

NAMS REPORT

Amended report from the NAMS Advisory Panel on Postmenopausal Hormone Therapy

The publication of two large, prospective, randomized, double-blind, placebo-controlled studies of continuous-combined estrogen-progestin therapy for postmenopausal women has engendered considerable attention from both the health profession and the public. The two studies – the Heart and Estrogen/Progestin Replacement Study (HERS) and the Women’s Health Initiative (WHI) – have provided new knowledge that questions long-standing clinical practice and prescribing. Although these studies evaluated only one hormone combination and have other potential methodologic concerns, they are the first well-controlled, adequately powered reports. Therefore, the Board of Trustees of The North American Menopause Society (NAMS) convened an Advisory Panel to develop clinical recommendations regarding the use of postmenopausal hormone therapy. This document is the panel’s report, reviewed and approved by the NAMS Board. The report was first presented at the NAMS Annual Meeting on October 3, 2002; discussion of the report at that meeting led to this amended and revised report, published October 6, 2002. NAMS will update its recommendations as more findings become available, including analyses of other outcomes and results from the other treatment arms of the WHI.

Advisory panel members

The panel was composed of healthcare professionals from different areas of medical science related to the issue. They were selected because of their expertise, regardless of whether they were NAMS members. The Society is grateful to the following individuals who served on the panel:

Co-Chair Margery L.S. Gass, MD – Professor of Clinical Obstetrics and Gynecology, University of Cincinnati College of Medicine; Director, University Hospital Menopause and Osteoporosis Center, Cincinnati, OH; NAMS President-Elect; WHI Investigator.

Co-Chair Wulf H. Utian, MD, PhD, FACOG, FRCOG – Arthur H. Bill Professor Emeritus of Reproductive Biology and Obstetrics and Gynecology, Case Western Reserve School of Medicine; Consultant in

Gynecology, the Cleveland Clinic Foundation, Cleveland, OH; NAMS Executive Director and Past-President.

Bruce Ettinger, MD, FACP – Senior Investigator, Division of Research, Kaiser Permanente Medical Care Program, Oakland, CA; NAMS Past-President.

J. Chris Gallagher, MD – Professor of Medicine, Creighton University; Department of Metabolism, St. Joseph’s Hospital, Omaha, NE; NAMS Past-President.

David M. Herrington, MD, MHS – Professor of Internal Medicine/Cardiology, Associate in Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, NC; HERS and WHI Investigator.

Marian C. Limacher, MD – Professor of Medicine, Division of Cardiovascular Medicine, University of Florida College of Medicine, Gainesville, FL; WHI Investigator.

Rogério A. Lobo, MD – Willard C. Rappleye Professor of Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons, New York, NY.

Meir J. Stampfer, MD, DrPH – Professor of Epidemiology and Nutrition and Chair, Department of Epidemiology, Harvard School of Public Health, Boston, MA.

Marcia L. Stefanick, PhD – Associate Professor of Medicine, Associate Professor of Gynecology and Obstetrics (by courtesy), Stanford University, Stanford Center for Research in Disease Prevention, Palo Alto, CA; HERS and WHI Investigator; Chair, WHI Steering Committee.

Nancy Fugate Woods, PhD, RN, FAAN – Dean, School of Nursing, and Professor, Family and Child Nursing, University of Washington, Seattle, WA; NAMS Past-President; WHI Investigator.

Methodology

The panelists developed a set of clinically relevant questions, and each provided responses. Their responses were not always in agreement, especially for issues without available research findings, indicating areas needing further study. The panelists met by con-

ference call to attempt to reach consensus for this document. The clinical recommendations indicate where consensus was achieved as well as where opinions differed. In reaching conclusions, data from HERS (both HERS and HERS II), WHI, and other published studies of hormone use were considered. Key references are listed at the end of this report.

Terminology

In this document, the following terms are used:

Estrogen therapy (ET) – Unopposed estrogen regimens, administered to postmenopausal women after hysterectomy.

Estrogen-progestogen therapy (EPT) – Estrogen plus progestogen.

Continuous-combined EPT (CCEPT) – Daily administration of both estrogen and progestogen.

