

# Oestrogen plus progestogen did not reduce the risk of 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;**349**:523–34.

Clinical impact ratings GP/FP/Primary care ★★★★★☆☆ IM/Ambulatory care ★★★★★☆☆ Endocrine ★★★★★☆☆ Cardiology ★★★★★☆☆

## Q In postmenopausal women, how does oestrogen plus progestogen influence the risk of coronary heart disease (CHD)?

### METHODS

	<b>Design:</b> randomised placebo controlled trial.
	<b>Allocation:</b> {concealed}*.†
	<b>Blinding:</b> blinded (clinicians, participants, data collectors, outcome assessors, and monitoring committee).†
	<b>Follow up period:</b> 5.6 years (Women's Health Initiative [WHI]).
	<b>Setting:</b> {40 US clinical centres}*.
	<b>Patients:</b> 16 608 postmenopausal women who were 50–79 years of age (mean age 63 y), had an intact uterus, and resided in the same geographic area for ≥3 years.
	<b>Interventions:</b> patients were allocated to oral conjugated equine oestrogen, 0.625 mg/day, plus medroxyprogesterone acetate, 2.5 mg/day (n=8506), or placebo (n=8102).
	<b>Outcomes:</b> CHD (ie, acute myocardial infarction [MI] requiring overnight hospital admission; death caused by CHD; or silent MI. Secondary outcomes: coronary revascularisation, angina, and congestive heart failure.
	<b>Patient follow up:</b> 94%.
	*Writing Group for the Women's Health Initiative Investigators. <i>JAMA</i> . 2002;288:321-33. †See glossary.

### MAIN RESULTS

Analysis was by intention to treat. Patients who received oestrogen plus progestogen had a greater risk of 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 of coronary heart disease (CHD) during the first year of hormone therapy. Risk of CHD was not reduced during longer follow up.

*Abstract and commentary also appear in ACP Journal Club.*

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### Commentary

The study by Manson *et al* 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 of 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 does this and other randomised 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 (eg, lower blood pressure, weight, glucose, and cholesterol) than women who are not taking oestrogen.<sup>1 2</sup> Because of baseline differences between users and non-users of HT, randomisation 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 studies, may have perpetuated incorrect impressions. The hypothesis that the timing of HT in these women was too late to halt an already irrevocable 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 counselling for women who are starting HT.

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1 Barrett-Connor E, Wingard DL, Criqui MH. *JAMA* 1989;**261**:2095–100.  
2 Barrett-Connor E. *Ann Intern Med* 1991;**115**:455–6.

### Oestrogen plus progestogen v placebo (HT) for incidence of coronary heart disease (CHD) in postmenopausal women at mean 5.6 years\*

Outcomes	Annualised percentage developing CHD		Adjusted hazard ratio (95% CI)
	HT	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 revascularisation and sequential monitoring.