Postmenopausal Hormone Treatment

SUMMARY OF THE ORIGINAL ARTICLE

Randomized Trial of Estrogen Plus Progestin for Secondary Prevention of Coronary Heart Disease in Postmenopausal Women

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Context: Observational studies have found lower rates of coronary heart disease (CHD) in postmenopausal women who take estrogen than in women who do not, but this potential benefit has not been confirmed in clinical trials.
Objective: To determine if estrogen plus progestin therapy alters the risk for CHD events in postmenopausal women with established coronary disease.
Design: Randomized, blinded, placebo-controlled secondary prevention trial.
Setting: Outpatient and community settings at 20 US clinical centers.
Participants: A total of 2763 women with coronary disease, younger than 80 years, and postmenopausal with an intact uterus. Mean age was 66.7 years.
Intervention: Either 0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate in 1 tablet daily (n=1380) or a placebo of identical appearance (n=1383). Follow-up averaged 4.1 years; 82% of those assigned to hormone treatment were taking it at the end of 1 year, and 75% at the end of 3 years.
Main Outcome Measures: The primary outcome was the occurrence of nonfatal myocardial infarction (MI) or CHD death. Secondary cardiovascular outcomes included coronary revascularization, unstable angina, congestive heart failure, resuscitated cardiac arrest, stroke or transient ischemic attack, and peripheral arterial disease. All-cause mortality was also considered.
Results: Overall, there were no significant differences between groups in the primary outcome or in any of the secondary cardiovascular outcomes: 172 women in the hormone group and 176 women in the placebo group had MI or CHD death (relative hazard [RH], 0.99; 95% confidence interval [CI], 0.80-1.22). The lack of an overall effect occurred despite a net 11% lower low-density lipoprotein cholesterol level and 10% higher high-density lipoprotein cholesterol level in the hormone group compared with the placebo group (each $P<.001$). Within the overall null effect, there was a statistically significant time trend, with more CHD events in the hormone group than in the placebo group in year 1 and fewer in years 4 and 5. More women in the hormone group than in the placebo group experienced venous thromboembolic events (34 vs 12; RH, 2.89; 95% CI, 1.50-5.58) and gallbladder disease (84 vs 62; RH, 1.38; 95% CI, 1.00-1.92). There were no significant differences in several other end points for which power was limited, including fracture, cancer, and total mortality (131 vs 123 deaths; RH, 1.08; 95% CI, 0.84-1.38).
Conclusions: During an average follow-up of 4.1 years, treatment with oral conjugated equine estrogen plus medroxyprogesterone acetate did not reduce the overall rate of CHD events in postmenopausal women with established coronary disease. The treatment did increase the rate of thromboembolic events and gallbladder disease. Based on the finding of no overall cardiovascular benefit and a pattern of early increase in risk of CHD events, we do not recommend starting this treatment for the purpose of secondary prevention of CHD. However, given the favorable pattern of CHD events after several years of therapy, it could be appropriate for women already receiving this treatment to continue.

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Commentary by Stephen Hulley, MD, MPH, and Deborah Grady, MD, MPH

When the HERS report[1] was published in *JAMA* in 1998, the most widely prescribed drug in the United States was Premarin, conjugated equine estrogens (CEE) extracted from the urine of pregnant mares. The popularity of this drug was based in part on its historic role in the treatment of menopause-related vasomotor symptoms (Premarin was approved for treatment of hot flashes by the US Food and Drug Administration [FDA] in 1942) and in part on a philosophy popularized by an influential book entitled *Feminine Forever*, which asserted that "menopause is a hormone deficiency and totally preventable."[2] Enthusiasm for post-

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menopausal estrogen therapy waned in the 1970s with the recognition that estrogen substantially increased the risk for uterine cancer, but resumed in the next 2 decades when adding a progestin to the estrogen therapy was found to obviate this risk.

A major stimulus for the popularity of CEE was the growing evidence that in addition to relieving menopausal symptoms, "replacing" the natural hormone that had gone missing might prevent coronary heart disease (CHD). Animal studies suggested that estrogen slowed rates of atherogenesis; epidemiologic studies found a lower risk of CHD among middle-aged women compared with men and among CEE users compared with nonusers; and small-scale trials showed that CEE decreased low-density lipoprotein cholesterol levels, increased high-density lipoprotein cholesterol levels, and improved endothelial function. Although it was recognized that progestins could oppose some effects of estrogen, medroxyprogesterone acetate (MPA) seemed to preserve most of the favorable effects of CEE in epidemiologic, surrogate outcome, and animal studies. By the early 1990s CEE + MPA had become the most commonly used combination hormone therapy for US women, in part in the belief that the therapy reduced CHD risk. But a full-scale trial with CHD events as the outcome had never been done.

