
Special News Update

In recent months, several important studies have been published that Menopause Management believes are of great interest to its readers. In this issue, we bring you a special expanded news section focusing on these recently published studies with commentary from experts in the clinical practice and research communities. Unless specifically stated otherwise, the comments are opinions or information of the authors and not necessarily the opinions or information of Menopause Management or The North American Menopause Society, its officers, agents, or trustees.

Note. The level of evidence indicated for each study is based on the following grading system: [reference: US Preventive Services Task Force]

- **Level I:** Properly randomized, controlled trial.
- **Level II-1:** Well-designed controlled trial but without randomization.
- **Level II-2:** Well-designed cohort or case-control study, preferably from more than one center or research group.
- **Level II-3:** Multiple time series with or without the intervention (eg, cross-sectional and uncontrolled investigational studies); uncontrolled experiments with dramatic results could also be regarded as this type of evidence.
- **Level III:** Opinions of respected authorities that are based on clinical experience; descriptive studies and case reports; reports from expert committees.

WHI publishes additional data analysis regarding CHD effects with EPT

Manson JE, Hsia J, Johnson KC, et al, for the Women's Health Initiative Investigators. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med* 2003;349:523-534.

Estrogen plus progestin therapy (EPT) increases the risk of coronary heart disease (CHD) among generally healthy postmenopausal women, espe-

cially during the first year of EPT use, according to this analysis of data from the Women's Health Initiative (WHI). The WHI, a randomized, placebo-controlled trial, enrolled 16,608 postmenopausal women aged 50 to 79 (mean age, 63.3 years). Women were randomly assigned to therapy with either placebo or conjugated equine estrogens (0.625 mg/day) plus medroxyprogesterone acetate (2.5 mg/day). The primary endpoint was CHD, defined as nonfatal myocardial infarction or death due to CHD. After a mean follow-up of 5.2 years (from a planned duration of 8.5 years), EPT recipients had an overall 24% increased risk for CHD (95% CI, 1.00-1.54; adjusted analysis 95% CI, 0.97-1.60). The risk was highest after 1 year of therapy (hazard ratio, 1.81; 95% CI, 1.09-3.01) and decreased to 1.45 at year 5 (95% CI, 0.89-2.59). EPT use for 6 years was associated with a 30% decrease in CHD risk (95% CI, 0.42-1.14). Higher baseline levels of low-density lipoprotein (>155 mg/dL) were associated with an excess risk (HR, 1.68) of CHD among EPT recipients. However, higher baseline levels of C-reactive protein, other biomarkers, and other clinical characteristics of CHD did not significantly affect the CHD risks.

Level I evidence

Comment. These data by Manson et al are reported to be the "final" results regarding CHD in the EPT trial from

the WHI. The data are not very different from the initial report [WHI Writing Group *JAMA* 2002] but do shed some additional light on the subject. The overall data now show only a borderline significant hazard ratio (HR) of 1.24 (95% CI, 1.00-1.54) using nominal statistics, and with a confidence interval of 0.97 to 1.60 for sequential monitoring. Only MI risk was increased, not revascularization, angina, CHF, or death due to CHD. The risk is principally due to more events witnessed in the first year ("early harm"), with a decreasing trend thereafter that was statistically significant. These data are very reminiscent of HERS [Hulley *JAMA* 1998], a secondary prevention trial. For many women in the WHI, this was a prevention trial in women with coronary disease even if they had not had a cardiovascular event. Most women in the WHI were many years postmenopause, and we know that coronary disease is related to time from menopause. [Hu *Arch Intern Med* 1999] In this report, women who were less than 10 years postmenopause had an overall HR of 0.89, while women 20 or more years postmenopause had an HR of 1.7. A breakdown by each year of exposure was not provided.