BRIEF DESCRIPTION OF HERS AND WHI

HERS was a randomized, blinded, placebo-controlled trial of CCEPT in postmenopausal women ($N = 2,763$) with documented coronary heart disease (CHD). Mean age was 67 years (range 55-79). The initial study ended after 4.1 years average follow-up. Because a post-hoc analysis suggested a possible higher risk of coronary events during the first year but a reduced risk after years 3 to 5, the study was extended in an open-label design (HERS II) by asking participants to consider remaining on their assigned treatment (estrogen plus progestogen or no active hormones) after consultation with their physicians. In all, 93% of the original HERS participants ($N = 2,321$) continued treatment for an additional 2.7 years (mean total, 6.8 years). The proportion of women at least 80% adherent to hormone therapy declined from 81% in year 1 to 45% in year 6; in the placebo group, use of hormone therapy increased from 0% in year 1 to 8% in year 6.

WHI is an NIH-sponsored, multicenter study begun in 1993, consisting of a set of three interrelated clinical trials and an observational study in apparently healthy postmenopausal women aged 50 to 79 (mean age 63.2). At study entry, 7.7% had prior cardiovascular disease. The randomized, blinded, placebo-controlled hormone study of WHI has an arm of CCEPT for women with a uterus ($n = 16,608$) and an estrogen-only arm ($n = 10,739$) for women who had undergone a hysterectomy. Among the 8,506 randomized to CCEPT, 33.4% were ages 50 to 59, 45.3% were 60 to 69, and 21.3% were 70 to 79. The CCEPT arm of the study was terminated in July 2002 after an average of 5.2 years follow-up because the overall risks exceeded benefits. At study

end, adherence rates were 58% for the CCEPT arm and 62% for the placebo arm. The ET arm of WHI continues, as do ancillary WHI studies evaluating memory, dementia, low-fat diet, calcium, and vitamin D.

For CCEPT, both trials utilized oral estrogen plus oral progestogen therapy (0.625 mg/day of conjugated equine estrogens plus 2.5 mg/day of medroxyprogesterone acetate). The majority of participants in these trials were randomized at least 10 years after menopause.

Neither trial evaluated perimenopausal women or women with early menopause (ie, 40-50 years of age) or premature menopause (ie, < 40 years of age).

Clinically important facts from HERS and WHI

CCEPT was associated with the following clinically important outcomes (RR = relative risk; AR = absolute risk; CI = nominal 95% confidence interval; data marked “HERS” combine both HERS and HERS II results):

- *Effect on the risk of coronary heart disease*

WHI: Significant increased risk

RR 1.29 (CI 1.02-1.63); 29% increased risk

AR 0.37% v 0.30% (ie, 37 v 30 events annually per 10,000 women)

HERS: Nonsignificant decreased risk

RR 0.99 (CI 0.84-1.17); 1% decreased risk

AR 3.66% v 3.68% (ie, 366 v 368 events annually per 10,000 women)

- *Effect on the risk of stroke*

WHI: Significant increased risk

RR 1.41 (CI 1.07-1.85); 41% increased risk

AR 0.29% v 0.21% (ie, 29 v 21 events annually per 10,000 women)

HERS: Nonsignificant increased risk

RR 1.09 (CI 0.88-1.35); 9% increased risk

AR 2.12% v 1.95% (ie, 212 v 195 events annually per 10,000 women)

- *Effect on the risk of venous thromboembolism*

WHI: Significant increased risk

RR 2.11 (CI 1.58-2.82); 111% increased risk

AR 0.34% v 0.16% (ie, 34 v 16 events annually per 10,000 women)

HERS: Significant increased risk

RR 2.08 (CI 1.28-3.40); 108% increased risk

AR 0.59% v 0.28% (ie, 59 v 28 events annually per 10,000 women)

- *Effect on the risk of breast cancer*

WHI: Nonsignificant increased risk
 RR 1.26 (CI 1.00-1.59); 26% increased risk
 AR 0.38% v 0.30% (ie, 38 v 30 events annually per 10,000 women)

HERS: Nonsignificant increased risk
 RR 1.27 (CI 0.84-1.94); 27% increased risk
 AR 0.59% v 0.47% (ie, 59 v 47 events annually per 10,000 women)

- *Effect on the incidence of biliary tract surgery*

HERS: Significant increased incidence
 RR 1.48 (CI 1.12-1.95); 48% increased risk
 AR 1.91% v 1.29% (ie, 191 v 129 events annually per 10,000 women)

- *Effect on the risk of colon cancer*

WHI: Significant decreased risk
 RR 0.63 (CI 0.43-0.92); 37% decreased risk
 AR 0.10% v 0.16% (ie, 10 v 16 events annually per 10,000 women)

HERS: Nonsignificant decreased risk
 RR 0.81 (CI 0.46-1.45); 19% decreased risk
 AR 0.25% v 0.31% (ie, 25 v 31 events annually per 10,000 women)

