

Clinical News

HRT and Stroke Risk

Findings from a study of women enrolled in the Nurses' Health Study suggest that postmenopausal hormone use appears to decrease the risk for major coronary events in women without previous heart disease; however, stroke risk might be increased by as much as 40% with the use of estrogen doses of ≥ 0.625 mg/day plus progestin.

The prospective, observational cohort study (Grodstein F, Manson JE, Colditz GA, et al. A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. *Ann Intern Med* 2000;133:933-41,999-1001) involved evaluation of questionnaires and medical records from 70,533 postmenopausal women in the study population. During the 20 years between 1976 and 1996, a total of 1,258 major coronary events (nonfatal myocardial infarction or fatal coronary disease) and 767 strokes were identified in the cohort.

The authors report that after considering all cardiovascular risk factors, they found the risk for major coronary events to be lower among current users of hormone therapy (relative risk, 0.61), including short-term users, compared with never-users. The risk for coronary events was similarly reduced in women currently taking 0.625 mg/day oral conjugated estrogens (relative risk, 0.54) and in those taking 0.3 mg/day (relative risk, 0.58), compared with never-users. The risk for stroke was, however, significantly increased in women taking ≥ 0.625 mg/day of oral conjugated estrogen (relative risk, 1.35 for 0.625 mg/day and 1.63 for ≥ 1.25 mg/day), and in those taking estrogen plus progestin (relative risk, 1.45).

The investigators conclude that, "overall, little relation was observed between combination hormone therapy and risk for cardiovascular disease (major coro-



nary heart disease plus stroke) (relative risk, 0.91)," and that women without previous heart disease appear to have a decreased risk of major coronary events with the use of postmenopausal hormone therapy. They add that daily doses of 0.3 mg of oral conjugated estrogen is associated with a risk reduction similar to that seen with the standard (0.625 mg) dose, but note the possible increased risk of stroke with the use of estrogen at daily doses of ≥ 0.625 mg, and in combination with progestin.

ERT/HRT Adherence and BMD

Findings from a recent study (Greendale GA, Wells B, Marcus R, et al. How many women lose bone mineral density while taking hormone replacement therapy? Results from the Postmenopausal Estrogen/Progestin Interventions Trial. *Arch Intern Med* 2000;160(20):3065-71) underscore the importance of adherence to hormone replacement therapy (HRT) regimens for the prevention of postmenopausal bone loss.

Investigators used data from the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial to analyze bone loss in 538 women considered adherent to therapy (having taken at least 80% of pills at each 6-month clinic visit over a period of 3 years); these women were among 701 randomized to receive conjugated equine estrogens alone (estrogen replacement therapy [ERT]) or with a progestin

(HRT). Also analyzed was bone loss among 132 women who adhered to a placebo regimen.

Bone mineral density (BMD) was measured at baseline and at 12 and 36 months, and an annual loss of $\geq 1\%$ established as the criterion for bone loss at the 75% confidence level. The authors reported that lumbar spine BMD loss was seen in 5.1% of ERT/HRT users at 12 months, and in 8.0% at 36 months; among those receiving placebo, 58.6% experienced lumbar spine BMD losses at 12 months, and 39.8% demonstrated such losses at 36 months. With respect to total hip BMD, 14.5% and 11.8% of ERT/HRT users lost BMD at 12 and 36 months, respectively, compared with 50.4% and 35.4% of placebo recipients.

National Toxicology Program Recommends "Known Carcinogen" Designation of Steroidal Estrogens

An advisory panel to the National Toxicology Program has recommended that steroidal estrogens be listed in the "known to be a human carcinogen" category. The recommendation was made despite the panel's acknowledgment of estrogen's clear medical benefits and important medical uses.

The recommendation appears in the Department of Health and Human Services' *Report on Carcinogens (RoC)*, 9th edition. Prepared by the National Toxicology Program, the *RoC* is published every 2 years and identifies substances (e.g., metals, pesticides, drugs, natural synthetic chemicals) and mixtures or exposure circumstances that are "known" or "reasonably anticipated" to cause cancer, and to which a significant number of Americans are exposed.