Other recently available data also confirm that healthy women within five years of menopause do not experience "early harm." Although the conclusion of this report—that "this treatment should not be prescribed for the

prevention of CVD”—is evidence based, it is intriguing to speculate that younger women who do not experience “early harm” may have a decreasing rate of CHD with time and, indeed, may have some protection with some form of hormonal therapy. This would be in concert with the data from observational trials. In a nested case-control study of biomarkers, significant positive findings in this report are reductions of glucose, body weight, and waist circumference ($P < 0.05$) in the EPT group, although systolic blood pressure increased. The lipid data were also consistent with multiple previous reports. The only biomarker showing greater excess risk from CHD with EPT was baseline LDL-cholesterol (not even C-reactive protein had a significantly increased risk). If not due to chance, perhaps this higher LDL-cholesterol signifies more silent coronary disease in this cohort with a greater chance for “early harm.”

Rogério A. Lobo, MD
Chair, Department of Obstetrics
and Gynecology
Columbia Presbyterian Medical Center
New York, NY

Comment. This report describes the final results of the WHI primary prevention trial of combined EPT and CHD risk in postmenopausal women. The investigators conclude, as they did previously, that combined EPT does not confer cardiac protection and that initiation of EPT may increase the risk of CHD among generally healthy postmenopausal women (mean age, 63.3 years), especially during the first year. Advances in this new analysis are modest and include an additional 0.4 years of follow-up, centralized adjudication of cardiovascular events, an analysis of several additional coronary endpoints, and a more detailed examination of potential demographic, clinical, and biomarker modulators of risk. The apparent slight increase in CHD risk observed in women receiving EPT is

better characterized in this report. Intriguingly, the increased risk in women receiving EPT is found to be for MI but not for coronary revascularization, angina, or congestive heart failure, which suggests that initiating EPT somehow increased the risk for acute arterial thrombosis. This paper reinforces that EPT should not be initiated for the prevention of cardiovascular disease in postmenopausal women.

What is new here? The report describes, though cautiously, a statistically significant trend toward a decreased risk of CHD over time in women receiving EPT. More striking, however, is that the only subgroup in this study identified to be at increased risk for CHD with EPT is women with higher baseline LDL-cholesterol levels. No other variable is identified that might be useful for coronary risk stratification of women treated with EPT. Notably, there are no differences in the risk for CHD associated with EPT based on the presence or absence of vasomotor symptoms, use of aspirin or statin therapy, or baseline levels of C-reactive protein.

What testable differences could be sought in future studies that might prove useful for such stratification? Genetic variants in the estrogen receptors themselves and/or those genes involved in regulating the thrombotic and fibrinolytic pathways are logical candidates. Despite the stated conclusions, the study does not actually address whether EPT should be “continued” in women who have been on treatment for some time or the role of EPT for the short-term treatment of menopausal symptoms. This report also does not address whether perimenopausal EPT alters the progression of early, subclinical atherosclerosis before it has developed as fully as in older postmenopausal women (see Hodis study on this page).

Michael E. Mendelsohn, MD
Department of Cardiology
Tufts-New England Medical Center
Boston, MA

ET/EPT does not appear to increase or decrease atherosclerosis rate

Hodis HN, Mack WJ, Azen SP, et al, for the Women’s Estrogen-Progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial Research Group. Hormone therapy and the progression of coronary-artery atherosclerosis in postmenopausal women. *N Engl J Med* 2003;349:535-545.

In older postmenopausal women with established coronary artery atherosclerosis, 17 β -estradiol, administered either alone or with sequentially administered medroxyprogesterone acetate (MPA), has no significant positive or negative effect on the progression of atherosclerosis, according to data from the Women’s Estrogen-Progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial (WELL-HART), a randomized, placebo-controlled trial. A total of 226 postmenopausal women (mean age, 63.5 years) with at least one coronary artery lesion were assigned to one of three groups: estrogen alone (1 mg/day oral micronized 17 β -estradiol; Estrace) plus placebo for 12 days/mo; estrogen plus progestin (5 mg/day MPA; Provera) for 12 days/mo; or a matching placebo regimen. After a median of 3.3 years follow-up, the mean percentage point changes in stenosis were 2.18 in the estrogen alone group, 1.24 in the estrogen plus progestin group, and 1.89 in the control group. Compared with the control group, the between-group differences were not significant. The authors note that in contrast to previous trials using continuous-combined conjugated estrogens and MPA, this study found no increase in the rate of coronary events during the first year of EPT therapy.

