# WHI Shows Unopposed Estrogen Is Risk Neutral

BY MARY ANN MOON

FROM JAMA

The most recent findings from the Women's Health Initiative study of short-term unopposed estrogen therapy suggest that after 10 years, the treatment neither increases nor decreases risks for coronary heart disease, deep vein thrombosis, stroke, hip fracture, colorectal cancer, or total mortality.

This portion of the WHI study was halted early when interim analysis in 2004 showed an increased risk of stroke in women taking conjugated equine estrogens (CEE) compared with those taking placebo. "All previous reports of this trial were limited to outcomes occurring during the intervention phase. [Now] we report data on postintervention outcomes through a mean of 10.7 years of follow-up," said Andrea Z. LaCroix, Ph.D., of Fred Hutchinson Cancer Research Center, Seattle, and her associates (JAMA 2011;305:1305-14).

**VITALS**

**Major Finding:** The short-term increase in risks of stroke, DVT, and pulmonary embolism did not persist over the long term after unopposed estrogen therapy; the equivalent risks of CHD, colorectal cancer, and total mortality did persist; the reduction in hip fracture risk did not persist; and the reduction in breast cancer risk did persist.

**Data Source:** Extended (10-year) follow-up of approximately 78% of subjects who participated in the Women's Health Initiative-Estrogen Alone trial (3,778 postmenopausal women who took conjugated equine estrogen and 3,867 who took matching placebo for a median of 6 years).

**Disclosures:** The WHI was funded by the National Heart, Lung, and Blood Institute; the National Institutes of Health; and the U.S. Department of Health and Human Services. Wyeth Ayerst donated the study drugs. Dr. LaCroix reported ties to Warner Chilcott, Sanofi-Aventis, Amgen, and Pfizer. Her associates reported ties to numerous other industry sources.

In the estrogen-only portion of the WHI study, 10,739 postmenopausal women who had undergone hysterectomy had been randomly assigned to receive either CEE or placebo. They were followed during this intervention phase for a median of 6 years, but the median "adherent time" – the interval during which the women actually took more than 80% of their study pills – was only 3.5 years because more than half stopped taking the pills even before the early halt of the trial.

Approximately 78% of the surviving study subjects (3,778 who took CEE and 3,867 who took placebo) agreed to participate in the extended follow-up reported here.

The increased risks of stroke, deep vein thrombosis, and pulmonary embolism that had been noted during the intervention phase did not persist during extended follow-up. In addition, active treatment, which had showed no effect on CHD risks during the intervention, continued to show no effect on CHD risks. For all cardiovascular events, the cumulative hazard ratio was 2.26% with active treatment and 2.12% with placebo.

Colorectal cancer incidence did not differ between women who received CEE and those who received placebo during the intervention phase, and this lack of effect persisted during extended follow-up.

Hip fracture risk had been reduced with CEE therapy during the intervention phase, but this benefit did not persist during the extended follow-up. Numerically, hip fracture incidence was slightly higher in the CEE group than in the placebo group.

Total mortality risk remained similar between the two study groups both during the intervention and during extended follow-up.

Only one benefit of CEE therapy that was seen during the intervention phase persisted in the extended follow-up and became statistically significant: Breast cancer incidence was 0.27% with active treatment and 0.35% with placebo. These results differ from those of the

other portion of the WHI trial in which subjects received combined estrogen-plus-progestin. In that study arm, active treatment impeded mammographic accuracy and was associated with significantly higher rates of breast cancer and breast cancer mortality, the researchers noted.

The women's age at commencing treatment showed a significant interaction with outcomes, both in the intervention phase and during extended follow-up. The results suggest there may be greater benefit and safety for women who start CEE in their early 50s, and less benefit with more potential harm for women who are older when they begin treatment. ■

VIEW ON THE NEWS

## Findings Don't Agree With the Body of Evidence

"The lack of an adverse effect of unopposed estrogen when used for a short period in the WHI does not counter the larger," long-standing, corroborated body of evidence that the treatment generally elevates the risk of breast cancer, said Dr. Emily S. Jungheim and Dr. Graham A. Colditz.

One can question whether results in the WHI study population, in which nearly 70% of the subjects were older than 60 years at baseline, can even be applied to younger women, particularly with regard to breast cancer risk and hormone therapy.

In addition, the duration of CEE use in the WHI remains problematic since the median "adherent time" was 3.5 years. "Thus, the WHI results do not address the balance of risks and benefits associated with longer term estrogen use," they said.

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*Dr. Jungheim and Dr. Colditz are at Washington University, St. Louis. These remarks were taken from their editorial comment accompanying Dr. LaCroix's report (JAMA 2011;305:1354-5). They reported no relevant financial disclosures.*