

# NEWS Commentary

The following news items are reviews of important scientific articles with commentary that address clinical relevance. This material comes from the First to Know® program of The North American Menopause Society (NAMS), offered to its members via broadcast e-mail. You can receive the complete program by joining the Society ([www.menopause.org](http://www.menopause.org)). Please note that the opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS.

## Long-term alendronate use appears safe and effective

Bone HG, Hosking D, Devogelaer J-P, et al, for the Alendronate Phase III Osteoporosis Treatment Study Group. Ten years' experience with alendronate for osteoporosis in postmenopausal women. *N Engl J Med* 2004; 350:1189-99.

Use of alendronate provides sustained effects on bone mineral density (BMD) and bone turnover markers, according to analyses of 164 women who took alendronate for 10 years. This report publishes data from a planned 3-year extension of two randomized, double-blind, placebo-controlled trials (10 years total). In these trials, 994 postmenopausal women with osteoporosis were assigned to receive either placebo or alendronate (Fosamax) at oral doses of 5, 10, or 20 mg for 3 years.

After 3 years, women in the placebo group were given open-label alendronate for 2 years, and women taking 20 mg for the first 3 years were switched to 5 mg for years 3 through 5, followed placebo for the final 5 years. The 5- and 10-mg dose recipients continued on the same dose. Compared

with baseline, 10-year results showed that women treated with 10 mg alendronate had statistically significant increases in mean BMD of 13.7% at the lumbar spine, 10.3% at the femoral trochanter, 5.4% at the femoral neck, 6.7% at the total proximal femur, and 2.9% for the total body. The 5-mg dose group had smaller but still statistically significant increases for lumbar spine (9.3%), femoral neck (2.8%), femoral trochanter (4.8%), and total hip (2.9%) BMD; increases in total body BMD (1.0%) did not reach statistical significance. Women who discontinued alendronate had a gradual loss of effect during the 5-year span, although the 10-year results were still significant versus baseline for the lumbar spine (9.3%), trochanter (5.3%), total hip (3.4%) and total body (1.8%). Based on safety data that included fracture rates, the authors concluded that the results do not suggest any association between prolonged use of alendronate and an excess risk of fracture. No significant adverse gastrointestinal events were noted.

**Comment.** This important study demonstrates that alendronate therapy continues to inhibit bone resorption during the full 10 years of therapy without obvious adverse skeletal or clinical consequences. However, without a control group beyond 3 years, the antifracture efficacy of long-term therapy cannot be evaluated from these data. Bone loss ensued and the indices of bone remodeling increased when therapy was discontinued after 5 years.

Because the bone remodeling tests do not return to baseline values, it is often assumed that it is appropriate to stop treatment after 5 years, providing a so-called "drug holiday." However, whether fracture protection persists or wanes after stopping therapy is unknown. In the absence of evidence of significant safety issues with ongoing therapy, it is my opinion that alendronate treatment

should not be stopped after 5 years in women who are still at moderate or high fracture risk.

Michael McClung, MD  
Director  
Oregon Osteoporosis Center  
Portland

**Comment.** The authors of this article conclude that "there is no excess risk of fracture" among women exposed to long-term alendronate. However, my reading of the article does not lead me to the same conclusion. In large part, my concern is that the data and analyses suffer from serious limitations, and the presentation appears to lack candor.

First, for limitations, comparisons with placebo are not possible because the placebo group was stopped after 3 years. Second, comparisons are based on fracture rates with alendronate use during years 1 to 3 versus years 6 to 10, omitting from analysis any increase in events that may have occurred during years 4 and 5. Third, baseline vertebral fracture prevalence differed considerably between groups (17.5% of the 10-mg group, 30.8% of the 5-mg group). Because presence of baseline fracture is a very strong predictor of future fracture, the 10-mg group was at much lower risk of future spine fracture and thus would create a positive bias toward a good treatment effect. Pooling the data for the 5- and 10-mg groups when comparing treatment to placebo would have been a more reasonable approach.