- *Effect on the risk of osteoporotic fracture*

WHI:
 Hip: Significant decreased risk
 RR 0.66 (CI 0.45-0.98); 34% decreased risk
 AR 0.10% v 0.15% (ie, 10 v 15 events annually per 10,000 women)

Vertebral: Significant decreased risk
 RR 0.66 (CI 0.44-0.98); 34% decreased risk
 AR 0.09% v 0.15% (ie, 9 v 15 events annually per 10,000 women)

Total: Significant decreased risk
 RR 0.76 (CI 0.69-0.85); 24% decreased risk
 AR 1.47% v 1.91% (ie, 147 v 191 events annually per 10,000 women)

HERS:
 Hip: Nonsignificant increased risk
 RR 1.61 (CI 0.98-2.66); 61% increased risk
 AR 0.48% vs 0.30% (ie, 48 vs 30 events annually per 10,000 women)

Vertebral: Nonsignificant decreased risk
 RR 0.87 (CI 0.52-1.48); 13% decreased risk

AR 0.31% vs 0.35% (ie, 31 vs 35 events annually per 10,000 women)

Total: Nonsignificant increased risk
 RR 1.04 (CI 0.87-1.25); 4% increased risk
 AR 2.97% vs 2.84% (ie, 297 vs 284 events annually per 10,000 women)

These increased risks and benefits of CCEPT persisted throughout the duration of the WHI and HERS trials. Breast cancer risk was directly related to duration of therapy. Significant risk for coronary heart disease (CHD) and venous thromboembolism was observed during the first year of therapy, although CHD risk was not significantly elevated in following years.

In women who are at risk for CHD, stroke, or thromboembolism or those who are older, the absolute risks of CCEPT will be higher. For older women, the absolute benefits may be higher as well because osteoporosis and colon cancer are more prevalent at that age. Conversely, because CHD, stroke, and osteoporotic fractures are less common in younger women, the absolute risks and benefits will be lower in younger postmenopausal women.

Based on data other than WHI and HERS, the risk for breast cancer may be higher on CCEPT than on unopposed estrogen (ET). The actual breast cancer risk in the ongoing ET arm of the WHI study has not been published and may not be available until the study's planned conclusion in 2005. However, after 5.2 years, WHI has not reported that the ET arm has shown excess risk over benefit. The risk for breast cancer while using CCEPT appears to be related to duration of use. This may also apply to ET use, as reported from observational studies.

The present WHI report did not address a variety of other conditions for which CCEPT may or may not provide a favorable effect, including gallbladder disease, diabetes, cognitive function, and quality of life (QOL). HERS reported the adverse effect on gallbladder disease; WHI and HERS reported the effect on osteoporotic fracture. Neither study was designed to address QOL in highly symptomatic women. The WHI ancillary studies, WHI Memory Study (WHIMS) and WHI Study of Cognitive Aging (WHISCA), may help determine whether CCEPT or ET has an effect on changes in cognitive function with aging. HERS reported no effect of CCEPT on QOL after menopause. However, this component of HERS has been criticized for not being designed to evaluate QOL in the most relevant population – symptomatic menopausal women. HERS evaluated an elderly population with CHD; furthermore, a validated QOL instrument was not utilized. Extrapolat-

ing these QOL data to a typical perimenopausal population using CCEPT is not appropriate.

BASIC RECOMMENDATIONS FOR CLINICAL PRACTICE

The panel agreed on the following:

- Treatment of menopause symptoms (eg, vasomotor and urogenital) remains the primary indication for EPT and ET.
- The only menopause-related indication for chronic progestogen use appears to be endometrial protection from unopposed estrogen therapy. For all women with an intact uterus who are using estrogen therapy, clinicians are advised to prescribe adequate progestogen, whereas women without a uterus should not be prescribed a progestogen.
- No EPT regimen should be used for primary or secondary prevention of coronary heart disease (CHD). Proven alternate cardioprotective regimens should be considered. The effect of ET on CHD is not yet clear. Until confirming data are available, ET should not be used for primary or secondary prevention of CHD.
- WHI and HERS data cannot be directly extrapolated to symptomatic perimenopausal women or to women experiencing early menopause (ie, 40-50 years of age) or premature menopause (ie, < 40 years).
- Many EPT and ET products are FDA-approved for the prevention of postmenopausal osteoporosis; however, because of the risks associated with these forms of therapy, alternatives should also be considered, weighing the risks and benefits of each.
- Use of EPT or ET should be limited to the shortest duration consistent with treatment goals, benefits, and risks for the individual woman, taking into account issues of quality of life.
- Lower-than-standard doses of EPT and ET should be considered. The Women's Health, Osteoporosis, Progestin, Estrogen (HOPE) trial demonstrated equivalent symptom relief and preservation of bone density without an increase in endometrial hyperplasia with lower doses of EPT.
- Alternate routes of administration of EPT may offer advantages, but the long-term benefit-risk ratio has not been demonstrated.
- An individual risk profile is essential for every woman contemplating any regimen of EPT or ET. Women should be informed of known risks.