Level I evidence

Comment. The results of WELL-HART using 17 β -estradiol, with or without sequential MPA, are concordant with previous studies demonstrating no effect of conjugated estrogens or estrogen plus continuous MPA on angiographic coronary lesions.

Although not designed as a clinical endpoint study, the similarity of findings now provides sound support that two different estrogens and two different progestin regimens (17 α -estradiol or conjugated estrogens; continuous or sequential MPA) are not cardioprotective in women with atherosclerosis. The attention to LDL-cholesterol lowering in this study also points out the need to lower all risk factors to established target levels for women with known coronary artery disease. In this study, an LDL goal of 130 mg/dL is actually too high; women with coronary disease have an LDL treatment goal of less than 100 mg/dL. The angiographic outcomes may have been better with adherence to standard management guidelines. Some argue that estrogen may still prove effective in preventing the development of advanced atherosclerosis by initiating treatment earlier, but long-term clinical trial evidence supporting that theory is required before prolonged administration (beyond the duration needed for symptom treatment) can be recommended.

Marian C. Limacher, MD
Professor of Medicine
University of Florida
Division of Cardiovascular Medicine
Gainesville, FL

Comment. This report describes the results of WELL-HART, a randomized, controlled trial of the effects of oral estradiol versus placebo on the progression of carotid intima-media thickness (IMT) in women without pre-existing cardiovascular disease, all of whom received cholesterol lowering therapy. The primary outcome in WELL-HART is the change in a single coronary artery stenosis. The WELL-HART investigators also conducted the Estrogen in the Prevention of Atherosclerosis Trial (EPAT). [Hodis *Ann Intern Med* 2001] EPAT demonstrated that 17 α -estradiol therapy alone significantly slowed the pro-

gression of carotid IMT in women who did not receive lipid-lowering therapy, but had no such effect in women receiving cholesterol lowering therapy (40% of participants). In contrast, the WELL-HART investigators now report that neither estradiol nor estradiol plus MPA have any effect on the progression of coronary atherosclerosis.

Why are the WELL-HART results different from the EPAT results? The investigators suggest that the most likely explanation is the degree to which atherosclerosis was established in the blood vessels studied in the two trials. They note that the time from menopause to randomization was approximately five years shorter in EPAT than in WELL-HART and that carotid IMT is a measure of early, subclinical atherosclerosis, whereas coronary angiography is used to evaluate late-stage, symptomatic atherosclerosis. This is a plausible hypothesis that is supported by substantial animal data. Other differences between WELL-HART and EPAT to bear in mind are the predominantly minority study population and high percentage of women with diabetes mellitus in WELL-HART. Perhaps most importantly, in contrast to EPAT, all participants randomized in WELL-HART were given statin therapy, the most effective treatment we have for slowing the progression of atherosclerosis.

Michael E. Mendelsohn, MD
Department of Cardiology
Tufts-New England Medical Center
Boston, MA

Three clinical trials show isoflavone supplements lack efficacy for treating hot flashes

Penotti M, Fabio E, Modena AB, Rinaldi M, Omodei U, Vigano P. Effect of soy-derived isoflavones on hot flashes, endometrial thickness, and the pulsatility index of the uterine and cerebral arteries. *Fertil Steril* 2003;79:1112-1117.

Soy-derived isoflavones are no more

effective than placebo in reducing hot flashes, according to this six-month, randomized, double-blind, placebo-controlled trial. In all, 62 postmenopausal women aged 45 to 60 years who had been experiencing at least 7 hot flashes per day were randomized to either soy-derived isoflavones (at a dose of 72 mg/day) or placebo. Primary endpoints were the daily number of hot flashes, endometrial thickness, and arterial pulsatility index. At study end, both the isoflavone and placebo groups had a 40% reduction in the number of hot flashes. Soy had no effect on either endometrial thickness or the arterial pulsatility index of either the uterine or cerebral arteries.

