

Estrogen plus progestin did not reduce the risk for coronary heart disease in postmenopausal women

Manson JE, Hsia J, Johnson KC, et al. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med.* 2002;347:523-34.

QUESTION

In postmenopausal women, does estrogen plus progestin decrease or increase the risk for coronary heart disease (CHD)?

DESIGN

Randomized {(allocation concealed*), blinded (clinicians, participants, data collectors, outcome assessors, and monitoring committee),*}† placebo-controlled trial with mean 5.6-year follow-up (Women's Health Initiative [WHI]).

SETTING

{40 U.S. clinical centers}†.

PATIENTS

16 608 postmenopausal women who were 50 to 79 years of age (mean age 63 y), had an intact uterus, and had resided in the same geographic area for ≥ 3 years. Follow-up was 94%.

INTERVENTION

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

MAIN OUTCOME MEASURES

CHD (defined as acute myocardial infarction [MI] needing overnight hospitalization [diagnosed according to standardized criteria

including cardiac pain, cardiac enzyme and troponin levels, and electrocardiographic readings]; death caused by CHD [death consistent with an underlying cause of CHD plus ≥ 1 of hospitalization for MI within 28 d before death, previous angina or MI, death caused by a procedure related to CHD, or a death certificate consistent with an underlying cause of CHD]; or silent MI diagnosed by change in electrocardiographic readings from baseline to follow-up at 3 and 6 y). Secondary outcomes included coronary revascularization, angina, and congestive heart failure.

MAIN RESULTS

Analysis was by intention to treat. Patients who received estrogen plus progestin had a greater risk for CHD during the first year (hazard ratio 1.81, 95% CI 1.09 to 3.01).

The groups did not differ for CHD risk by the end of follow-up or for any other CHD outcomes (Table).

CONCLUSIONS

Postmenopausal women were at increased risk for coronary heart disease (CHD) during the first year of estrogen plus progestin hormone therapy. Risk for CHD was not reduced during longer follow-up.

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*See Glossary.

†Rossouw JE, Anderson GL, Prentice RL, et al. *JAMA.* 2002;288:321-33.

Estrogen plus progestin vs placebo for incidence of coronary heart disease (CHD) in postmenopausal women at mean 5.6 years†

Outcomes	Annualized percentage developing CHD		Adjusted hazard ratio (95% CI)
	Estrogen plus progestin	Placebo	
All CHD	0.39%	0.33%	1.24 (0.97 to 1.60)
Nonfatal MI (including silent MI)	0.31%	0.25%	1.28 (0.96 to 1.70)
Nonfatal MI (excluding silent MI)	0.31%	0.24%	1.30 (0.97 to 1.74)
Death caused by CHD	0.08%	0.08%	1.10 (0.65 to 1.89)

‡MI = myocardial infarction. CI defined in Glossary. Hazard ratio adjusted for the presence or absence of previous coronary revascularization and sequential monitoring.

COMMENTARY

The study by Manson and colleagues updates previous WHI data and provides information on additional clinical endpoints. Although CHD rates were higher in women who received hormone therapy (HT) than in women who received placebo, the conservative 95% CIs for CHD and other outcomes each overlapped 1 after adjustment for sequential monitoring and multiple outcomes. In addition, coronary risk factor status was not significantly associated with the risk for CHD for those taking HT. The high rate of discontinuation of HT (42%) and placebo (38%) suggests that the adverse effects of HT may have been underestimated.

Why do this and other randomized trials contradict previous observational studies, which showed a benefit of HT for CHD? Menopausal women who choose to take HT are more likely to be well-educated and have lower cardiovascular risk (e.g., lower blood pressure, weight, glucose, and cholesterol) than women who are not taking estrogen (1, 2). Because of baseline differences between users and nonusers of HT, randomization in the WHI study revealed the potential for an increase in CHD risk attributable to HT that was not apparent in observational studies. As the investigators point out, differences in age and years since menopause, as well as methodological limitations of observational stud-

ies, may have perpetuated incorrect impressions. The hypothesis that the timing of HT in these women was too late to halt an already-irreversible atherosclerotic process seems unlikely.

Several important questions remain. Will we find a way to predict which HT users will have increased CHD risk? What are the risks and benefits for women with current menopause symptoms (which was not the focus of WHI)? Considering the current state of evidence, clinicians cannot use coronary risk factor status to predict CHD risk associated with HT use and should integrate the possibility of adverse cardiovascular consequences (although uncommon) into their counseling for women who are starting HT.

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References

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2. Barrett-Connor E. Postmenopausal estrogen and prevention bias. *Ann Intern Med.* 1991;115:455-6.