WHI Winners and Losers

Hormone Therapy *from page 1*

both studies, and harm from hormone therapy based on the rates of strokes, venous clotting, and dementia in women aged 65 or older. The major benefits were a reduction in hip and clinical vertebral fractions with both forms of hormone therapy, and a reduction in the rate of invasive colorectal cancer in patients treated with estrogen plus progestin, said Dr. Marcia L. Stefanick, professor of medicine at Stanford (Calif.) University.

A global index of risk and benefit showed a net increased risk among the 16,608 women who were randomized to active drug in the estrogen-plus-progestin study, and no net benefit compared with risk among the 10,739 women with a prior hysterectomy who received the hormone in the estrogen-only study, said Dr. Stefanick, who also chairs the WHI steering and executive committees.

A large panel of WHI investigators from the National Heart, Lung, and Blood Institute and more than 40 clinical centers across the United States, as well as several of the more than 160,000 participating women, gathered this month to review the WHI's results. A series of study collaborators took the podium to discuss the following aspects of the WHI:

▶ **Coronary diseases.** The incidence of coronary heart disease was the primary end point for both arms of the hormone study, and in both arms estrogen failed to show any benefit—a surprise given the expectation that estrogen would prevent heart disease, said Dr. Judith Hsia, professor of medicine at George Washington University, Washington. In the estrogen-plus-progestin arm, hormone therapy boosted the risk of myocardial infarction (MI) or coronary death by 24%. The increase in risk began to appear 1 year into the study, which was "not very reassuring" for estrogen-plus-progestin use, she said.

The picture was not as bad for estrogen alone, which overall led to a 5% decline in the incidence of MI and coronary deaths, compared with placebo, a difference that was not statistically significant.

Results from a recent analysis of the estrogen-only data that divided participants by their age at entry further showed that estrogen-only treatment produced a stronger trend toward fewer coronary events in the youngest women, who were aged 50-59 at entry. In this subgroup of 2,300, estrogen-only treatment cut the combined incidence of MI or coronary death by 37%, a result that came close to statistical significance. The combined incidence of MI, coronary death, or need for revascularization therapy was cut by 34% by estrogen only, a difference that was statistically significant. But among women aged 60-69, estrogen only had essentially no impact on coronary events, and in women aged 70-79, estrogen was linked with a nonsignificant 11% rise in the event rate.

Dr. Hsia and other investigators stressed that this new finding in no way justifies routinely using estrogen only to treat women aged 50-59. Rather, the result was seen as "reassuring for women who need hormone therapy for menopausal symptoms," said Dr. JoAnn E. Manson, chief of the division of preventive medicine at Brigham and Women's Hospital, Boston.

▶ **Stroke.** Both forms of hormone therapy led to a significant rise in stroke risk. Estrogen plus progestin produced a 31% higher rate, compared with placebo, and estrogen alone led to a 39% higher rate.

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▶ **Venous thrombosis.** The impact of hormone therapy on pulmonary embolism and deep vein thrombosis was even worse. Estrogen plus progestin more than doubled the risk for pulmonary embolism and nearly doubled the rate of deep vein thrombosis. Estrogen alone wasn't as dangerous, but it still produced a significant 47% rise in deep vein thrombosis. Estrogen alone raised the pulmonary embolism rate by 34%, a nonsignificant increase.

▶ **Urinary incontinence.** Hormone therapy's adverse effect on urinary incontinence is "one of the least-known results from WHI," said Susan L. Hendrix, D.O., a professor of ob.gyn. at Wayne State University, Detroit.

Women who had incontinence symptoms at baseline showed an increased severity after 1 year of treatment in both hormone-therapy arms of the study, and hormone therapy also boosted the incidence of new cases. In women getting estrogen plus progestin, stress incontinence was 87% more common than in the placebo group, a significant difference, and urge incontinence was 15% more common, a trend that just missed statistical significance. Women treated with estrogen only had more than twice the rate of new stress incontinence, compared with the placebo group, while urge incontinence again rose by 15%.

"This is a paradigm switch. For years we used estrogen to treat incontinence," Dr. Hendrix said. After the first report of this finding, in February 2005, the American College of Obstetricians and Gynecologists issued an updated practice bulletin in June that warned against using oral estrogen to treat or prevent urinary incontinence. But this month, the American Urogynecologic Society still had a patient information page on its Web site that said hormone therapy could improve urine control, she said.

▶ **Cancer.** The biggest surprise for this end point was that estrogen alone had a neutral effect on the rate of invasive breast cancer. Estrogen plus progestin led to a significant 24% rise in the incidence of breast cancer, and it was this increased rate that crossed a prespecified risk threshold in late May of 2002 and led to the early halt of the estrogen-plus-progestin arm.

