

NEWS Commentary

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Estrogen-progestin therapy reduces osteoporotic fracture risk, but provides no overall beneficial effect: WHI data

Cauley JA, Robbins J, Chen Z, et al, for the Women's Health Initiative Investigators. Effects of estrogen plus progestin on risk of fracture and bone mineral density. *JAMA* 2003;290:1729-1738.

Combination estrogen-progestin therapy (EPT) increases bone mineral density (BMD) and reduces the risk of osteoporotic fracture in healthy postmenopausal women, according to these data from the Women's Health Initiative. In this randomized, placebo-controlled clinical trial, 16,608 women aged 50 to 79 received either EPT (0.625 mg/day conjugated equine estrogens plus 2.5 mg/day medroxyprogesterone acetate) or a placebo. Follow-up lasted 5.6 years. The main skeletal end-points were osteoporotic fractures, BMD (measured in 1,024 women at baseline and at years 1 and 3), and a global index of risk-benefit for EPT based on hip fracture risk. Fewer EPT recipients suffered an osteo-

porotic fracture (8.6%; n=733) than placebo recipients (11.1%; n=896), which is a significantly reduced hazard ratio (HR) for total fracture of 0.76 (95% CI, 0.69-0.83). Individually, the HRs were 0.67 (95% CI, 0.47-0.96) for hip fracture, 0.71 (95% CI, 0.59-0.85) for lower arm/wrist fracture, and 0.65 (95% CI, 0.46-0.92) for vertebral fracture. No significant differences in relative risk reduction were noted when the results were adjusted for age, BMI, smoking status, history of falls, history of fracture, calcium intake, or past EPT use. Among the BMD measurements, total hip BMD at year 3 increased from baseline by 3.7% in the EPT group compared with a 0.14% increase in the placebo group, a significant difference ($P < 0.001$). Similar significant findings were observed at the lumbar spine (4.5% greater increase than placebo).

The global index assessment, which was designed to summarize the risk and benefits of EPT, was calculated for women determined to be at high, middle, and low levels of fracture risk. The global index assessment was similar for all three fracture risk groups (P value for interaction = 0.54). The authors note that the global index analysis indicates no overall treatment benefit for EPT, even in women at high risk for fracture.

Comment. This paper expands the analyses of the skeletal aspects of the WHI that were initially published in July 2002. These analyses confirm the significant reduction in fractures of the spine, hip, and other sites with EPT. An attempt was made to identify a subgroup of women whose skeletal benefit was so substantial that it outweighed the risks associated with EPT.

Participants were stratified on the basis of a fracture risk score designed to assess the risk of hip fracture. Although the relative risk of fracture was reduced similarly in all risk groups, the absolute risk reduction was greatest with EPT in the higher risk group. However, even in

this group, the benefit (protection from hip fracture) used in the global index assessment (GIA) did not outweigh the risks included in the assessment. Unfortunately, the fracture risk score did not identify women at high risk for spine fracture, the fracture of most clinical importance for younger postmenopausal women most likely to receive EPT for symptom control. Additionally, the GIA does not include fractures other than hip fracture and does not include non-life-threatening clinical problems such as vasomotor symptoms. Thus, it is possible that a subgroup of women exists who are at high risk for spine fracture in whom the clear fracture protection benefits of EPT would outweigh the well-defined risks. Before recommending that ET or EPT be used for osteoporosis prevention in women who do not have vasomotor symptoms, this subgroup would have to be defined. Until or unless such a group is identified, estrogen is no longer a first-line drug for osteoporosis prevention, despite the WHI data documenting the skeletal benefits of EPT. Other effective options are available, and estrogen would only be an option in women who had contraindications to, were intolerant of, or were unresponsive to the other options.

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Comment. This sub-study from the WHI confirms the long suspected efficacy of EPT on osteoporosis prevention and fracture reduction, including hip fracture. These findings are even more interesting since the women in the WHI were relatively young (for hip fracture), moderately to significantly overweight (a strong preventive factor for bone loss), and ethnically diverse (yet another negative risk factor). Without trying to determine global risk,

these findings should stand on their own—hormones reduce fractures.

When trying to assess global risk versus benefit, this paper suffers from the same problems as other papers from the WHI; namely, both the benefits of EPT on fracture reduction and the risks are dependent on the study population investigated. While a study population of much younger and thinner Caucasian women would likely have had few or no hip fractures and, therefore, no hip fracture reduction, that population would have had significantly less cardiovascular risk. The global risk and benefit balance would still be in dispute as it applies to the average hormone user who initiates therapy for vasomotor symptoms and gets osteoporosis prevention as a byproduct. One must be extremely careful about extending both the benefits and the risks seen here beyond the population in which they were assessed.

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Raloxifene effectively reduces the rate of new vertebral fractures in women with low BMD

Kanis JA, Johnell O, Black DM, et al. Effect of raloxifene on the risk of new vertebral fracture in postmenopausal women with osteopenia or osteoporosis: A reanalysis of the Multiple Outcomes of Raloxifene Evaluation trial. *Bone* 2003;33:293-300.

Treatment with 60 mg/day raloxifene significantly decreases the risk of new vertebral fractures in postmenopausal women with osteopenia or osteoporosis, according to a post-hoc analysis of data from the Multiple Outcomes of Raloxifene Evaluation (MORE) trial. This randomized, double-blind, placebo-controlled trial enrolled 3,204 postmenopausal women with either osteope-

nia or osteoporosis as defined by the BMD *T*-score at the total hip and no evidence of vertebral fracture at baseline. Women received either 60 mg/day raloxifene or placebo. At 3 years, raloxifene-treated women had significantly fewer new vertebral fractures than placebo recipients, independent of baseline BMD. Compared with placebo, women with osteopenia had a relative risk (RR) of 0.53 (95% CI, 0.32-0.88) and women with osteoporosis had an RR of 0.31 (95% CI, 0.06-0.71); the between-group difference was not significant. In an analysis of clinically apparent vertebral fractures, raloxifene-treated women with osteopenia had an RR of 0.25 (95% CI, 0.04-0.63) compared with placebo; women with osteoporosis had no clinically apparent vertebral fractures.

Comment. The MORE trial included 7,705 postmenopausal women with osteoporosis as defined by a *T*-score of -2.5 or less at the lumbar spine or femoral neck [Ettinger, *JAMA* 1999]. It found that raloxifene was effective in decreasing new vertebral fractures in women with or without a prior history of vertebral fracture. This reanalysis of the data redefines the women without a prior vertebral fracture as either osteoporotic (n=635) or osteopenic (n=2,257) based on BMD of the total hip (versus BMD of the lumbar spine or femoral neck, where they were all defined as osteoporotic). The reanalysis found raloxifene was effective in reducing first vertebral fractures in both the osteoporotic and osteopenic subgroups.

Since it is important to prevent the first vertebral fracture and the cohort of women with osteopenia is larger than that of osteoporosis, the significance of a protective effect by raloxifene in osteopenic women is substantial. The limitation of this study, however, is that all of these women had osteoporosis as defined by BMD of the lumbar spine/femoral neck, and the results may not necessarily be extrapolated to women

who have osteopenia as defined by BMD at these sites.

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