

The HERS Trial Results: Paradigms Lost?

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The Heart and Estrogen/progestin Replacement Study (HERS) found no overall effect of 4.1 years of therapy with estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. However, within the overall null effect, a 50% increase in cardiovascular events was seen in the first year, followed by fewer events after 2 years of treatment in the hormone therapy group than in the placebo group. Understanding the cause of this pattern of early increase and late reduction in risk is key to interpreting the HERS results and reconciling them with the large number of observational and other studies of the cardiovascular effects of estrogen. There are two possibilities. One is that the HERS regimen of estrogen plus progestin has no effect on risk for heart disease, and the pattern of changing risk over time is simply the result of chance or confounding. The other is that the pattern of early increase and late reduction in risk is due to real but opposing effects of this regimen. Several lines of evidence support each possibility. Attrition of a susceptible cohort of women uniquely at risk for a cardiovascular complication from hormone therapy coupled with a gradually progressive beneficial effect due to lipid lowering and other factors is a promising potential explanation. The HERS results remind us of the need for clinical trials to evaluate both the benefits and risks of new therapies. They also illustrate how much more we need to know about the cardiovascular effects of hormone replacement therapy.

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The Heart and Estrogen/progestin Replacement Study (HERS) showed no overall effect of long-term use of estrogen plus progestin (Prempro, Wyeth-Ayerst Research, Radnor, Pennsylvania) for secondary prevention of coronary heart disease in postmenopausal women. In HERS, the first large clinical trial to examine effects of postmenopausal hormone replacement therapy (HRT) on risk for cardiovascular disease, 2763 women with established coronary disease were randomly assigned to receive daily conjugated equine estrogen plus medroxyprogesterone acetate or to placebo. After a mean of 4.1 years of follow-up, no differences were seen in the primary composite outcome of nonfatal myocardial infarction or death from coronary heart disease (HRT group, 179 events; placebo group, 182 events; relative hazard, 0.99 [95% CI, 0.81 to 1.22]) or any of the secondary clinical cardiovascular outcomes (1, 2).

This null result has shaken a foundation on which recommendations for widespread use of estrogen replacement (3–5) have been built—that estrogen reduces a woman's risk for heart disease. On the basis of the HERS results, such assertions regarding secondary prevention of coronary heart disease can no longer be made with confidence. However, a more detailed analysis of the HERS results reveals that within the overall null effect, risk for coronary heart disease was reduced in years 3 to 5, but this reduction was offset by an unexpected 50% increase in risk during year 1 (Table).

In my view, the key to understanding the HERS trial results—and reconciling them with the vast body of evidence from observational, mechanistic, and animal model studies suggesting a cardioprotective effect of estrogen—rests in the explanation of this pattern of varying risk over time, including the possibility of an increased risk for coronary heart disease early after initiation of therapy. At least two possible explanations exist for the time-trend data in HERS. One is that estrogen plus progestin had no real effect on risk for heart disease, and the observed pattern of changing risk over time was simply the result of chance or confounding. The other is that the pattern of early increase and late reduction in risk for coronary heart disease reflects real and opposing effects of this regimen.

No Real Effect

The hypothesis that the HERS regimen had no real effect on coronary heart disease risk has statistical and biological merits. From a statistical perspective, although the final test for trend in the relative hazards over time had a *P* value of 0.03, this time-trend analysis was not explicitly prespecified; in fact, several analyses of the changing risk over time were performed. Thus, it is possible that the observed time trend was simply a chance result of exploratory data analysis or multiple comparisons. Although the HERS power calculations included a 1-year lag for half of the treatment effect (thereby acknowledging possible varying effects over time), it is not clear that this fact enhances the validity of the time-trend result.

There are also concerns about the validity of the

Table. Outcomes by Treatment Groups and Year Since Randomization in the Heart and Estrogen/progestin Replacement Study*

Outcome	Women with Events Who Received Estrogen plus Progestin	Events per 1000 Woman-Years	Women with Events Who Received Placebo	Events per 1000 Woman-Years	Relative Hazard Ratio (95% CI)	P Value for Trend†
	<i>n</i>		<i>n</i>			
Primary coronary heart disease event‡						
Year 1	57	42.5	38	28.0	1.52 (1.01–2.29)	0.03
Year 2	47	36.9	49	37.8	0.98 (0.66–1.46)	–
Year 3	35	28.7	42	33.9	0.85 (0.54–1.33)	–
Years 4 and 5	40	28.0	53	37.4	0.75 (0.50–1.13)	–

* A more detailed version of this table, as well as updated versions of all the tables from the original Heart and Estrogen/progestin Replacement Study report (1), is available on the World Wide Web at <http://www.epibiostat.ucsf.edu/HERS/> (posted 24 February 1999). This table reflects the final results after inclusion of 13 additional primary events that were not yet adjudicated at the time of the original publication.

