Oestrogen plus progestin was not effective for long term secondary prevention of coronary heart disease in postmenopausal women


QUESTION: In postmenopausal women with established coronary heart disease (CHD), does oestrogen plus progestin reduce the risks of CHD events after 6.8 years of follow up?

Design
Randomised (allocation concealed*), placebo controlled trial. The study was blinded (patients, investigators, and outcome assessors)* for the initial mean 4.1 years of follow up and unblinded* for the subsequent 2.7 years of follow up (the latter 2.7 years was the HERS II study).

Setting
20 US outpatient and community centres.

Patients
2763 postmenopausal women < 80 years of age (mean age 67 y) with established CHD who had not had a hysterectomy. Of those alive at 4.1 years (n=2510), follow up was 84% at 6.8 years.

Intervention
Women were allocated to conjugated oestrogen, 0.625 mg/day, plus medroxyprogesterone acetate, 2.5 mg/day (n=1380), or placebo (n=1383) for 4.1 years. In the subsequent 2.7 years (during HERS II), 1156 women in the oestrogen plus progestin group and 1165 women in the placebo group continued follow up, and open label hormone therapy was prescribed at the discretion of the women’s personal physicians.

Main outcome measures
The main outcome was the composite end point of CHD death or nonfatal myocardial infarction (MI). Secondary outcomes included coronary artery bypass graft surgery, percutaneous coronary revascularisation, hospital admission for unstable angina or congestive heart failure, nonfatal ventricular arrhythmia, sudden death, stroke or transient ischaemic attack, and peripheral arterial disease.

Main results
Analysis was by intention to treat. The composite end point rate of CHD death or nonfatal MI did not differ between groups after mean follow up durations of 4.1 years, between 4.1 and 6.8 years, or at 6.8 years (table). Rates of CHD death, nonfatal MI, and secondary cardiovascular outcomes also did not differ between groups (p ≥ 0.27).

Conclusion
In postmenopausal women with established coronary heart disease, oestrogen plus progestin did not reduce the risk of coronary heart disease events after 6.8 years of follow up.

*See glossary.

COMMENTARY
The saga of hormone replacement therapy (HRT) offers a valuable lesson in the importance of clinical trials in guiding practice. The first publication of the HERS trial in 1998,6 which showed no benefit of oestrogen plus progestin in women with pre-existing CHD, was the first to challenge the assumption that HRT could reduce CHD. The hope that beneficial effects of HRT would emerge with longer follow up was effectively dispelled by the additional 2.7 years of follow up.

The HERS follow up provides additional support to the WHI conclusions about the non-coronary effects of oestrogen and progestin. Although some effects were not significant in the smaller HERS trial, both studies reported similar increases in thromboembolism, breast cancer, and stroke and decreases in colorectal cancer with HRT. Coronary events were increased in WHI but not in HERS. Although HRT did not reduce hip fractures in HERS, the number of events was small and the results are compatible with the one third reduction in hip fractures seen in the larger WHI. Taken together, HERS and WHI suggest that over 5–7 years, the harms of oestrogen and progestin, although modest for an individual woman, exceed the benefits of preventing fracture and colorectal cancer. Whether different HRT regimens are any better is not known.

In an ongoing WHI study of oestrogen alone in women with a hysterectomy, investigators have reported that neither clear benefit nor harm has yet emerged. Although no statistically significant increase in breast cancer has yet been observed, an early small increase in CHD events was seen with unsupported oestrogen.7

Commentary continued on next page
Long term oestrogen plus progestin increased venous thromboembolism and biliary tract surgery in postmenopausal women


QUESTION: In postmenopausal women with established coronary heart disease (CHD), what is the effect of oestrogen plus progestin on the risks of common noncardiovascular disease outcomes after 6.8 years of follow up?

Design
Randomised (allocation concealed*), placebo controlled trial. The study was blinded (patients, investigators, and outcome assessors*) for the mean 4.1 years of follow up and unblinded* for the subsequent mean 2.7 years of follow up (the latter 2.7 years was the HERS II study).

Setting
20 US outpatient and community centres.

Patients
2763 postmenopausal women < 80 years of age (mean age 67 y) with established CHD who had not had a hysterectomy. Exclusion criteria included deep venous thrombosis, pulmonary embolism, breast cancer, endometrial hyperplasia or cancer, abnormal Papanicolaou result, hormone use in the previous 3 months, and life threatening disease. Of those alive at 4.1 years, (n=2510), follow up was 84% at 6.8 years.

Intervention
Women were allocated to conjugated oestrogen, 0.625 mg/day, plus medroxyprogesterone acetate, 2.5 mg/day (Oest + Prog) or placebo (n=1383 for 4.1 years. In the subsequent 2.7 years (during HERS II), 1156 women in the oestrogen plus progestin group and 1165 women in the placebo group continued follow up, and open label hormone therapy was prescribed at the discretion of the women’s personal physicians.

Main outcome measures
Venous thromboembolism, biliary tract surgery, cancer, fractures, and mortality.

Main results
Analysis was by intention to treat. At 6.8 years, women who received oestrogen plus progestin had increased risks of venous thromboembolism and biliary tract surgery (table). Rates of cancer, fractures, and total mortality did not differ between groups (table).

Conclusion
In postmenopausal women with established coronary heart disease, treatment for 6.8 years with oestrogen plus progestin increased the risks of venous thromboembolism and biliary tract surgery.

*See glossary.

Effects of oestrogen plus progestin (Oest + Prog) v placebo on non-cardiovascular disease outcomes in postmenopausal women with coronary heart disease at 6.8 years†

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Oest + Prog</th>
<th>Placebo</th>
<th>Adjusted relative hazard (95% CI)‡</th>
<th>NNH (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous thromboembolism</td>
<td>5.9</td>
<td>2.8</td>
<td>2.06 (1.26 to 3.36)</td>
<td>65 (35 to 187)</td>
</tr>
<tr>
<td>Biliary tract surgery</td>
<td>19.1</td>
<td>12.9</td>
<td>1.44 (1.10 to 1.90)</td>
<td>32 (19 to 107)</td>
</tr>
<tr>
<td>Any cancer</td>
<td>19.7</td>
<td>16.5</td>
<td>1.19 (0.95 to 1.50)</td>
<td>Not significant</td>
</tr>
<tr>
<td>Any fracture</td>
<td>28.7</td>
<td>28.4</td>
<td>1.07 (0.89 to 1.29)</td>
<td>Not significant</td>
</tr>
<tr>
<td>Total mortality</td>
<td>30.6</td>
<td>27.8</td>
<td>1.06 (0.91 to 1.29)</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

Abbreviations defined in glossary; NNH and CI provided by author.

†Relative hazard calculated using a Cox proportional hazards model with intention to treat analyses and adjusted for some demographic and baseline characteristics.

COMMENTARY—continued from previous page

A reasonable consensus is now emerging.4–5 Firstly, HRT should not be prescribed to prevent CHD or used for general “prevention” purposes. Secondly, other alternatives for osteoporosis prevention should be considered and clinicians should be cautious about using HRT for the sole purpose of osteoporosis prevention. Finally, women should be advised of the risks and benefits before taking HRT to relieve menopausal symptoms. Although women may decide that the risks are worth relief of troublesome symptoms, they should use the lowest effective dose for the shortest time possible.

David Atkins, MD, MPH
Agency for Healthcare Research and Quality
Rockville, Maryland, USA


*See glossary.