Therapeutics

Oestrogen plus progestogen 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.*

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QUESTION: In postmenopausal women, what are the risks and benefits of oestrogen plus progestogen use, particularly with respect to coronary heart disease (CHD) events?

Design
Randomised (allocation concealed*), blinded (clinicians, participants, data collectors, outcome assessors, and monitoring committee),* placebo controlled trial with a mean 5.2 years of follow up.

Setting
40 US clinical centres.

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 haematocrit or platelet counts. Follow up was 96.5%.

Intervention
Women were allocated to 1 daily tablet of conjugated equine oestrogen, 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 (non-fatal 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 of follow up. Women who received oestrogen plus progestogen had more total cardiovascular disease than did women who received placebo, including CHD (mainly non-fatal 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, oestrogen plus progestogen use increased the risk for cardiovascular disease, particularly coronary heart disease events.

*See glossary.

COMMENTARY

Since the publication 38 years ago of *Feminine Forever*,[1] the view that menopause (and vascular disease in women) is a disease of oestrogen 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 embolisms. 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 coronary events, breast cancer, and VTE events is consistent with the results of HERS,[2] re-analyses of epidemiological studies,[3] and a meta-analysis by Miller *et al.*[4] This is more than enough evidence to conclude that long term treatment with oestrogen and progestogen combinations to prevent cardiovascular disease 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 benefit and harm of both HRT and alternative treatments 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 cardiovascular outcomes 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 healthcare provider.

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1 Wilson R. *Feminine forever.* New York: Evans, 1964.
2 Grady D, Herrington D, Bittner V, *et al.* Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and estrogen/progestin replacement study follow-up (HERS II). *JAMA* 2002;**228**:49–57.
3 Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. *Lancet* 1997;**350**:1047–59.
4 Miller J, Chan BK, Nelson HD. Postmenopausal estrogen replacement and risk for venous thromboembolism: a systematic review and meta-analysis for the U.S. Preventive Services Task Force. *Ann Intern Med* 2002 May 7;**136**:680–90.

Oestrogen plus progestogen (Est + Prog) v placebo for postmenopausal women†

	Event rates per patient year			
Unfavourable outcomes	**Est + Prog**	**Placebo**	**RRI (95% CI)**	**NNH (CI)**
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)
Favourable 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.