† Nominal test for trend in Ln (hazard ratio).

‡ Includes nonfatal myocardial infarction and death from coronary heart disease.

year-specific estimates of relative risk that were used in the time-trend analyses. Treatment group comparisons from any portion of follow-up that do not begin at randomization may be biased if there is differential loss of high-risk (or low-risk) participants relative to treatment group assignment. This could cause the comparability of the original random groups to be eroded over time. In addition, estimates of risk during individual years of follow-up are less precise than for the entire study period. For these reasons, the time-trend analyses should be interpreted with caution. It is encouraging, however, that the drop-out rate by the end of the trial was the same (2%) in the two groups. Furthermore, the mean values of variables examined at baseline remained equal between the two groups at the beginning of year 4 (although differences in other unmeasured factors are still possible). Nevertheless, because of the statistical uncertainties concerning the time-trend analysis, it is clear that the results need independent confirmation.

From a biological perspective, it is possible that the estrogen replacement in HERS had no effect on risk for coronary heart disease because it was opposed by a progestin. The specific progestin used in HERS was medroxyprogesterone acetate, which is known to attenuate beneficial effects of estrogen on atherosclerosis (6) and endothelial function (7) in animal models. In the Postmenopausal Estrogen/Progestin Interventions Trial, women taking estrogen plus medroxyprogesterone acetate had less favorable changes in high-density lipoprotein cholesterol levels than did women taking estrogen alone or estrogen plus micronized progesterone (8). Nonetheless, observational studies of HRT report no differences in risk for clinical cardiovascular events between users of estrogen alone and users of estrogen plus progestins, including women using predominantly medroxyprogesterone acetate (9–11). This consistency in observational data between un-

opposed estrogen and estrogen plus progestins, coupled with the null effect of estrogen plus medroxyprogesterone acetate in a clinical trial, suggests that the observational data on unopposed estrogen may also need to be interpreted with more caution.

Early Harm and Late Benefit

The other possibility regarding the time-trend data is that they reflect real and opposing effects of estrogen plus medroxyprogesterone acetate on risk for cardiovascular events over time. A pattern of early harm and late benefit could explain the discordance between the null HERS results and the many favorable observational studies of estrogen replacement and risk for coronary heart disease. Most observational studies are not well suited to detect early adverse effects of treatment because users of a therapy who experience early treatment-related morbidity are often unavailable for cross-sectional or cohort studies; if they are available, they are less likely to still be using the therapy in question. Only prospective data that include the initiation of therapy can truly quantify the early risks of treatment and the extent to which early risk might offset a later benefit.

A pattern of early harm and late benefit from therapy for vascular disease is not without precedent in clinical trials. Consider, for example, the progression of diabetic retinopathy that occurs early after initiating intensive insulin therapy, only to be followed by long-term beneficial vascular effects in the retina and other organ systems (12). There may be other examples of clinical trials with offsetting effects that are not readily evident because of reporting bias against trials with negative results.

Attrition of a susceptible cohort is one explanation for an early increased risk that rapidly returns to baseline. This concept presumes that a small cohort of women was uniquely susceptible to an

adverse effect of HRT, resulting in an increased risk for cardiovascular events in the active treatment group. Over the first year, the increased risk for primary events resulted in attrition of the susceptible cohort from the active treatment group, and the overall risk returned toward the null. In fact, within the first year of HERS, the risk was highest in the first 4 months, reached an intermediate level in the second 4 months, and returned almost to unity during the final 4 months.

The **Figure** illustrates how the combination of attrition of a susceptible cohort and a gradually accumulating long-term benefit from HRT could produce a pattern of risk over time similar to that observed in the HERS trial.

If a susceptible cohort accounts for the pattern of early risk in HERS, identifying this cohort is crucial. Subgroup analyses from the HERS data set provide an excellent opportunity to generate hypotheses about such a cohort. However, these hypotheses based on post hoc analyses will need independent confirmation before inferences can be made with confidence about possible high-risk subgroups. Several important possibilities are now being considered by the HERS investigators. Given the hepatic effects and metabolism of estrogen, the age of the HERS participants (average age at baseline, 67 years), and their numerous concomitant medications, an adverse drug interaction is a real possibility. Another possibility is that among the HERS participants with heart disease, only a few had truly vulnerable coronary plaques at baseline. Perhaps estrogen plus medroxyprogesterone acetate, through a proinflammatory or other unknown effect, caused a destabilization of these vulnerable plaques while concurrently slowing the progression of other more stable plaques through lipid lowering and other favorable effects. A third intriguing possibility is that in a small group of women with a specific coagulation or fibrinolytic factor mutation, estrogen plus medroxyprogesterone acetate produced a greatly enhanced prothrombotic state that conferred an unusually