For alendronate users, only pooled data for years 0 to 3 are provided, yet fracture data for years 6 to 10 are given separately for the 5- and 10-mg dose groups. From the data provided, one can estimate that the annual rate of fracture during years 6 to 10 in these groups combined is about 2%. Compared with the 1.1% annual rate during the first 3 years of the study, this is not reassuring. However, the number of women with fractures is quite low (I estimate there were

only 15 women with fractures among long-term users of both the 5- and 10-mg doses who were evaluated for fracture). Thus, one really cannot make conclusions about decreased (treatment efficacy) or increased (treatment harm) fracture risk.

At my practice, I am monitoring bone turnover in all long-term (>3 years) alendronate users. For those with bone turnover levels close to the bottom of the normal premenopausal range, I am recommending three possible alternatives that could possibly reduce the risk and consequences of over-suppressed bone turnover: (1) take a 6- to 12-month vacation from treatment, (2) lower the weekly alendronate dosage to 20 or 40 mg, or (3) switch to a milder antiresorptive agent such as raloxifene. Rechecking bone turnover after 6 to 12 months should give a good idea of adequacy of the antiresorptive effect. The principle "do no harm" requires us to be vigilant in those exposed to long-term alendronate.

Bruce Ettinger, MD  
Clinical Professor of  
Medicine and Radiology  
University of California  
San Francisco

### Estrogen's hip fracture protection disappears 5 years after withdrawal

Yates J, Barrett-Connor E, Barlas S, Chen Y-T, et al. Rapid loss of hip fracture protection after estrogen cessation: evidence from the National Osteoporosis Risk Assessment. *Obstet Gynecol* 2004;103:440-6.

Fracture risk benefits provided by hormone therapy (HT; either estrogen alone or estrogen plus progestogen) are lost within 5 years of discontinuation of therapy, according to data from the National Osteoporosis Risk Assessment (NORA) study, a longitudinal, observational study. In all, 140,584 postmenopausal women (at least 50 years of age) with no previous diagnosis of osteoporosis were enrolled in this 1-year

study. At baseline, 48% were using HT and another 14% had used HT in the past. A multivariate analysis showed that current HT users had a 40% reduced risk of hip fracture (95% CI, 0.44–0.82) compared with never users. In contrast, women who had discontinued HT within the past 5 years had a 35% *increased* risk of hip fracture (95% CI, 1.05–2.59) compared with never users. In women who had discontinued HT use for more than 5 years, their hip fracture risk was similar to never users.

**Comment.** This study's objective was to analyze the hip fracture data from the NORA study (Siris, *JAMA* 2001). Similar to the Women's Health Initiative (WHI), women in NORA who were current HT users had a 40% reduction in hip fractures compared to those who had never used HT. This supports previously published data indicating that estrogen use in a general population of women without established osteoporosis was associated with a decreased risk of hip fracture.

The most important result of this study, however, is the observation of increased hip fracture risk for women who had discontinued estrogen therapy within the last 5 years. These women actually had a higher risk of fracture than never users. This is a major concern. It is thought to occur as a result of the high rate of bone turnover and increased resorption associated with estrogen withdrawal. Rapid decreases in bone mineral density are known to be associated with microarchitectural deterioration and a profound reduction in bone strength. Since the publication of the WHI results, many women have discontinued HT. This study suggests that those women will be at a high risk for hip fracture during the first 5 years after discontinuation.

Although the NORA study has the intrinsic problems associated with observational trials, these data are still compelling. They should remind clinicians to consider alternatives to estrogen for frac-

ture prevention in women who decide to discontinue hormone use.

Risa Kagan, MD, FACOG  
Co-Medical Director, Foundation for  
Osteoporosis Research and Education  
Oakland, CA  
Associate Clinical Professor  
Department of Obstetrics and  
Gynecology and Reproductive Sciences  
University of California  
at San Francisco