

Postmenopausal Hormone Replacement Therapy: How Could We Have Been So Wrong?

While the public is hungry for medical discoveries that will immediately change clinical practice, evidence typically accumulates piecemeal and practice changes slowly. The early stoppage and release of the main results of the estrogen plus progestin component of the Women's Health Initiative (WHI) broke the typical pattern. This very large, methodologically rigorous randomized, controlled trial found that for every 10 000 women taking the hormone combination for 1 year (10 000 person-years), 7 more would have coronary events, 8 more would have strokes, 8 more would have pulmonary emboli, and 8 more would have invasive breast cancer than would 10 000 women taking placebo (1). Benefits of combination hormone therapy were 6 fewer cases of colorectal cancer and 5 fewer hip fractures per 10 000 women. This single study caused a leap in knowledge that should drastically change practices of millions of postmenopausal American women who are taking combination hormone replacement therapy (HRT) (2, 3).

As postmenopausal women confront their medicine cabinets in confusion, clinicians, researchers, pharmaceutical companies, and expert panels are asking, "How could we have been so wrong?" A large body of observational data (and trials that looked at intermediate end points) pointed toward a sizable reduction in the risk for coronary events in women who took HRT after menopause (4, 5). In this issue, Humphrey and colleagues (6) summarize those data. *Annals* accepted their systematic review for publication before the release of the WHI results. Their careful analysis not only presaged the WHI results but offers invaluable answers to the question, "How could we have been so wrong?" They convincingly demonstrate that the observational data misled us because much of it did not adequately account for socioeconomic status. Studies that reported a protective association of cardiovascular disease did not adjust for socioeconomic status. Studies that did account for socioeconomic status showed little or no protective association. Higher socioeconomic status is associated with lower rates of cardiovascular disease and higher rates of HRT. Thus, rather than HRT keeping women healthy, healthy women were taking HRT.

While many women have stopped or will stop taking combination HRT because of the WHI results, cessation of all use is neither likely nor appropriate. Some women will find the risks of HRT acceptable if they suffer dis-

abling vasomotor disturbances without it. An ongoing arm of the WHI may find that the balance of benefits and harms is different in women taking unopposed estrogen after hysterectomy. If new evidence supports a protective effect of estrogen in other major chronic diseases, especially Alzheimer dementia, women who fear these diseases more than heart disease, stroke, thromboembolism, or breast cancer might elect to take HRT, especially if their risk for cardiovascular disease and breast cancer is low.

Clinicians and patients need guidance. The U.S. Preventive Services Task Force is now working hard to formulate this guidance. In fact, Task Force recommendations on HRT in the prevention of chronic disease were also to appear in this issue, but the release of the WHI results made them out of date before they hit the presses. The Task Force has reconvened to modify the recommendations in light of the late-breaking evidence. *Annals* will publish these recommendations as soon as they are ready.

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