THERAPEUTICS

Estrogen plus progestin increased coronary heart disease and breast cancer events in postmenopausal women

Writing Group for the Women's Health Initiative Investigators. **Risks and benefits of estrogen plus progestin in healthy postmenopausal women. Principal results from the Women's Health Initiative Randomized Controlled Trial.** JAMA. 2002 Jul 17;288:321-33.

QUESTION

In postmenopausal women, what are the risks and benefits of estrogen-plus-progestin use, particularly with respect to coronary heart disease (CHD) events?

DESIGN

Randomized (allocation concealed*), blinded (clinicians, participants, data collectors, outcome assessors, and monitoring committee),* placebo-controlled trial with a mean 5.2-year follow-up.

SETTING

40 U.S. clinical centers.

PARTICIPANTS

16 608 postmenopausal women who were 50 to 79 years of age (mean age 63.3 y). Exclusion criteria included probable survival of < 3 years, previous breast cancer or other cancer in the past 10 years, and low hematocrit or platelet counts. Follow-up was 96.5%.

INTERVENTION

Women were allocated to 1 daily tablet of conjugated equine estrogen, 0.625 mg, and medroxyprogesterone acetate, 2.5 mg (Prempro, Wyeth Ayerst, Philadelphia, PA, USA) (n = 8506), or placebo (n = 8102).

MAIN OUTCOME MEASURES

CHD (nonfatal myocardial infarction [MI] or CHD death) and invasive breast cancer. Other outcomes included stroke, venous thromboembolism (VTE), colorectal cancer, fractures, and death from other causes.

MAIN RESULTS

Analysis was by intention to treat. Because of early increases in breast cancer, follow-up was stopped at a mean of 5.2 years instead of the expected 8.5 years. Women who received estrogen plus progestin had more total cardiovascular disease (CVD) than those who received placebo, including CHD (mainly nonfatal MI), stroke, and VTE (Table). Invasive breast cancer was increased to a nearly statistically significant extent (Table). Colorectal cancer and fractures were reduced (Table). Groups did not differ for mortality.

CONCLUSION

In postmenopausal women, estrogen plus progestin use increased the risk for CVD, particularly coronary heart disease events.

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For correspondence: Dr. J.E. Rossouw, National Heart, Lung, and Blood Institute, Bethesda, Maryland, USA. E-mail rossouw@nih.gov. ■

*See Glossary.

Estrogen plus progestin (Est + Prog) vs placebo for postmenopausal women†

Unfavorable outcomes	Event rates per patient-y		RRI (95% CI)	NNH (CI)
	Est + Prog	Placebo		
All cardiovascular disease	1.57%	1.32%	22% (9 to 36)	348 (213 to 848)
Coronary heart disease	0.37%	0.30%	29% (2 to 63)	1152 (531 to 16 693)
Stroke	0.29%	0.21%	41% (7 to 85)	1164 (562 to 6811)
Venous thromboembolism	0.34%	0.16%	111% (58 to 182)	565 (345 to 1079)
Invasive breast cancer	0.38%	0.30%	26% (0 to 59)	1285 (567 to infinity)
Favorable outcomes			**RRR (CI)**	**NNT (CI)**
Hip fracture	0.10%	0.15%	34% (2 to 55)	1962 (1213 to 33 358)
Colorectal cancer	0.10%	0.16%	37% (8 to 57)	1691 (1097 to 7819)

†Abbreviations defined in Glossary; RRI, RRR, NNH, NNT, and CI calculated from the hazard ratio, CI, and control event rate in article.

COMMENTARY

Since the publication 38 years ago of *Feminine Forever* (1), the view that menopause (and CVD in women) is a disease of estrogen deficiency requiring treatment has dominated medical thinking. The results of the Women's Health Initiative are a major challenge to this view. On the debit side, for every 10 000 women receiving combination hormone replacement therapy (HRT) for 1 year, there are 7 more coronary events, 8 more occurrences of breast cancer, 8 more strokes, and 8 more pulmonary emboli. On the credit side, there are 6 fewer occurrences of colorectal cancer and 5 fewer hip fractures. Put another way, for every 100 women treated for 5 years, 1 additional woman will have a serious adverse event. The finding of excess CHD, breast cancer, and VTE is consistent with the results of HERS (2), reanalyses of epidemiologic studies (3), and a recent meta-analysis (4). This is more than enough evidence to conclude that long-term treatment with estrogen-and-progestin combinations to prevent CVD is not appropriate.

Women cannot be confident that combination HRT is safe for short-term relief of menopausal symptoms because the increased risk for CHD is apparent within the first year. For those requesting treatment for hot flushes, the benefits and harms of both HRT and alternative therapies should be explained. Individual women can be reassured that the absolute risks associated with short-term HRT use are small; on average, the risk is < 0.1% for either of the main outcomes. For postmenopausal osteoporosis, bisphosphonates should be considered first-line treatment. A substantial drawback to these drugs is their high cost.

Unfortunately, in this study predictors of CVD associated with HRT were not identified. While the results do not necessarily apply to other forms of HRT, proof of safety is lacking. Women currently receiving HRT should review the reasons they take it and discuss continuation with their health care provider.

Julia Lowe, MBChB, MMedSci
John Hunter Hospital
Newcastle, New South Wales, Australia

References

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