The panel did not reach consensus on the following, but the summary of responses is of relevance to clinicians:

What are current acceptable definitions of short-term and long-term hormone therapy?

Short-term hormone therapy has been generally defined as 3 to 5 years, whereas long-term hormone therapy has been defined as longer than 3 to 5 years. In reviewing these prevailing definitions, panelists had varying opinions regarding maintaining these definitions. Current data provide no assistance in determining at what time point risks would outweigh benefits for an individual woman. Panelists concluded that potential benefits and risks of hormone therapy should be determined by the individual woman's risk profile, including age and the reason(s) for the prescription. In this context, there appeared little purpose in differentiating short- and long-term therapy and, thus, the panel recommended that these terms no longer be used. Clinicians should reevaluate the benefit-risk profile of an individual woman and the indication(s) for ongoing therapy at each visit.

How long should hormone therapy be prescribed for symptom relief?

The duration of therapy for symptom relief cannot be answered using existing data. Women with severe menopause symptoms were unlikely to enroll in WHI because of their reluctance to possibly be randomized to placebo. The ongoing Study of Women's Health Across the Nation (SWAN) may clarify how long symptoms persist beyond the menopause transition or hormone therapy cessation and the severity of these symptoms. Follow-up of the terminated CCEPT arm of the WHI study may provide insight; however, no symptom diaries are being used. Although no definitive recommendations were made, the panelists agreed that a guiding principal should be the lowest effective dose for the shortest time.

Do reasons exist for extended hormone therapy?

The panel considered whether there are individual circumstances for which extended use of hormone therapy would be appropriate. Even though the WHI reported the first definitive data supporting the ability of postmenopausal EPT to prevent fractures at the hip, vertebrae, and other sites, a consensus was not reached. Some panelists expressed the opinion that there is no preventive indication for any EPT/ET therapy. However, the majority of the panelists believed that extended use of EPT or ET would be acceptable under special circumstances, provided women are well aware of the potential risks and there is strict clinical supervision. These circumstances include:

1. Any woman for whom, in her opinion, benefits of symptom relief outweigh risks

2. Women with menopause symptoms who are at risk for osteoporosis
3. Women with increased osteoporosis risk unable to tolerate other therapeutic options

Does either premature menopause or premature ovarian failure represent an indication for preventive EPT or ET?

Although these conditions are associated with earlier onset of osteoporosis and CHD, there are no clear data as to whether administration of EPT/ET will reduce morbidity or mortality from these conditions. The benefit-risk ratio may be different for younger women.

Is there a consensus on how best to discontinue hormone therapy?

In the absence of adequate data, there was no consensus on this issue. The suggested options include abrupt cessation (“cold turkey”) and tapering off therapy by either skipping progressively more days between doses or lowering doses every 4 to 6 weeks. Past history of severe symptoms may favor tapering.

Is it possible to make general conclusions about all members of the estrogen and progestogen families?

The panel concluded that it is not possible to generalize the HERS and WHI data on continuous-combined oral conjugated equine estrogens (0.625 mg/day) and medroxyprogesterone acetate (2.5 mg/day) to other estrogens and progestogens, routes of administration, dosages, and regimens. Nonetheless, it was strongly held that an improved benefit-risk profile of other EPT agents and regimens cannot be assumed until proven.

It is premature to assume that ET will have a more favorable profile than EPT. Low-dose vaginal ET may have an acceptable benefit-risk profile for extended use in women with vaginal symptomatology, but no long-term data exist. This assumption is based on minimal increase in systemic estrogen levels.

IMMEDIATE NEEDS FOR FUTURE RESEARCH

Panelists identified the following research needs, presented in no particular order:

- Beyond symptoms, are there biologic differences between symptomatic and asymptomatic women that affect the benefit-risk profile?
- Do different estrogens and progestogens, different doses, and different routes of administration have the same benefit-risk profiles as the hormones used in HERS and WHI?
- Do women experiencing early or premature menopause and highly symptomatic perimenopausal

women have the same benefit-risk profiles as the women studied in WHI?