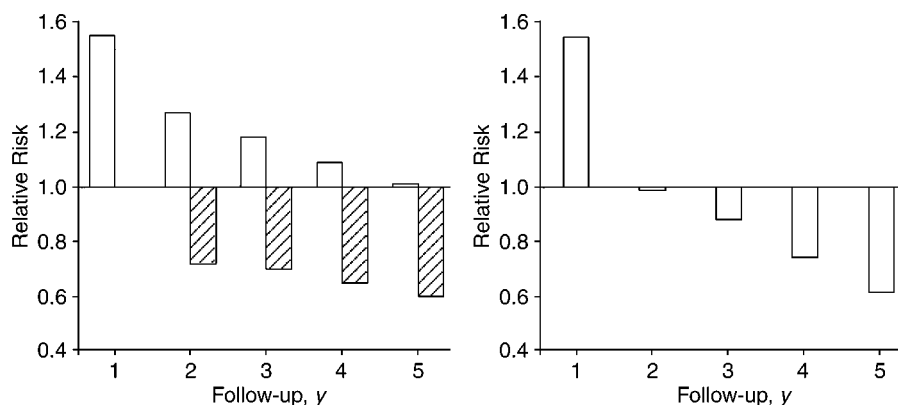
high risk for cardiovascular events. A plausible group to consider is women with the factor V Leiden mutation, in whom oral contraceptive use or pregnancy is associated with dramatic increases in risk for venous thrombosis (13).

Another potential explanation for an early increased risk that rapidly returns to baseline is tachyphylaxis of a generalized adverse effect. This is an important consideration because drug effects, good or bad, that are attenuated over time often recur when therapy with the drug is restarted after an interruption. If tachyphylaxis of an adverse effect indeed occurs, it would raise vexing clinical questions about long-term HRT users with coronary heart disease who encounter an interruption in therapy. For example, if a physician recommends stopping HRT before a planned knee replacement surgery to minimize the risk for a venous thromboembolic complication (14–16), will the risk for cardiovascular events go up when HRT is resumed? If so, by how much? Will it be related to the length of the interruption in therapy? Most important, is there a way to prevent a period of increased risk? With the data we now have, we cannot answer these questions or even be sure that they are the right questions to ask.

Valuable Lessons Learned

The overall null effect and the possible early increased risk seen in HERS are dramatic reminders of the value of clinical trials to evaluate both the benefits and the risks of new therapies. Animal model studies, observational studies, and even clinical trials of mechanisms or intermediate end points have value, but they cannot replace a clinical end point trial to establish the overall effects of a treatment. The HERS results also illustrate how incomplete our understanding of estrogen action and the pathogenesis of coronary heart disease remains. For example, the effects of estrogen on both venous and

Figure. Model of the possible impact of attrition of women with a susceptibility factor on the pattern of relative risk for myocardial infarction and death from coronary heart disease among women assigned to estrogen plus progestin or placebo over time in the Heart and Estrogen/progestin Study. **Left.** White bars represent a projected pattern of relative risk, assuming attrition of a susceptible cohort and no beneficial effects of hormone replacement therapy. Striped bars represent a projected pattern of relative risk, assuming a monotonic reduction in risk beginning in year 2 and no harmful effects of the intervention in year 1. **Right.** Results when these effects are combined.



arterial thrombosis are poorly understood and will certainly be the focus of new investigations as a consequence of the HERS results.

Many people were counting on HERS to confirm a belief that estrogen offered a unique way to prevent the leading cause of morbidity and death in postmenopausal women. Obviously, the situation is more complex than originally assumed. Nonetheless, it is important to recognize the tremendous progress that was made with HERS in our ongoing efforts to improve the health of women. The HERS results raise concerns about the efficacy and possibly the safety of estrogen plus medroxyprogesterone acetate for secondary prevention of heart disease, and they force us to re-examine the evidence for benefit of other estrogen replacement regimens and their use in other settings, including primary prevention. If the overall null effect in HERS is later shown to be due to an early adverse and late beneficial effect, and if the cause of the early risk can be identified and prevented, many women may still be able to benefit from estrogen replacement for secondary prevention of coronary heart disease. Finally, the effort to confirm or refute a possible early increased risk undoubtedly will stimulate new research on the thrombotic and other cardiovascular effects of estrogen and progestins that may lead to fundamentally new knowledge about estrogen action and the pathogenesis of coronary heart disease. Thus, out of the struggle to interpret the results of HERS will emerge new hypotheses, research questions, and paradigms about estrogen and heart disease prevention that will ultimately lead to improvements in the health of all postmenopausal women.

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