



# EDITORIAL

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## Latest data on HT side effects: Further reinforcement, some reassurance

The status of hormone therapy (HT) for menopausal women changed forever in July 2002 when the estrogen-progestin arm of the Women's Health Initiative (WHI) was halted. Recent additional WHI data on estrogen-progestin's impact on heart disease and breast cancer buttress both the concerns raised by the initial breast cancer findings and the positive glimmers from earlier data on heart disease. Further, the new findings affirm our view on the importance of HT individualization.

One development that has *not* occurred also has important clinical relevance. Last July, the WHI's Data Safety Monitoring Board concluded that heart disease, stroke, and breast cancer risks associated with estrogen-progestin therapy in this population of largely asymptomatic women exceeded documented benefits on bone and colon cancer. The high-quality evidence from this study precipitated the discontinuation of the estrogen-progestin arm. Remarkably, the estrogen-only arm of the study has not been discontinued.

### Breast cancer concerns

The news about breast cancer continues to cause concern.<sup>1</sup> In analyses that used an "intent to treat" model, estrogen-progestin HT was associated with an increased risk of total cases (hazard ratio [HR] 1.24,  $P < 0.001$ ) and invasive cases (HR 1.24,  $P < 0.003$ ) of breast cancer compared to placebo. The invasive breast cancers in the estrogen-progestin treatment group were larger (1.7 cm versus 1.5 cm,  $P = 0.04$ ) and more likely to be lymph node positive (25.9% versus 15.8%,  $P = 0.03$ ) at diag-

nosis than in the placebo group. In addition, after 1 year of therapy, the percentage of women with abnormal mammograms was significantly greater with estrogen-progestin therapy than with placebo (9.4% versus 5.4%,  $P < 0.001$ ); this finding is cause for concern because follow-up tests may be needed to investigate the abnormality discovered on screening.

### Heartening findings

The news about heart disease is much better.<sup>2</sup> In the WHI, the women studied were predominantly healthy and relatively free of cardiovascular disease at the beginning of the study. In the first year of treatment, the risk of coronary heart disease in the women treated with HT increased (HR 1.81, confidence interval 1.09-3.01); however, after the first year, the risk of coronary heart disease was similar in the estrogen-progestin and placebo groups.

After 6 years of treatment, there was no difference in the cumulative risk of coronary heart disease between the estrogen-progestin and placebo groups. This means that women who have already completed their first year of estrogen-progestin treatment are unlikely to be at additional increased risk for coronary heart disease based on estrogen-progestin treatment.

### Clear implications

The implications of WHI data for clinical practice are coming into sharper focus:

- The clear and central indication for HT is treatment of vasomotor symptoms; no other treatments are as effective. Given the great impact of these symptoms on quality of life,

this indication remains very important. In addition, HT remains a primary treatment for vulvar and vaginal atrophy.

- A key point is the need to individualize HT. In part, this means that physicians should determine the lowest dose that is effective for each patient, and base the hormone preparation and route of delivery on the patient's unique clinical situation.
- HT should not be prescribed for prevention of heart disease.
- For the treatment of osteoporosis, other agents, such as the bisphosphonates, should be considered prior to HT.

### The silent-watchdog phenomenon

As Sherlock Holmes perceived in the case of "Silver Blaze," silence can be a telling clue: a watchdog that did *not* bark in the night was the clue pointing to an "inside job."

The Data Safety Monitoring Board of the

WHI has not discontinued the study's estrogen-only portion, in which hysterectomized women receive 0.625 mg conjugated equine estrogen or placebo. It is therefore likely that this dose and formulation has a superior overall benefit-risk profile than combination estrogen-progestin. Much of this benefit likely will be associated with reduced risk of breast cancer compared to estrogen-progestin therapy—a finding of numerous observational studies.

Estrogen-only treatment for hysterectomized women is a common clinical practice and it is reassuring that it appears to be safe. ■



#### REFERENCES

1. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women. *JAMA*. 2003;289:3243-3253.
2. Manson JE, Hsia J, Johnson KC, et al. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med*. 2003;349:523-534.