Cleveland Clinic Florida, 2950 Cleveland Clinic Blvd., Weston, FL 33331; or call (954) 659-5490; or e-mail schmidk@ccf.org; or see http://www.ClevelandClinicFloridaCME.org/.

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Contact Linda Musumeci, Daland Fellowships in Clinical Investigation, American Philosophical Society, 104 S. Fifth St., Philadelphia, PA 19106-3387; or call (215) 440-3429; or e-mail LMusumeci@amphilsoc.org; or see http://www.amphilsoc.org/grants/daland.

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Contact Boston Children's Hospital, 300 Longwood Ave., Pavilion 121, Boston, MA 02115; or call (617) 384 8600; or e-mail hms cme@hms.harvard.edu; or see http://www.pediatricsedationconference.com/Sep/html/home.html.

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Contact Educational Symposia, 5620 W Sligh Ave., Tampa, FL 33634; or call (800) 338-5901 or (813) 806-1000; or see http://www.edusymp.com.

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The symposium will be held in Lebanon, NH, on Nov. 8.

Contact Dartmouth-Hitchcock Medical Center, One Medical Center Dr., Lebanon, NH 03756; or call (603) 653-1234; or e-mail ccehs@hitchcock.org; or see https://ccehs.dartmouth-hitchcock.org/Activity/2556949/Detail.aspx.

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The symposium will be held in Las Vegas, Dec. 4–6.

Contact Kim Kirchner, Global Academy for Medical Education, 7 Century Dr., Suite 301, Parsippany, NJ 07054; or call (502) 574-9023; or fax (502) 589-3602; or e-mail kkirchner@hqtrs.com; or see http://www.pags-cme.org.

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The symposium will be held in Lake Tahoe, CA, Feb. 5–8.

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