

Estrogen plus progestin reduced risk for fracture in postmenopausal women

Cauley JA, Robbins J, Chen Z, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. *JAMA*. 2003;290:1729-38.

QUESTION

In postmenopausal women, does estrogen plus progestin reduce the risk for fracture?

DESIGN

Randomized {allocation concealed*}†, blinded {clinicians, participants, data collectors, outcome assessors, and monitoring committee}†,* placebo-controlled trial with mean 5.6-year follow-up.

SETTING

{40 U.S. clinical centers.}†

PARTICIPANTS

16 608 women who were 50 to 79 years of age (mean age 63 y) and had an intact uterus. {Exclusion criteria included probable survival of < 3 years, cancer in the past 10 years, and low hematocrit or platelet counts.}† Follow-up was 94%.

INTERVENTION

Women were allocated to a single table† of conjugated equine estrogen, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d ($n = 8506$), or placebo ($n = 8102$).

MAIN OUTCOME MEASURES

Fracture (except fracture of the ribs, chest or sternum, skull or face, fingers, toes, and cervical vertebrae). A global index assessed the

benefits and risks of treatment by incorporating other disease outcomes (coronary heart disease; invasive breast, endometrial, or colorectal cancer; stroke; pulmonary embolism; hip fracture; and death from other causes).

MAIN RESULTS

Analysis was by intention to treat. Fewer women in the hormone therapy group than in the placebo group had a fracture (Table). The effect for total fracture risk remained constant across different subgroups. When treatment effects on other important outcomes were included in a global model, hormone therapy had no net benefit, even in women with high risk for fracture.

CONCLUSIONS

In postmenopausal women, estrogen plus progestin reduced the risk for fracture. In a global model assessing treatment effects on all outcomes, hormone therapy had no net benefit.

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*See Glossary.

†Writing Group for the Women's Health Initiative Investigators. *JAMA*. 2002;288:321-33.

Estrogen plus progestin vs placebo in postmenopausal women at mean 5.6 years†

Outcomes	Estrogen plus progestin	Placebo	RRR (95% CI)	NNT (CI)
Any fracture	8.6%	11%	23% (16 to 30)	40 (31 to 56)
Hip fracture	0.6%	0.9%	33% (4.0 to 53)	338 (210 to 2787)
Hazard ratio (CI)				
Lower arm or wrist fracture	Not reported		0.71 (0.59 to 0.85)	
Vertebral fracture	Not reported		0.65 (0.46 to 0.92)	

†Abbreviations defined in Glossary; RRR, NNT, and CI calculated from Cox proportional-hazards model in article.

COMMENTARY

The study by Cauley and colleagues provides final analysis of fracture endpoints previously reported in the Women's Health Initiative (WHI) trial (1). The authors, using a global index, confirmed there was no net benefit of estrogen and progestin therapy even in women at high risk for fracture. However, the global index did not include such factors as the risk for dementia and the increase of gynecologic diagnostic procedures because of vaginal bleeding. The risk for probable dementia increased 2-fold in older women allocated to the estrogen and progestin therapy and probably resulted from the increase in vascular dementia in the WHI Memory Study (2). In addition, the number of women requiring diagnostic biopsies increased more than 5-fold among those allocated to combined hormones (3).

Of interest is the finding that estrogen plus progestin reduced the risk for hip fractures only in women who reported a baseline calcium intake of > 1200 mg/d. However, vitamin D intake was not reported.

These studies will assist women and their practitioners in making informed choices. Hormone therapy is no longer generally recommended preventive therapy, but in postmenopausal women with substantial vasomotor symptoms, hormone replacement may be a short-term option primarily to treat symptoms and secondarily to decrease

the risk for fractures. However, other therapies, such as bisphosphonates and selective receptor modulators, should be considered first-line therapy for preventing and treating osteoporosis (4).

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