Note: This is a two-article spread with a shared commentary. Please scroll down for the second article.

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

Grady D, Herrington D, Bittner V, et al., for the HERS Research Group. **Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II).** JAMA. 2002;288:49-57.

QUESTION

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

DESIGN

Randomized (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 mean 2.7 years of follow-up (the latter 2.7 years was the HERS II study).

SETTING

20 U.S. outpatient and community centers.

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 estrogen, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d (n = 1380), or placebo (n = 1383) for 4.1 years. In the subsequent 2.7 years (during HERS II), 1156 women in the estrogen-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 revascularization, hospitalization for unstable angina or congestive heart failure, nonfatal ventricular arrhythmia, sudden death, stroke or transient ischemic 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 ($P \geq 0.27$).

CONCLUSION

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

Source of funding: Wyeth-Ayerst Research.

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*See Glossary.

Estrogen plus progestin (Est + Prog) vs placebo for the composite end point of coronary heart disease (CHD) death or nonfatal myocardial infarction in postmenopausal women with CHD†

Follow-up	Events/1000 person-y		Adjusted relative hazard (95% CI)‡	NNT
	EST + Prog	Placebo		
4.1 y	34.0	34.3	0.96 (0.78 to 1.18)	Not significant
4.1 to 6.8 y	41.8	42.1	0.98 (0.75 to 1.22)	Not significant
6.8 y	36.6	36.8	0.97 (0.82 to 1.14)	Not significant

†Abbreviations defined in Glossary.
‡Relative hazard calculated using a Cox proportional hazards model with intention-to-treat analyses and adjusted for some demographic and baseline characteristics.

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 (1), which showed no benefit of estrogen plus progestin in women with preexisting 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 to HERS, which also showed no benefit. The last hope, that preventive effects of HRT would be clearer in healthy women, was diminished this summer by the Women's Health Initiative (WHI)—the same HRT regimen caused more harm than benefit in healthy women (2).

The HERS follow-up provides additional support to the WHI conclusions about the noncoronary effects of estrogen 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 to 7 years, the harms of estrogen and progestin, although modest for an individual woman, exceed the benefits of preventing fracture and colorectal cancer. Whether different HRT regimens are any better, or whether the balance of benefits and risks is more favorable for any subgroup of women, is not known.

In an ongoing WHI study of estrogen 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 unopposed estrogen (3).

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Long-term estrogen-plus-progestin increased venous thromboembolism and biliary tract surgery in postmenopausal women

Hulley S, Furberg C, Barrett-Connor E, et al., for the HERS Research Group. **Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II).** JAMA. 2002;288:58-66.

QUESTION

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

DESIGN

Randomized (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 mean 2.7 years of follow-up (the latter 2.7 years was the HERS II study).

SETTING

20 U.S. outpatient and community centers.

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 estrogen, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d (n = 1380), or placebo (n = 1383) for 4.1 years. In the subsequent 2.7 years (during HERS II), 1156 women in the estrogen-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 estrogen plus progestin had increased risks for venous thromboembolism and biliary tract surger (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 estrogen plus progestin increased the risks for venous thromboembolism and biliary tract surgery.

Source of funding: Wyeth-Ayerst Research.

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*See Glossary.

Effects of estrogen plus progestin (Est + Prog) vs placebo on noncardiovascular disease outcomes in postmenopausal women with coronary heart disease at 6.8 years†

Outcomes	Events/1000 person-y		Adjusted relative hazard (95% CI)‡	NNH (CI)
	Est + Prog	Placebo		
Venous thromboembolism	5.9	2.8	2.06 (1.26 to 3.36)	65 (35 to 187)
Biliary tract surgery	19.1	12.9	1.44 (1.10 to 1.90)	32 (19 to 107)
Any cancer	19.7	16.5	1.19 (0.95 to 1.50)	Not significant
Any fracture	29.7	28.4	1.07 (0.89 to 1.29)	Not significant
Total mortality	30.6	27.8	1.08 (0.91 to 1.29)	Not significant

†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 page 6)*

A reasonable consensus is now emerging (4, 5). First, HRT should not be prescribed to prevent CHD or used for general "prevention" purposes. Second, 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.

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References

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