



Effect of ERT/HRT Cessation on Bone Loss

Greendale GA, Espeland M, Slone S, et al. Bone mass response to discontinuation of long-term hormone replacement therapy: Results from the Postmenopausal Estrogen/Progestin Interventions (PEPI) Safety Follow-up Study. *Arch Intern Med* 2002;162:665-72.

When a postmenopausal woman stops estrogen replacement therapy or hormone replacement therapy (ERT/HRT), bone loss does not accelerate at an unusually high rate, according to this analysis of data from the Postmenopausal Estrogen/Progestin Interventions (PEPI) study. Also, long-term ERT/HRT use does not appear to lead to additional bone mineral density (BMD) gains beyond that seen after 3 years.

For this report, 495 women who were adherent to assigned treatment in the 3-year PEPI trial, a randomized, double-blind, placebo-controlled trial, were followed for an average of 4 additional years. Changes in BMD among women who stopped ERT/HRT either during or after the trial did not differ significantly from those of placebo recipients. Annual rates of BMD loss among women who stopped ERT/HRT after 1 year were 0.54% (hip) and 0.81% (spine) during the next 2 years. Women who completed 3 years of ERT/HRT and then discontinued it had annual decreases of 1.01% and 1.04%, respectively. In comparison, placebo recipients had annual bone losses of approximately 1% during the first year of the trial and 0.5% thereafter. Women who continued ERT/HRT during the follow-up did not show additional BMD gains greater than placebo recipients.

Comment. This paper addresses the question, Does bone loss accelerate after discontinuation of estrogen? In the PEPI study, BMD measurements were performed in women treated with ERT/HRT for 3 years. Women were then followed off treatment for another 2 years. The rate of bone loss in the group who stopped ERT/HRT was not significantly different from that seen in the group treated with placebo. In short, the authors found no evidence of accelerated loss after discontinuation of ERT/HRT. Other published data have shown conflicting results regarding accelerated bone loss after stopping ERT/HRT. The question remains unresolved, and there is no obvious explanation for the reported differences.

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Mammography and Decreased Breast Cancer Mortality

Nystrom L, Andersson I, Bjurstam N, et al. Long-term effects of mammography screening: Updated overview of the Swedish randomised trials. *Lancet* 2002;359:909-19.

Breast cancer screening using mammography significantly reduces breast cancer mortality in women aged 55 to 70 years, according to this analysis of data from four published Swedish randomized trials: Malmo, Two-County, Stockholm and Göteborg. Relative risks for breast cancer mortality were analyzed for nearly 250,000 women (including 117,000 women in control groups). The median follow-up was 15.8 years. Overall, the mammography group had a significant 21% decrease in breast cancer mortality compared with the control group. Age-group results showed significant mortality declines in women aged 55 to 59, 60 to 64 and 65 to 69. Women aged 50 to 54 had a small mortality decline that

did not reach statistical significance.

Comment. This article, which reports long-term outcomes for four of five Swedish, randomized, controlled trials of mammography and gives details pertaining to randomization procedures, is in response to the two recently published reviews of mammography from Danish investigators (Gotzsche, *Lancet* 2000; Olsen, *Lancet* 2001). Those reviews excluded the Malmo trial because of perceived poor randomization processes and stated that the remaining trials showed no benefit in mortality with screening mammography.

Nystrom and colleagues note that the Malmo and Göteborg (later part) trials used individual randomization. The Stockholm and Göteborg (early part) trials used cluster randomization based on day of birth. The Two-County trial used geographic cluster randomization. Small differences in demographic variables are expected with use of cluster randomization, a point not realized in the "Danish Study," which excluded the Stockholm, Göteborg and Two-County trials because small differences (1 to 5 months) in the mean age of study and control groups were thought to be due to poor randomization technique.

This trial also reports long-term outcome of the Malmo trial, which does show a significant decrease in mortality. Of note, the divergence in mortality curves between study and control groups is first noted at 4 years and peaks at 10 years, with the difference maintained at the latest follow-up of 18 years. The delay in apparent benefit of screening of 5 to 10 years is important when reviewing outcomes of other mammography trials in which longer-term data are not included or available, because this delay will underestimate the benefit of screening. Although the Malmo trial has previously reported a benefit, only the initial report of no benefit is included in the Danish study.

Thus, this article carefully addresses

concerns regarding randomization and offers reassurance regarding the positive outcomes of the Swedish randomized, controlled trials of screening mammography.

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Improved Efficacy With Combined Antiresorptive Agents

Johnell O, Scheele WH, Lu Y, et al. Additive effects of raloxifene and alendronate on bone density and biochemical markers of bone remodeling in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab* 2002; 87:985-92.

Ettinger B, Bilezikian JP. For osteoporosis, are two antiresorptive drugs better than one? [editorial] *J Clin Endocrinol Metab* 2002;87:983-4.

Combining the antiresorptive agents raloxifene HCl (Evista) and alendronate (Fosamax) results in greater bone density and lower levels of bone turnover markers than are produced by either agent alone, according to this randomized, double-blind,

placebo-controlled trial. In 331 postmenopausal women aged 75 years or younger, the effects of raloxifene (60 mg/day) and alendronate (10 mg/day), either alone or combined, were evaluated. Spinal BMD was measured by dual x-ray absorptiometry. Bone turnover was measured by levels of serum osteocalcin, bone-specific alkaline phosphatase and urinary N- and C-telopeptide.

At 1 year, spinal BMD increased from baseline by 2.1%, 4.3% and 5.3% for raloxifene, alendronate and combined therapy, respectively; all BMD changes were significantly better than seen with placebo. Changes in bone turnover markers also were significantly better than placebo for all active-treatment groups. Increases in all endpoints were greater for combined therapy compared with either drug alone, although the increases reached statistical significance only when compared with raloxifene alone. Effects of alendronate alone also were significantly greater than raloxifene alone.

Comment. This article by Johnell et al adds to the burgeoning literature about combinations of antiresorptive agents in the treatment of postmenopausal women with osteoporosis. In most cases, combined use of two drugs increases bone density more than either drug alone, although in this case, the difference was significant only when the combined agents were compared with raloxifene and not alendronate.

As the accompanying editorial stresses, this is a two-edged weapon. The greater reduction in bone remodeling and, thus, increase in bone mineralization might be good or bad. Studies with fracture as the outcome are needed to determine which (if either) is the case, and none has been done or even contemplated. For the clinician, it is still worth resisting any pressure to use combination therapy with which the fracture response is unknown.

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Fluoxetine for Hot Flashes

Loprinzi CL, Sloan JA, Perez EA, et al. Phase III evaluation of fluoxetine for treatment of hot flashes. *J Clin Oncol* 2002;20:1578-83.

The antidepressant fluoxetine HCl (Prozac) decreases the incidence of hot flashes in postmenopausal women, according to this double-blind, placebo-controlled, crossover trial. A total of 81 women with a history of or at risk for breast cancer who were experiencing hot flashes enrolled in the study. Approximately half of the women were randomly assigned to receive 20 mg per

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