Level I evidence

Nikander E, Kikkinen A, Metsa-Heikkilä M, et al. A randomized placebo-controlled crossover trial with phytoestrogens in treatment of menopause in breast cancer patients. *Obstet Gynecol* 2003;101:1213-1220.

Phytoestrogen tablets do not provide effective relief from menopause-related symptoms, including hot flashes, in postmenopausal women with breast cancer, according to this randomized, placebo-controlled, double-blind, crossover trial from Finland. Investigators enrolled 62 postmenopausal women (mean age, 54) who had been treated for breast cancer but were not currently receiving tamoxifen therapy. Participants received either phytoestrogen tablets (at a dose of 114 mg/day) or placebo for 3 months. After a two-month washout period, women were switched to the other treatment. Menopause-related symptoms, including hot flashes, were recorded on the Kupperman index. At study end, the overall Kupperman index score was reduced by 15.5% in the phytoestrogen group (mean drop, 4.2) and by 14.7% in the placebo group (mean, 4.0); the between-group difference was not statistically significant. When evaluated separately from the rest of the Kupperman index, the hot flash component was reduced more in the placebo group than in the

phytoestrogen group (by 14.3% and 10.0%, respectively), although the difference was not statistically significant. The quality of life parameters measured—capacity to work and mood changes—were not affected by phytoestrogen therapy. Phytoestrogen treatment was well tolerated and caused no significant changes in liver enzymes, creatinine, body mass index, or blood pressure. In a subset analysis, investigators evaluated results among women based on high and low levels of endogenous equol; results did not differ between the groups.

Level I evidence

Tice JA, Ettinger B, Ensrud K, Wallace R, Blackwell T, Cummings SR. Phytoestrogen supplements for the treatment of hot flashes: the Isoflavone Clover Extract (ICE) study. *JAMA* 2003;290:207-214.

Isoflavones derived from red clover are no more effective than placebo in reducing the incidence of hot flashes in women, according to this randomized, double-blind, placebo-controlled trial. A total of 252 women were randomly assigned either to placebo or active treatment with one of two red clover isoflavone products: Promensil (82 mg/day isoflavones) or Rimostil (57 mg/day isoflavones). Follow-up lasted 12 weeks. The primary outcome measure was frequency of hot flashes. Secondary outcome measures were quality of life and side effects. After 12 weeks, the mean reduction in hot flash incidence was 41% for Promensil, 34% for Rimostil, and 36% for placebo, a significant reduction from baseline for all three groups ($P < 0.001$). However, results in the isoflavone groups were not statistically different from placebo, even though Promensil recipients had significantly more rapid reductions in hot flashes than either Rimostil or placebo. Quality of life improvements and side effect profiles were similar in the three groups.

Level I evidence

Comment. The reports by Penotti et al and Nikander et al add to a growing

literature indicating that the isoflavones (phytoestrogens) of soy have minimal or no effects on postmenopausal hot flashes. The report by Penotti et al provides further evidence that soy isoflavones are not estrogen agonists for the endometrium. There has been evidence suggesting that those women who can convert daidzein to equol (about 25–30% of American women) may derive hot flash benefits. However, this was not the case in the women studied by Nikander et al. The isoflavone mixture studied by Nikander et al was unlike that studied by most investigators—only 6% genistein (usually 30–35%) and 58% glycitein (usually 2–4%).

The Tice et al article reports the results of a randomized clinical trial designed to test the efficacy of two red clover phytoestrogen products for the treatment of hot flashes, either Promensil (providing primarily genistein) or Rimostil (providing primarily daidzein). The authors conclude that neither supplement had a clinically important effect on hot flashes or other menopausal symptoms. Urine was collected for measurements of isoflavones/isoflavone metabolite excretion. No significant correlations were found between change in the number of hot flashes and urinary excretion of the primary isoflavones or their metabolites. Whether 83 women consuming Rimostil is an adequate number to see some association between equol production/excretion and reduction in numbers of hot flashes is uncertain, since only about 25% of the women would likely have been equol producers. While an association between equol production and hot flash control has not been disproven, it seems less likely given the result of recent trials.

