

Guest Editorial

Anticipating HERS: Questions from the Heart and Estrogen/Progestin Replacement Study

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OF ALL THE PURPORTED BENEFITS of long-term postmenopausal hormone replacement therapy (HRT), the promise of a reduction in women's risk of coronary heart disease (CHD) and death is the most significant because CHD is the single most common cause of death in women, ultimately accounting for more than half of all deaths. The considerable enthusiasm for the thesis that estrogen prevents heart disease is based on the consistency of results from observational studies. A recent meta-analysis of more than 30 observational studies¹ found a summary 35% reduction in cardiac events and deaths in women prescribed estrogen, and a retrospective analysis by Sullivan et al.² suggested that women who already have CHD may derive an even greater benefit from estrogen replacement (up to an 89% risk reduction). Multiple biologically plausible mechanisms for a cardioprotective effect of estrogen have been reported.³

Despite these tantalizing statistics, the premise that estrogen prevents heart disease has not yet been proven in a randomized clinical trial in women. Bias in prescribing practices of estrogen may spuriously increase or explain the apparent benefits shown in observational studies.¹ Healthier, more educated, and wealthier women, who tend actively to plan and maintain a healthy lifestyle, are more likely to be prescribed estrogen and are prob-

ably more likely to take their pills. It is important to know whether and how well HRT protects against CHD because there are some inherent risks associated with long-term use of HRT, including the risk of breast cancer.⁴

Although CHD is the most common cause of death in women, event rates in women <80 years of age are nevertheless low enough that very large numbers of healthy women would need to be studied to determine if HRT is cardioprotective. Because women who already have heart disease have a 3-fold to 5-fold increased risk of another cardiac event, a secondary prevention study requires many fewer women. The possibility of testing the estrogen-heart disease hypothesis in a relatively small number of women formed the rationale for the Heart and Estrogen/Progestin Replacement Study (HERS), a \$40 million, 5-year, double-blind, randomized, placebo-controlled trial of HRT in women with known CHD. The primary outcome is new CHD events (myocardial infarction and death arising from CHD). The sample size was calculated to be 2340 women, based on an expected new CHD event rate of 5% per year in the placebo group. The HERS was designed by Steven B. Hulley, M.D., M.P.H., at the University of California, San Francisco, and funded by Wyeth-Ayerst (Philadelphia, PA).

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Authors' note: This editorial was written before the long-anticipated HERS results to prepare the reader for the inevitable discussion that will follow publication of the HERS findings. Neither of the authors of this editorial knows the outcome of HERS, although both are HERS investigators.

to October 1994, 2763 women with documented CHD and an intact uterus were enrolled in 20 different centers throughout the United States. Women were randomized to placebo or continuous daily oral HRT, conjugated equine estrogens (CEE) 0.625 mg with medroxyprogesterone acetate (MPA) 2.5 mg. They were evaluated every 4 months for 4–5 years with annual physical examinations, electrocardiograms (ECGs), and safety monitoring.

Event reporting included any overnight hospitalization. Hospital discharge summaries, ECGs, cardiac enzyme levels, and code assignments (following the International Classification Disease, 9th rev. ed. [ICD]) were incorporated into event packets, which were used by an independent committee to adjudicate outcome. A Data and Safety Monitoring Board regularly reviewed the progress of the study and any adverse events over the course of the study. The HERS closeout is proceeding according to schedule, and the last HERS subject will be seen for her last visit in June 1998. Publication of the results is expected in August 1998.

We consider here what answers will or will not be provided by HERS, assuming cardio-protection is or is not shown.

IF HERS RESULTS ARE POSITIVE

If the HERS shows that women assigned to HRT had fewer new cardiac events than women assigned to placebo, the estrogen-heart disease hypothesis will be proved for the first time (although some purists may argue that a single trial cannot prove a hypothesis). This finding would be a groundbreaking achievement, with a potential impact comparable to that of the results of the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), published in 1984, which proved the cholesterol-heart disease hypothesis by showing that lowering cholesterol (with medication) could prevent heart attacks in middle-aged men.⁵

Positive results in the HERS will also raise the inevitable questions about generalizability: Should high-risk women without heart disease be treated? Should all women be treated, as

heart disease is the most common cause of death in women? Should men be treated? Clearly, HERS cannot answer these questions.

Like most trials of lipid-lowering medications, positive HERS results will also raise issues of safety. The Scandinavian Simvastatin Survival Study (4S)⁶ was actually the first trial of lipid-lowering medication unclouded by an unexpected excess risk of one or more noncardiovascular conditions. The 4S showed an overall reduction in death, not just cardiovascular disease—an important risk-benefit ratio consideration. The HERS was not designed to examine all-cause mortality or an excess risk of even relatively common diseases, such as breast cancer.¹ The study was, however, large enough to show that HRT increases the risk of venous thromboembolic events,⁷ confirming in a clinical trial an association previously reported only from observational studies.

If the HERS results are positive, much larger trials will be necessary to determine the risk-benefit ratio of HRT in women without known heart disease. The Women's Health Initiative in the United States⁸ and the Medical Research Council Study in the U.K.⁹ each calculated that 25,000–30,000 women are needed for a trial designed to determine if HRT prevents CHD and has a good risk-benefit ratio in healthy women.

Thus, a strongly positive HERS result will prove the estrogen-heart disease hypothesis but probably will not help most patients and physicians decide for or against HRT.

IF HERS RESULTS ARE NEGATIVE

If the HERS shows no significant difference in the rates of new cardiac events in women assigned to HRT versus placebo, it will not necessarily refute the estrogen-heart disease hypothesis. Estrogen may be preventive rather than curative. Estrogen may not work in women who already have heart disease because their atherosclerosis is too far advanced.

The HERS may end up having too few events to observe a statistically significant difference because the sample size may be too small and there may be too few events in the placebo group. Women who enter trials are healthier than women who do not, and compliant

women, even those assigned to placebo, have fewer events than do noncompliant women.¹⁰ In addition, secular trends in awareness about heart disease could have led to a healthier lifestyle or wider use of medical interventions, such as the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA), reductase inhibitors, and angiotensin-converting enzyme inhibitors, which would have reduced new event rates. Finally, primary outcomes may have been reduced by surgical interventions such that there could be a difference in choice of intervention, for example, angioplasty or coronary bypass surgery, but no decrease in fatal or nonfatal cardiac events.

Another possible explanation for a negative result could be that the treatment regimen, CEE plus MPA, was a poor choice. Several lines of evidence suggest that MPA may compromise the estrogen-associated cardiovascular benefit. In the Postmenopausal Estrogen and Progestin Intervention (PEPI) clinical trial,¹¹ women treated with CEE and cyclic or continuous MPA had significantly less elevation of high-density lipoprotein (HDL) and more elevation of glucose than had women treated with CEE alone or CEE plus micronized progesterone. Clinical trials conducted in nonhuman primates showed that cynomolgus monkeys treated with 17 β estradiol and progesterone had significantly reduced coronary plaque size compared with placebo-treated monkeys, but this benefit was reduced or absent in monkeys treated with CEE plus MPA.¹² Further, vasodilation after acetylcholine occurred with estradiol or CEE plus micronized progesterone but less with CEE plus MPA.¹² Thus, the estrogen-heart disease hypothesis could be true but could be obscured by undesirable effects of MPA.

CONCLUSIONS

No matter what the results, the HERS will not remove the need for large clinical trials, such as the Women's Health Initiative now in progress. As with the LRC-CPPT, other studies will follow and with them possible confirmation of the HERS results and, it is hoped, identification of optimal treatment regimens.

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