

HRT did not reduce coronary events in postmenopausal women with existing heart disease

Hulley S, Grady D, Bush T, et al, for the Heart and Estrogen/progestin Replacement Study (HERS) Research Group. **Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women.** *JAMA* 1998 Aug 19;280:605-13.

Question

Can oestrogen plus progestin prevent recurrent non-fatal myocardial infarction (MI) and coronary heart disease (CHD) mortality in postmenopausal women with established CHD?

Design

Randomised, double blind, placebo controlled trial with mean follow up of 4.1 years (Heart and Estrogen/progestin Replacement Study [HERS]).

Setting

20 outpatient and community settings in the US.

Patients

2763 postmenopausal women between 44 and 79 years of age (mean age 67 y, 89% white) with established CHD who had not had a hysterectomy. Exclusion criteria were CHD event \leq 6 months before study; sex hormone use \leq 3 months before study; history of breast cancer, deep vein thrombosis, pulmonary embolism, hyperplasia, or endometrial cancer; abnormal mammogram or Papanicolaou test; increased serum triglyceride or serum aspartate aminotransferase concentrations; geographic inaccessibility; other fatal disease; congestive heart failure; alcoholism or drug abuse; uncontrolled hypertension or diabetes; participation in another study; $<$ 80% compliance with prestudy placebo; or intolerance to hormone therapy. Follow up was 100%.

Intervention

1380 women were allocated to 1 tablet (conjugated equine oestrogens, 0.625 mg, and medroxyprogesterone acetate, 2.5 mg), once/day; and 1383 women to placebo.

Main outcome measures

Primary outcome was the combined rate of non-fatal MI and CHD mortality. Secondary cardiovascular outcomes included plasma lipids, other cardiac events, and gallbladder disease. All cause and cancer mortality, and adverse events were also assessed.

Main results

Analysis was by intention to treat. The combined rate of non-fatal MI and CHD mortality did not differ for women who received hormones (12.5%) and those who received placebo (12.7%), (relative hazard [RH] 0.99, 95% CI 0.80 to 1.22). Similarly, rates of non-fatal MI, CHD mortality, secondary cardiovascular outcomes, cancer mortality, and all cause mortality did not differ between groups. At 1 year, women who received hormones had a greater decrease in mean low density lipoprotein cholesterol concentrations, a greater increase in mean high density lipoprotein cholesterol concentrations, and a greater increase in mean triglyceride concentrations ($p < 0.001$ for all). These changes were not associated with subsequent primary CHD events. Women who received hormones had higher rates of venous thromboembolic events (34 v 12; RH 2.89, CI 1.50 to 5.58) and gallbladder disease (84 v 62; RH 1.38, CI 1.00 to 1.92).

Conclusion

Oestrogen plus progestin did not reduce non-fatal myocardial infarction and coronary heart disease mortality in postmenopausal women with established coronary disease.

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A modified version of this abstract appears in ACP Journal Club.

Commentary

Evidence from observational studies has suggested the use of oestrogen alone, and oestrogen and progestin therapy (hormone replacement therapy, [HRT]) for postmenopausal women with CHD on the basis of a potential risk reduction in the order of 40% for recurrent events.^{1,2}

The HERS is the first large scale, randomised controlled trial in which the effects of HRT on CHD mortality and morbidity have been examined in postmenopausal women with established CHD. The findings of no difference in CHD mortality and non-fatal cardiac events, and increases in venous thrombosis among patients in the treated group have led to much discussion in the cardiovascular community.

Past observational studies may have been hampered by selection bias. For example, women who choose to use HRT may already be proactive in managing

their health through other behaviours such as exercise and diet, and positive outcomes may have been confounded by this bias.

The increase in venous thrombosis in the treated group is an important secondary outcome. Progestins may offset some of the beneficial effects of oestrogen on lipids. Some evidence exists that different progestin preparations give different levels of risk and benefit. A different preparation than the one used in the HERS may lead to different rates of thrombosis. None the less, the procoagulant effect of these hormones would be greatest in women who are treated because of other existing thrombosis risk factors.

The HERS was rigorously conducted with careful follow up. A longer follow up period would have helped to clarify the observed pattern of early harm and later benefit associated with HRT. The findings

do not suggest that women who have used HRT for many years need to stop taking it. The HERS conclusions apply to women with heart disease and we do not know whether they generalise to healthy women for whom there is no clinical trial evidence of the effect of HRT on CHD events. The decision to use HRT is an individual one and should be made by women in partnership with their healthcare professionals. Furthermore, this decision should be made in light of considerations beyond CHD, such as osteoporosis and menopausal symptoms.

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1 Newton KM, LaCroix AZ, McKnight B, et al. *Am J Epidemiol* 1997;145:269-77.

2 Sullivan JM, El-Zeky F, Vander Zwaag R, et al. *Am J Cardiol* 1997;79:847-50.