Results from more recent analyses also showed that estrogen-plus-progestin treatment was linked to significant increases in breast tumor size and number of positive lymph nodes, and in the percentage of patients with advanced-stage cancer at diagnosis, said Dr. Rowan T. Chlebowski, chief of the division of medical oncology and hematology at Harbor-UCLA Medical Center, Torrance, Calif.

Rates of invasive colorectal cancer fell by a statistically significant 44% in patients taking estrogen plus progestin, compared with placebo, making estrogen plus progestin the only intervention that has been proven to cut the rate of colorectal cancer. The incidence of colorectal cancer was essentially unchanged in women taking estrogen only.

▶ **Dementia and cognitive function.** Before WHI, "older women were being put on hormone therapy in the belief that it would slow the decline in women with existing dementia and prevent new cognitive impairment," said Sally Shumaker, Ph.D., professor of public health science at Wake Forest University, Winston-Salem, N.C. The WHI results showed how misguided that was. "Hormone therapy may accelerate dementia," Dr. Shumaker said.

The WHI Memory Study focused on 7,479 women aged 65 or older at baseline, with a primary outcome of probable dementia and a secondary outcome of probable dementia or mild cognitive impairment. During an average 4 years of follow-up, women treated with estrogen plus progestin more than doubled their incidence of probable dementia, compared with the placebo group, with a similarly increased rate of mild cognitive impairment. During 5 years of follow-up in the estrogen-only arm, the rate of dementia was 49% higher in the treatment group and the rate of cognitive impairment rose by a third.

Overall, when results for both treatment groups are combined, hormone therapy produced a statistically significant 76% rise in the incidence of probable dementia.

▶ **Bones.** In what is deemed a clear-cut benefit, estrogen plus progestin led to significant drops in the rate of hip fractures, which fell by 33% compared with the placebo group, and clinical vertebral fractures, which dropped by 35%. Women taking estrogen only had almost identical declines.

▶ **Diabetes.** Hormone therapy improved serum levels of insulin and glucose in women who were undergoing treatment for diabetes at baseline, an effect that was probably related to an enhancement in insulin sensitivity, said Dr. Denise Bonds, a physician in the department of public health sciences at Wake Forest University.

Among a total of 464 women who reported treatment for diabetes at baseline in the estrogen-plus-progestin trial, hormone therapy led to a statistically significant 21% drop in serum levels of insulin and glucose. The estrogen-only study included 852 women who entered on diabetes treatment, and hormone therapy was linked with a nonsignificant 12% drop in insulin and glucose levels in this group.

▶ **Gallbladder disease.** In both treatment arms, women on hormone therapy had an increased rate of both gallbladder disease and gallbladder surgery. Both estrogen plus progestin and estrogen alone boosted the rates of disease and surgery by about 60%, statistically significant increases. ■

High Medication Burden Seen in Women With Osteoporosis

SAN DIEGO — About half of postmenopausal women who take bisphosphonates for osteoporosis take at least three concomitant medications and 15% take six or more, researchers led by Dr. Sydney Lou Bonnick reported during a poster session at the annual meeting of the International Society for Clinical Densitometry.

"Patients receiving bisphosphonate therapy for postmenopausal osteoporosis have a substantial pill burden," the researchers wrote in their poster. "Adherence to therapy may be improved if physicians consider prescribing more convenient, less frequently dosed medications."

Dr. Bonnick, medical director of the Clinical Research Center of North Texas in Denton, and her associates obtained patient prescription information from November 1999 to June 2004 from NDCHealth, a database that contains records from 14,000 retail pharmacies in the United States. They identified women aged 50 years and older who were receiving alendronate or risedronate, which were the bisphosphonates approved for osteoporosis treatment during the study period.

Concomitant medications were defined as a minimum of a 2-week supply of medications that are prescribed in the same month as are a minimum of a 2-week supply of bisphosphonates.

Between November 1999 and June 2004 the number of women in the database using bisphosphonates rose from 78,909 to 250,286. Of the women prescribed concomitant medications, 74% were on two or more additional medications, 52% were on three or more, and 15% were on six or more.

The percentage of women taking six or more concomitant medications increased from 12% to 19% during the study period.

The most common concomitant drugs taken were cholesterol reducers, synthetic thyroid hormones, calcium channel blockers, β-blockers, ACE inhibitors, and systemic antiarthritis medications.

Dr. Bonnick and her associates observed that by the end of the study, women on daily bisphosphonate therapy were on a higher mean number of concomitant medications, compared with those on weekly bisphosphonate therapy (4.16 vs. 3.77, respectively). In addition, women aged 75 years and older were on a higher mean number of concomitant medications, compared with those aged 50-64 years (3.97 vs. 3.09, respectively).

GlaxoSmithKline supported the study.

—Doug Brunk