When we began planning HERS in the early 1990s, some experts held that a CHD event trial was not needed and might even be unethical, given the epidemiologic, animal, and surrogate outcome evidence and practice guidelines[3] that supported CEE as a treatment to reduce risk of CHD in postmenopausal women. HERS investigators, motivated by the growing emphasis on evidence-based medicine, wanted a trial to assess the CHD risk reduction and to explore possible harms such as increased risk of breast cancer and thromboembolism. In addition, Wyeth, the maker of Premarin and Prempro (a single tablet containing CEE+MPA), wanted a trial to obtain FDA approval to expand the indication from treatment of vasomotor symptoms to include prevention of CHD. When the National Institutes of Health (NIH) refused to allow us to resubmit our investigator-initiated application for funding because planning was beginning on a similar trial in the NIH-funded Women's Health Initiative (WHI), Wyeth agreed to fund HERS. The contract specified that outcome data, analyses, and publications would be controlled by the coordinating center at the University of California, San Francisco.

When the HERS findings were published, the predominant reaction to the early increase of CHD and absence of overall benefit despite favorable lipid response was disbelief. Many reasons were proposed to discredit the HERS findings—a longer study would have revealed lower rates of CHD in treated women, hormone treatment would have worked if estrogen alone or a different estrogen/progestin combination had been used, or if women who did not already have coronary disease or younger women had been studied. The belief that estrogen improved the health of postmenopausal women remained strongly held, HERS was largely ignored by the lay press, and there were no appreciable changes in practice guidelines or in hormone sales. Yet there was an undercurrent of intense interest on the part of the scientific community, and the 1998 HERS report became one of the most cited articles in medicine.

The other shoe dropped 4 years later with the arrival of a wealth of new evidence. First, HERS investigators reported no reduction in CHD event rates in hormone-treated women after an additional 3 years of follow-up[4] and a continuing adverse trend for breast cancer. More importantly, results of the Women's Health Initiative CEE + MPA trial were published.[5] This trial used the same design, treatment, and outcome as HERS, but in a primary prevention cohort of 16 608 women free of coronary disease at the outset. The much larger size (because of the lower rate of primary CHD outcomes in this population) provided more power for detecting other outcomes, and the findings were conclusive. CEE + MPA significantly increased the rates of CHD, stroke, pulmonary embolism, and breast cancer. These risks outweighed the reduced rates of colon cancer and fractures, especially when risk of dementia was also shown to increase among hormone-treated women at least 65 years old at the start of the trial.[6] Two years later results of a second WHI trial that examined the effects of CEE alone among 10 739 women with hysterectomy were published. The findings were less adverse: rates of stroke and mild cognitive impairment or dementia increased significantly in the hormone-treated group while CHD and breast cancer incidence decreased, although not statistically significantly.[7,8]

Comparing the findings in the 3 trials,[9] the decision in the 1980s to add MPA to CEE when treating women with a uterus turned out to have unforeseen consequences: CEE + MPA appears to be more harmful than CEE alone. However, both regimens have important adverse effects, including increased rates of stroke, venous thromboembolism, and dementia or cognitive impairment. A residual loose end stems from the fact that the average age of women at enrollment for all 3 trials was the mid-60s, whereas the majority of women who use hormone therapy for treatment of vasomotor symptoms are in their early 50s. Hormone therapy among women aged 50 through 59 years in the WHI trials tended to have more favorable effects on CHD rates than in older women,[10] but even if this finding is confirmed, the concerns about increased risk of stroke, venous thromboembolism, and breast or endometrial cancer remain.

The absolute magnitude of the increased risk in these trials is small, but the harms are substantial for a treatment given to healthy women. The consequence was an FDA boxed warning recommending that estrogen preparations not be used to prevent CHD or considered first-line therapy for preventing osteoporosis. Revised practice guidelines recommended that postmenopausal hormone therapy still be used for treatment of bothersome menopausal symptoms, but at

the lowest dose and for the shortest possible time. In the next several years, many women who had been taking postmenopausal hormones stopped using them and the number receiving hormone prescriptions (which had held steady at about 15 million since the late 1990s, with about one-third of users being older than 60 years) decreased by half between 2002 and 2003.[11]

Research in recent years has studied other preparations for managing menopausal symptoms. Observational studies have suggested that transdermal estradiol avoids the increase in thromboembolism associated with oral estrogens,[12] and that reducing the dose markedly can still relieve menopausal symptoms[13] and prevent bone loss.[14] These strategies may also reduce the adverse effects on cardiovascular disease events and breast cancer incidence, but this remains to be demonstrated. Use of selective estrogen receptor β-agonists for menopausal symptoms is under investigation, as are nonhormonal treatments ranging from selective serotonin reuptake inhibitors to herbal remedies to yoga. Meanwhile, a gratifying possible consequence of the HERS and WHI trials has been the observation that the marked decrease in use of postmenopausal hormone therapy that began in 2002 is associated with a decline in the incidence of estrogen receptor–positive breast cancer rates among women older than 50 years in the United States.[15]

In conclusion, the story of HERS and WHI is an excellent illustration of the evidence-based medicine tenet that practice guidelines should be based on rigorously designed research—preferably 2 or more randomized blinded trials with disease end points—even if consistent observational and mechanistic evidence suggests that such trials are not needed. Animal studies and clinical trials of surrogate outcomes can be misleading, and epidemiologic studies of preventive treatments are particularly susceptible to confounding because healthier individuals are more likely to seek and adhere to preventive measures. Weighing benefits and harms is especially important when considering the use of preventive interventions in healthy individuals, in whom there is a special obligation to do no harm.

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