

The WHI Estrogen-Alone Trial— Do Things Look Any Better?

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OVER THE PAST HALF-CENTURY, A GROWING belief among women and their physicians held that “replacing” the estrogen lost at menopause would prevent many of the manifestations of aging, including coronary heart disease (CHD), osteoporotic fractures, and a decline in cognitive and sexual function. This attractive and plausible view led to widespread use of hormone therapy after menopause in the era before randomized trials with disease end points were required for proving the effects of new drugs. Clinicians were drawn in by other accumulating lines of evidence for CHD benefit that were consistently favorable: observational studies showed less heart disease among women taking estrogen,¹ pathophysiologic mechanisms provided biological plausibility,² and clinical trials revealed improvements in blood lipid levels and other surrogate measures.³

A fateful bump in the road in the 1980s was the recognition that postmenopausal estrogen treatment was causing endometrial cancer.⁴ Although uncommon and usually curable, this cancer could be prevented by antagonizing the estrogen with a progestin,⁴ and several estrogen plus progestin combinations were explored in the search for one that preserved the benefits of estrogen. In the 1990s, after it was demonstrated that lipid effects remained largely favorable when conjugated estrogens were combined with medroxyprogesterone acetate (MPA),³ this particular estrogen plus progestin regimen became the most widely used in the United States for postmenopausal women with a uterus.

In 1998, the Heart and Estrogen/progestin Replacement Study (HERS), the first major trial with disease event outcomes, surprised everyone by finding an increase in CHD events during the first year, and no overall cardiovascular benefit with longer follow-up, when estrogen plus progestin treatment was compared with placebo in 2763 women with prior coronary disease.⁵ This trial also found that estrogen plus progestin caused venous thromboembolism. Four years later, the Women’s Health Initiative (WHI) estrogen plus progestin trial was stopped early due to net harm. Among 16 608 healthy postmenopausal women with a uterus, es-

trogen plus progestin caused an increased risk of coronary events, stroke, breast cancer, and pulmonary embolism.⁶ A “global index” found these harmful outcomes to outweigh the decreased risk of hip fracture and colon cancer (TABLE). The net harm was markedly accentuated by a subsequent report of a significant 2-fold increase in dementia among WHI women older than 65 years.⁸

The findings of these 2 large trials led the US Food and Drug Administration to require a boxed warning of harm and to recommend that estrogen preparations not be used to prevent CHD or considered first-line therapy for prevention of osteoporosis.⁹ Medical organizations altered their guidelines to recommend that hormone therapy not be used for preventing disease, and when used for treating symptoms that it be at the lowest dose and for the shortest time possible.^{10,11} Many women using postmenopausal hormone therapy attempted to stop taking these agents,¹² and sales of Premarin (which had been the most-prescribed drug in the United States) dropped precipitously.¹³

In this issue of THE JOURNAL, the WHI investigators report findings from the eagerly awaited WHI estrogen-alone trial in 10 739 healthy women with hysterectomy who were randomly assigned to receive unopposed conjugated estrogen or placebo.¹⁴ Now that these important results are available, do things look any better?

As in the HERS and WHI estrogen plus progestin trials, the main hypothesis of the WHI estrogen-alone trial was that hormone therapy would reduce the risk of CHD. Once again this did not happen, although early CHD harm, which may be a consequence of progestin, appeared less pronounced. Given the absence of evidence in all 3 trials that these hormone regimens prevent CHD in these populations (Table), it is now clear that the previously available evidence was misleading. Observational studies were probably confounded by the tendency of healthier women to seek and comply with hormone treatment, and surrogate end point trials probably addressed the wrong mechanisms. This is an excellent illustration of the evidence-based medicine premise that disease end point trials are indispensable for examining the benefits and harms of treatments.

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See also p 1701.

Table. Hazard Ratios From 3 Hormone Therapy Trials

Clinical Event	Hazard Ratio (95% Confidence Interval)		
	HERS (Estrogen + Progestin) ^{5,7}	WHI (Estrogen + Progestin) ⁶	WHI Estrogen Alone ¹⁴
CHD events	0.99 (0.80-1.22)	1.29 (1.02-1.63)	0.91 (0.75-1.12)
Stroke	1.23 (0.89-1.70)	1.41 (1.07-1.85)	1.39 (1.10-1.77)
Pulmonary embolism	2.79 (0.89-8.75)	2.13 (1.39-3.25)	1.34 (0.87-2.06)
Breast cancer	1.30 (0.77-2.19)	1.26 (1.00-1.59)	0.77 (0.59-1.01)
Colon cancer	0.69 (0.32-1.49)	0.63 (0.43-0.92)	1.08 (0.75-1.55)
Hip fracture	1.10 (0.49-2.50)	0.66 (0.45-0.98)	0.61 (0.41-0.91)
Death	1.08 (0.84-1.38)	0.98 (0.82-1.18)	1.04 (0.88-1.22)
Global index†	...	1.15 (1.03-1.28)	1.01 (0.91-1.12)

Abbreviations: CHD, coronary heart disease; HERS, Heart and Estrogen/progestin Replacement Study; WHI, Women's Health Initiative; ellipses, not calculated.

*Data are based on the intent-to-treat analyses. For the primary CHD events outcome (myocardial infarction plus CHD death), the 3 trials had similar numbers of events and thus similar power. For other outcomes the smaller HERS trial had fewer events and less precise hazard ratios.

†The global index was composed of the first occurrence of any of the events listed in the table.

Another outcome that is consistent across the 3 trials is the increased risk of stroke among women assigned to estrogen alone or estrogen plus progestin, and this adverse effect is therefore attributable to the estrogen component of the hormone regimen. It is the only statistically significant adverse effect of estrogen alone, and at 0.12% additional strokes per year of treatment, it is relatively uncommon in this healthy cohort.