- Are the benefits and risks of ET substantially different from EPT? Is progestogen responsible for the negative effects of EPT?
- Is continuous progestin, as opposed to sequential progestin, responsible for adverse cardiovascular and breast effects?
- What is the effect of different progestogens on breast cancer risk?
- Is the endogenous level of estradiol and/or estrone a significant modifier of benefit and/or risk?
- Are there genetic or environmental factors that significantly alter the benefit-risk profile for EPT/ET?
- How are quality-of-life issues factored into the risk-benefit profile for EPT/ET?
- What is the role of ET in the primary prevention of CHD?
- Can women at risk for deep vein thrombosis and pulmonary embolism be identified?
- What are the long-term effects of EPT/ET on dementia and Alzheimer’s disease?

RECOMMENDED READING

WHI (Women’s Health Initiative)

Writing Group for the Women’s Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women’s Health Initiative randomized controlled trial. *JAMA* 2002;288:321-333.

HERS (Heart and Estrogen/Progestin Replacement Study)

Herrington DM, Vittinghoff E, Lin F, et al, for the HERS Study Group. Statin therapy, cardiovascular events, and total mortality in the Heart and Estrogen/Progestin Replacement Study (HERS). *Circulation* 2002; 105:2962-2967.

Hlatky MA, Boothroyd D, Vittinghoff E, Sharp P, Whooley MA, for the Heart and Estrogen/Progestin Replacement Study (HERS) Research Group. Quality-of-life and depressive symptoms in postmenopausal women after receiving hormone therapy: results from the Heart and Estrogen/Progestin Replacement Study (HERS) trial. *JAMA* 2002;287:591-597.

Hsia J, Simon JA, Lin F, et al. Peripheral arterial disease in randomized trial of estrogen with progestin in women with coronary heart disease: the Heart and Estrogen/Progestin Replacement Study. *Circulation* 2000;102:2228-2232.

Hulley S, Grady D, Bush T, et al, for the Heart and Estrogen/progestin Replacement Study (HERS) Re-

search Group. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* 1998;280:605-613.

Simon JA, Hsia J, Cauley JA, et al. Postmenopausal hormone therapy and risk of stroke: the Heart and Estrogen/progestin Replacement Study (HERS). *Circulation* 2001;103:638-642.

HERS II (Heart and Estrogen/Progestin Replacement Study)

Grady D, Herrington D, Bittner V, et al, for the HERS Research Group. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). *JAMA* 2002;288:49-57.

Hulley S, Furberg C, Barrett-Connor E, et al, for the HERS Research Group. Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). *JAMA* 2002;288:58-66.

WEST (Women's Estrogen for Stroke Trial)

Viscoli CM, Brass LM, Kernan WN, Sarrel PM, Sussman S, Horwitz RI. A clinical trial of estrogen-replacement therapy after ischemic stroke. *N Engl J Med* 2001;345:1243-1249.

Nurses' Health Study

Grodstein F, Manson JE, Colditz GA, Willett WC, Speizer FE, Stampfer MJ. A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. *Ann Intern Med* 2000;133:933-941.

Grodstein F, Stampfer MJ, Colditz GA, et al. Postmenopausal hormone therapy and mortality. *N Engl J Med* 1997;336:1769-1775.

Grodstein F, Stampfer MJ, Manson JE, et al. Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. *N Engl J Med* 1996;335:453-461.

HOPE (Women's Health, Osteoporosis, Progestin, Estrogen trial)

Archer DF, Dorin M, Lewis V, Schneider DL, Pickar JH. Effects of lower doses of conjugated equine estrogens and medroxyprogesterone acetate on endometrial bleeding. *Fertil Steril* 2001;75:1080-1087.

Lindsay R, Gallagher JC, Kleerekoper M, Pickar JH. Effect of lower doses of conjugated equine estrogens

with and without medroxyprogesterone acetate on bone in early postmenopausal women. *JAMA* 2002;287:2668-2676.

Lobo RA, Bush T, Carr BR, Pickar JH. Effects of lower doses of conjugated equine estrogens and medroxyprogesterone acetate on plasma lipids and lipoproteins, coagulation factors, and carbohydrate metabolism. *Fertil Steril* 2001;76:13-24.