According to the National Institute of Environmental Health Sciences, which headquarters the National Toxicology Program, "the 'known' category is reserved for substances for which there is sufficient evidence of carcinogenicity from studies in humans that indicates a cause-and-effect relationship between exposure

and human cancer." Steroidal estrogens were previously listed in the "reasonably anticipated to be a human carcinogen" category.

This most recent edition of the *RoC* contains 218 entries, 14 of which are new listings. Eight of these newly listed substances are in the "known" category.

See "NAMS News" (page 32) for details about NAMS' response to the press release on this topic.

Hip Protectors and Fracture Prevention in the Frail Elderly

The results of a study conducted in Finland (Kannus P, Parkkari J, Pasanen SNM, et al. Prevention of hip fracture in elderly people with use of a hip protector. *N Engl J Med* 2000;343:1506-13) suggest that hip fractures, a major cause of disability, functional impairment and death in elderly patients, can be reduced with the use of padded hip protectors.

Investigators randomly assigned 1,801 ambulatory, frail elderly adults (1,409 women; mean age 82 years) to a group in which hip protectors were worn, or to a control group in which no such device

was used. The protectors, placed into pockets on specially designed undergarments, were convex, padded and shield-shaped to fit over the greater trochanter and cover the proximal femur. After 1 month, hip fractures had been sustained in 13 of the individuals in the hip-protector group and in 67 of the patients assigned to the control group (relative risk, 0.4). Two of the patients wearing the protectors and 12 of those in the control group suffered pelvic fractures (relative risk, 0.4). The risk of other fractures was similar in the two groups.

Only four subjects assigned to the hip-protector group sustained a hip fracture while actually wearing the protector (total falls, 1,034), and the authors note that unwillingness to wear the hip protectors as part of daily clothing limits the extent to which the results of the study can be generalized to all elderly persons. Results were not broken down by gender.

ERT and Breast Cancer Risk in Women with Benign Breast Disease Histories

A history of proliferative benign breast disease (with or without atypia) has been shown to moderately increase the risk of postmenopausal breast carcinoma—more so than a history of nonproliferative benign histology. In a case-controlled study of a nested group of women enrolled in the Nurses' Health Study (Byrne C, Connolly JL, Colditz GA, et al. Biopsy-confirmed benign breast disease, postmenopausal use of exogenous female hormones, and breast carcinoma risk. *Cancer* 2000;89:2046-52), neither current nor long-term (≥ 5 years) use of estrogen replacement therapy had any effect on the relative risk of developing breast cancer in women with histories of benign breast disease.

The investigators reported that the relative risk for postmenopausal breast cancer was 1.8 in women with histories of proliferative benign disease and 3.6 in those with histories of atypical hyperplasia, compared with women who had had

nonproliferative benign disease. The analysis did not, however, exclude the possibility of increased risk with some particular hormone combination or dosage.

Estrogen, Raloxifene and Quality of Life

Investigators conducting a 12-month, double-blind, placebo-controlled study (Strickler R, Stovall DW, Merritt D, et al. Raloxifene and estrogen effects on quality of life in healthy postmenopausal women: A placebo-controlled randomized trial. *Obstet Gynecol* 2000;96:359-65) found that most quality-of-life domains evaluated in the study were not affected by treatment with estrogen or raloxifene.

The investigators assessed the effects of raloxifene and conjugated equine estrogens (CEE) on quality of life in 398 women (mean age, 54.7 years). The women were randomly assigned to one of four groups: raloxifene 60 mg/day, raloxifene 150 mg/day, CEE 0.625/day or placebo. The Women's Health Questionnaire, a validated quality-of-life instrument for perimenopausal and postmenopausal women, was used to measure a series of quality-of-life domains at baseline and at 3-month intervals throughout the study period.

Overall quality of life in each treatment group did not change significantly from baseline to the end of the study; 6 domains—depression, somatic symptoms, memory/concentration, sexual behavior, sleep problems and perceived attractiveness—were unchanged in all groups. At 12 months, however, mean scores for menstrual symptoms worsened significantly and mean scores for vasomotor symptoms improved significantly in the CEE group, compared with placebo recipients. Mean anxiety/fear scores improved significantly among the women receiving raloxifene 60 mg/day, irrespective of previous hormone use. Vasomotor symptoms did not worsen at any point in the raloxifene 60 mg/day group.

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