WHI at 10: Unopposed Estrogen Is Risk Neutral

BY MARY ANN MOON

FROM JAMA

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.

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, according to a report.

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).

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, a nonsignificant difference.

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, they reported.

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.

The researchers noted that 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, they noted.

The women's age at commencing treatment showed a significant interaction with outcomes, both during the intervention phase and during extended follow-up.

The results suggest that 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.

"Among younger women, no new safety concerns emerged and some risk reductions became apparent during the postintervention period.

"Among older women, risks of colorectal cancer, death, and the global index of chronic diseases were elevated over the cumulative follow-up period," Dr. LaCroix and her associates said. ■

VIEW ON THE NEWS

Findings Don't Jibe With Others

"The lack of an adverse effect of unopposed estrogen when used for a short period in the WHI does not counter the larger," longstanding, 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. 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 concluded.

DR. JUNGHEIM *and* DR. COLDITZ *are at Washington University, St. Louis. These remarks were taken from their accompanying editorial comment (JAMA 2011;305:1354-5). They reported no relevant financial disclosures.*

Women on Denosumab Maintain Bone Benefits After 5 Years

BY HEIDI SPLETE

FROM THE ANNUAL MEETING OF THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS

SAN DIEGO – Bone density and fracture risk continued to improve from baseline in postmenopausal women taking denosumab for osteoporosis, according to data from a 2-year extension of the FREEDOM study in more than 4,000 women.

The original FREEDOM study (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months) enrolled 7,808 postmenopausal women aged 60-80 years with osteoporosis to receive either a subcutaneous injection of denosumab (60 mg) or placebo along with daily calcium and vitamin D supplements every 6 months.

All subjects had bone mineral density (BMD) T scores of less than –2.5 but not less than –4.0 at the lumbar spine or total hip. At 36 months, denosumab was associated with reductions of 68% in vertebral fracture and 40% in hip fracture (N. Engl. J. Med. 2009;361:756-65).

The FREEDOM results were the basis of the Food and Drug Administration's approval of denosumab in June 2010. In the extension study, 2,343 patients from the original treatment group and 2,207 patients in the control group received the denosumab treatment for 2 years (as well as calcium and vitamin D), yielding follow-up data for up to 5 years of drug exposure, said Dr. Cesar Libanati at the meeting.

Women in the long-term group who received denosumab for 5 years showed significant BMD improvements from baseline, of 13.7% in the lumbar spine and 7.0% in the total hip. Women in crossover group showed significant BMD improvements from the start of the extension study, of 7.9% in the lumbar spine and 4.1% in the total hip.

Patients in the crossover group showed significant increased in BMD from the extension study baseline similar to those seen in the long-term patients during their first 2 years of denosumab use, noted Dr. Libanati, clinical research medical director at Amgen Pharmaceuticals, maker of denosumab (Prolia), in Newbury Park, Calif.

During years 4 and 5, the annualized yearly incidence of new vertebral fractures in the long-term patients was steady at 1.4%, compared with 1.1% at the end of the 3-year FREEDOM study.

The yearly incidence in the crossover treatment group was 0.9% for their first 2 years of denosumab exposure, compared with 2.5% in the first 2 years of the FREEDOM study.

The yearly incidence of nonvertebral fractures in the long-term patients was 1.4% after 4 years and 1.1% after 5 years.

Nonvertebral fracture data for the crossover patients were not presented.

Denosumab remained well tolerated during the extension study. The adverse event profile was "similar in years 4 and 5 to that observed in the 3 years of the placebo-controlled FREEDOM study," Dr. Libanati said.

Long-term patients also maintained the reductions in bone turnover seen during the original FREEDOM study, he added.

Dr. Libanati is employed by Amgen. ■