Pickar JH, Yeh I, Wheeler JE, Cunnane MF, Speroff L. Endometrial effects of lower doses of conjugated equine estrogens and medroxyprogesterone acetate. *Fertil Steril* 2001;76:25-31.

Utian WH, Shoupe D, Bachmann G, Pinkerton JV, Pickar JH. Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens and medroxyprogesterone acetate. *Fertil Steril* 2001;75:1065-1079.

ERA (Estrogen Replacement and Atherosclerosis trial)

Herrington DM, Reboussin DM, Brosnihan KB, et al. Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. *N Engl J Med* 2000;343:522-529.

EPAT (Estrogen in the Prevention of Atherosclerosis Trial)

Hodis HN, Mack WJ, Lobo RA, et al, for Estrogen in the Prevention of Atherosclerosis Trial Research Group. Estrogen in the prevention of atherosclerosis: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2001;135:939-953.

MORE (Multiple Outcomes of Raloxifene Evaluation)

Barrett-Connor E, Grady D, Sashegyi A, et al, for the MORE Investigators (Multiple Outcomes of Raloxifene Evaluation). Raloxifene and cardiovascular events in osteoporotic postmenopausal women: four-year results from the MORE (Multiple Outcomes of Raloxifene Evaluation) randomized trial. *JAMA* 2002;287:847-857.

Cauley JA, Norton L, Lippman ME, et al. Continued breast cancer risk reduction in postmenopausal women treated with raloxifene: 4-year results from the MORE trial. Multiple outcomes of raloxifene evaluation [erratum appears in *Breast Cancer Res Treat* 2001;67:191]. *Breast Cancer Res Treat* 2001;65:125-134.

Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation [er-

ratum appears in *JAMA* 1999;282:2124]. *JAMA* 1999; 281:2189-2197.

Delmas PD, Ensrud KE, Adachi JD, et al, for the Multiple Outcomes of Raloxifene Evaluation Investigators. Efficacy of raloxifene on vertebral fracture risk reduction in postmenopausal women with osteoporosis: four-year results from a randomized clinical trial. *J Clin Endocrinol Metab* 2002;87:3609-3617.

PEPI (Postmenopausal Estrogen/Progestin Interventions study)

Barrett-Connor E, Slone S, Greendale G, et al. The Postmenopausal Estrogen/Progestin Interventions Study: primary outcomes in adherent women. *Maturitas* 1997;27:261-274.

Greendale GA, Espeland M, Slone S, Marcus R, Barrett-Connor E, for the PEPI Safety Follow-up Study (PSFS) Investigators. Bone mass response to discontinuation of long-term hormone replacement therapy: results from the Postmenopausal Estrogen/Progestin Interventions (PEPI) safety follow-up study. *Arch Intern Med* 2002;162:665-672.

Greendale GA, Wells B, Marcus R, Barrett-Connor E, for the Postmenopausal Estrogen/Progestin Interventions trial investigators. How many women lose bone mineral density while taking hormone replacement therapy? Results from the Postmenopausal Estrogen/Progestin Interventions trial. *Arch Intern Med* 2000;160:3065-3071.

The Writing Group for the PEPI trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women: the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial [erratum appears in *JAMA* 1995;274:1676]. *JAMA* 1995;273:199-208.

The Writing Group for the PEPI trial. Effects of hormone therapy on bone mineral density: results from the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial. *JAMA* 1996;276:1389-1396.

SWAN (Study of Women's Health Across the Nation)

Huang M-H, Schocken M, Block G, et al. Variation in nutrient intakes by ethnicity: results from the Study of Women's Health Across the Nation (SWAN). *Menopause* 2002;9:309-319.

FIT (Fracture Intervention Trial)

Black DM, Thompson DE, Bauer DC, et al, for the Fracture Intervention Trial. Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial [erratum appears in *J Clin Endocrinol Metab* 2001;86:938]. *J Clin Endocrinol Metab* 2000;85:4118-4124.

Cummings SR, Black DM, Thompson D, et al, for the Fracture Intervention Trial Research Group. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA* 1998;280: 2077-2082.

VERT (Vertebral Efficacy With Risedronate Therapy study group)

Harris ST, Watts NB, Genant HK, et al, for the Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. *JAMA* 1999;282:1344-1352.

Reginster J-Y, Minne HW, Sorensen OH, et al, for the Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. *Osteoporos Int* 2000;11:83-91.

HIP (Hip Intervention Program study group)

McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women. *N Engl J Med* 2001;344:333-340.