A pattern of increased pulmonary embolism was observed in all 3 studies, although the risk was attenuated and not statistically significant in the estrogen-alone trial. Colon cancer was significantly less common with hormone treatment in the WHI estrogen plus progestin study but not in WHI estrogen alone for reasons that are not clear. One important benefit of hormone treatment in both WHI trials was the significant reduction in risk of hip fracture; in this instance, results of observational studies of estrogen and fracture risk¹⁵ and trials using a surrogate end point (bone mineral density)¹⁶ agree with the results of clinical trials of fracture prevention.

The findings of the WHI estrogen-alone trial differ markedly from the findings of the HERS and WHI estrogen plus progestin trials with respect to the effect of hormones on breast cancer. In the HERS and WHI estrogen plus progestin trials, the risk of breast cancer was increased about 25%, and in the WHI estrogen-alone trial it was reduced by 23%. Numerous lines of evidence support an increased risk of breast cancer with estrogen use, including cell culture studies,¹⁷ animal models,¹⁸ many observational studies,^{19,20} and the fact that antiestrogens reduce the risk of developing breast cancer in healthy women.²¹ The reduced risk of breast cancer observed in a single trial, which is not statistically significant and does not fit with prior evidence, is best interpreted, for now, as due to chance.

The higher risk for breast cancer observed in the estrogen plus progestin trials, on the other hand, probably represents a harmful effect of the MPA. The increased risk was statistically significant in WHI estrogen plus progestin, is matched

by a trend of the same magnitude in HERS (Table), and is supported by evidence from large observational studies strongly suggesting that MPA and other progestins increase risk for breast cancer above that associated with estrogen alone.²⁰

Does the WHI estrogen-alone trial have limitations that could help explain the surprising results? Probably not—like its companion estrogen plus progestin trial, the WHI estrogen-alone trial is a well-done study. Its smaller size should reduce the power to observe hormone effects, but this is offset by a longer study duration and higher rates of CHD, stroke, and death. Power was reduced by the high degree of noncompliance with study medication, reaching 50% by the seventh year of the study. This rate was higher than the 35% noncompliance in the estrogen plus progestin trial and has the effect of biasing intention-to-treat estimates of effect toward the null.

In all 3 major trials, the mean age of participants was in the mid-60s, raising the concern that these results may not apply to treatment begun early in menopause. In this regard, the WHI estrogen-alone trial found that the subgroup of women in the youngest decade (aged 50-59 years) appeared to respond to estrogen more favorably than older women for many of the outcomes, including the global index. However, the differences in hazard ratios among subgroups were statistically significant for only 1 of 23 tests and could well have occurred by chance.

Even if hazard ratios are similar in women of all ages, the absolute risks differ substantially. In general, absolute risk for many diseases approximately doubles with each decade of age. Thus, women in their 50s have about half the risk of women in their 60s and one quarter the risk of women in their 70s. This means that any effect of hormone therapy on these diseases will be less marked in younger than in older women. The possibility of more favorable findings in 50- to 59-year-old women and the low absolute risk of adverse outcomes at this age both suggest that use of estrogen alone to treat menopausal symptoms for a limited duration early in menopause is reasonable.

Additional findings from this study that could have an important impact on assessments of the overall effect of estrogen alone will appear in a later report. These outcomes were summarized in a National Institutes of Health (NIH) press release²² issued just after the study was stopped that noted "a trend toward increased risk of probable dementia and/or mild cognitive impairment" in the estrogen-alone group.

The WHI estrogen-alone trial was stopped almost a year before its scheduled conclusion, even though none of the pre-defined stopping boundaries had been crossed. Clearly this was a difficult decision, made by NIH based on reviews with unspecified additional advisers after the data and safety monitoring board could not reach a consensus. It is difficult to evaluate this decision because some of the facts that may have influenced it, such as the findings on dementia, are not yet available. It appears that the prospect of 2 or 3 additional strokes over the next year among the roughly 2500 women still receiving estrogen outweighed the prospect of obtaining more precise information about the possibility that 50- to 59-year-old women do well with this drug, and about other outcomes such as the surprising breast cancer trend. The follow-up that is planned may reveal delayed effects of hormone therapy and be of some help in interpreting these trends.

In summary, the WHI trials suggest that estrogen alone does have advantages over estrogen plus progestin for treating postmenopausal women—it has only 1 or 2 adverse outcomes (increased strokes and probably pulmonary emboli) rather than 4 (increased strokes, CHD, pulmonary emboli, and breast cancer), and both regimens have an important benefit (decreased fractures). However, this risk-benefit assessment does not take into account the dementia findings, and even in their absence, estrogen alone produced no improvement in the overall global index. In addition, estrogen alone in women with a uterus increases the risk of uterine cancer⁴ and rates of uterine bleeding, biopsy, and hysterectomy.²³

As more deliberate and exhaustive analyses of this trial become available, they will likely contribute to new practice guidelines. In the meantime, the available evidence supports these provisional clinical implications:

For Treatment of Menopausal Symptoms. Hormone therapy is effective for treating menopausal symptoms, and for this indication things do look better for estrogen alone than for estrogen plus progestin. However, estrogen alone does have adverse effects, and it remains prudent to keep the dose low and the duration of treatment short.

For Prevention of Chronic Disease. In the absence of evidence for an overall net benefit of postmenopausal treatment with estrogen alone, and with the evidence that estrogen plus progestin is harmful, neither therapy should be used for preventing disease. Although it is possible that other forms or doses of hormones could be more beneficial, this must be demonstrated in disease-end point trials before any hormone regimen can be recommended for disease prevention. Fortunately, there are other good approaches to preventing CHD

and fractures for which trials have found benefits to outweigh harms.^{24,25}

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