

Do bisphosphonates raise the risk of atypical femur fracture? And even if they do, are they worth using anyway?

The clinical issue: FDA revised the labeling for bisphosphonates (e.g., alendronate, risedronate, ibandronate) to warn of the potential risk of atypical femur fractures (AFF),¹ and several studies have reported higher rates of AFF in patients taking these drugs.²⁻³ These unusual fractures are generally in the subtrochanteric region or femoral shaft. They occur with minimal or no trauma, and may be bilateral; they are often preceded by pain in the groin or thigh.⁴

The new evidence: AFFs occur predominantly in patients taking bisphosphonates, especially long-term users. They are very rare in both the general population and treated patients.^{3,5} A recent meta-analysis of 11 observational studies found that use of these drugs more than doubled the risk of AFF (relative risk [RR] 3.9, 95% confidence interval [CI]: 1.2-13.1),⁶ but there was considerable heterogeneity among the studies. A subgroup analysis of 6 studies showed that long-term use (i.e., longer than 4-5 years) of bisphosphonates increased risk of AFF by 3.7 times (with a very wide 95% CI, 0.4-38.8) compared to non-use of bisphosphonates (see Figure 1). After limiting the analysis to two studies of long-term users, the relative risk of AFF associated with bisphosphonates was 13.8 (95% CI 1.5-130.4).

Limitations: Methodological difficulties in studying such a rare outcome and correctly diagnosing these unusual fractures have hampered adequate study of this problem.

Practice implications: Bisphosphonates remain effective and useful drugs for the prevention of common fractures in patients with osteoporosis, reducing the risk of the far more common typical hip fractures by 40% in high-risk patients.⁷ By contrast, AFFs represent less than 1% of all femoral fractures, and any risk of AFF that these drugs confer likely comes predominantly with long-term use (>5 years). There is little evidence that bisphosphonate use for longer than 5 years confers ongoing protection from any kind of fracture in most patients.

Bottom line:

- Concern about AFF should generally not prevent use of bisphosphonates in patients with osteoporosis.
- Limit bisphosphonate treatment to patients who actually have osteoporosis (e.g., T-score lower than -2.5) – yet another reason to refrain from using these drugs in low-risk patients who just have osteopenia (T-score higher than -2.5) and not actual osteoporosis.
- Reassess need for continuing use beyond 5 years, or consider a drug holiday for a year or two.
- Consider the possibility of AFF in a patient taking a bisphosphonate who develops new thigh or groin pain.

References: (1) FDA. Safety update for osteoporosis drugs, bisphosphonates, and atypical fractures.

<http://www.fda.gov/Drugs/DrugSafety/ucm229009.htm#healthcare>. (2) Park-Wyllie, L., et al. Bisphosphonate use and the risk of subtrochanteric or femoral shaft fractures in older women. *JAMA*. 2011; 305(8):783-789. (3) Schilcher, J., K. Michaelsson, and P. Aspenberg. Bisphosphonate use and atypical fractures of the femoral shaft. *N Engl J Med*. 2011; 364(18):1728-1737. (4) Shane, E., et al. Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res*. 2010; 25(11):2267-2294. (5) Kim, S., et al. Oral bisphosphonates and risk of subtrochanteric or diaphyseal femur fractures in a population-based cohort. *J Bone Miner Res*. 2011; 26(5):993-1001. (6) Kim, S., L. Gedmintas, and D. Solomon. Use of bisphosphonates and risk of atypical femur fracture: a systematic review and meta-analysis. *To be presented at the International Conference on Pharmaco-epidemiology*. August 2012. (7) Hopkins, R., et al. The relative efficacy of nine osteoporosis medications for reducing the rate of fractures in post-menopausal women. *BMC Musculoskelet Disord*. 2011; 12(209). (8) Watts, N. and D. Diab. Long-term use of bisphosphonates in osteoporosis. *J Clin Endocrinol Metab*. 2010; 95(4):1555-1565.

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These are recommendations only; specific clinical decisions should be made by the treating physician based on an individual patient's clinical condition.

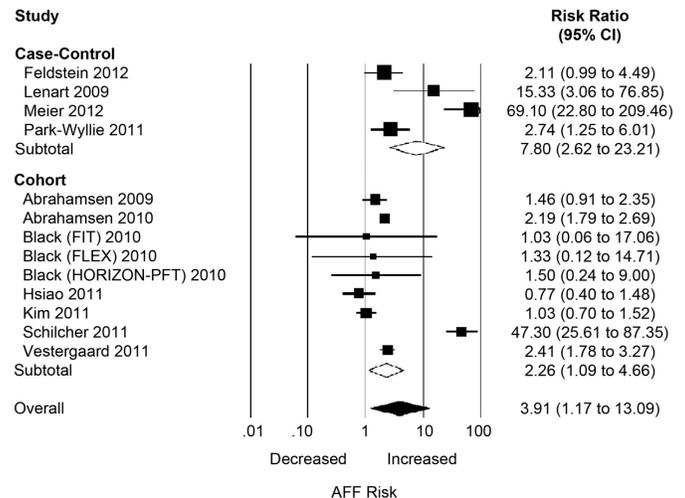


Figure 1. Random effects analysis of the studies for the association between bisphosphonate use and atypical femur fracture (AFF), stratified by study design.⁶ Point (square) and overall (diamond) estimates are given as risk ratios with 95% confidence interval.