Thomas B. Clarkson, DVM
Professor of Comparative Medicine
Wake Forest University School
of Medicine
Winston-Salem, NC

Comment. These three negative trials on isoflavone supplements (two were extracted from soy and one from red clover) confirm previous reports for the essential inefficacy of these products. The clinical implication is that women with mild vasomotor symptoms might consider either no pharmacotherapy or low-dose selective serotonin-reuptake inhibitors. However, women suffering from moderate to severe hot flashes that disrupt their quality of life would continue to benefit from short-term, low-dose hormone therapy.

Wulf H. Utian, MD, PhD
Arthur H. Bill Professor Emeritus of
Reproductive Biology and Ob/Gyn
Case Western Reserve University
School of Medicine
Consultant in Women's Health
Cleveland Clinic Foundation
Executive Director
The North American
Menopause Society
Cleveland, OH

Estrogen plus progestin therapy increases the risk of breast cancer in women

Chlebowski RT, Hendrix SL, Langer RD, et al, for the WHI investigators. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative randomized trial. *JAMA* 2003;289:3243-3253.

Combined estrogen plus progestin therapy can stimulate breast cancer growth and increase abnormal mammogram readings, according to data from the Women's Health Initiative (WHI), a randomized, double-blind, placebo-controlled trial. In the WHI, 16,608 postmenopausal women (aged 50 to 79 years) with a uterus received either placebo or estrogen plus progestin (EPT), at a dose of 0.625 mg/day of conjugated equine estrogens plus 2.5 mg/day medroxyprogesterone acetate. For this analysis, the primary endpoints

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were the number and characteristics of breast cancers and the number of abnormal mammograms. Screening mammography and clinical breast examinations were performed at baseline and then annually thereafter. After a mean of 5.2 years, EPT use increased the total risk of breast cancer by 24% (weighted $P < 0.001$) and the risk of invasive breast cancer by 24% ($P = 0.003$) when compared with placebo recipients. Among the invasive breast cancers that occurred, the tumors were significantly larger (mean 1.7 vs 1.5 cm for EPT and placebo, respectively; $P = 0.04$) and at more advanced stages (regional/metastatic 25.4% vs 16.0%, respectively; $P = 0.04$). Data on mammograms showed that at 1 year, EPT significantly increased the percentage of women with abnormal mammograms (9.4% vs 5.4%; $P < 0.001$), a pattern that continued throughout the study.

Level I evidence

Comment. This study needs to be kept in perspective. The absolute increased risk of breast cancer seen after 5 years of EPT use in WHI was 8 cases per 10,000 women per year, or 40 cases per 10,000 women at 5 years. These tumors would be 0.2 cm larger with a 10% higher incidence of regional spread and would be harder to find on standard mammography. For the group of women aged 45 to 55 who have less of an underlying risk of breast cancer and are more likely to take EPT for severe menopausal symptoms, the attributable risk of developing breast cancer would be smaller.

The increase in abnormal mammograms seen at year one and continuing throughout the study needs to be relayed to patients. There were 9.4% (716 of 7,656) abnormal mammograms in the EPT group versus 5.4% (398 of 7,310) in the placebo group. Use of EPT increases breast density, which can

make mammography more difficult to interpret. Going off EPT for 2 weeks will cause resolution of 75% of abnormalities seen. [Harvey *J Natl Cancer Inst* 1997] However, the need for repeat mammograms, spot compressions, or extra views substantially increases patient anxiety. The use of digital mammography may lessen this problem. In the ongoing estrogen-only arm of the WHI, no increase in adverse events significant enough to stop the trial had been found as of May 2003.

In conclusion, the findings of this article—slightly larger and more advanced regional lymph node spread—is in sharp contrast to prior observational studies that found smaller breast cancers with less node positivity and better survival in women on postmenopausal hormone therapy. This study adds to the evidence against the use of long-term EPT therapy in asymptomatic older women. For symptomatic women who are younger (aged 45-55) and at less risk for breast cancer as a function of age, postmenopausal hormone therapy can still be considered for relief of severe menopausal symptoms after full discussion with the woman of the risks and benefits of both ET/EPT and alternatives. This study should increase our caution with using ET/EPT, and it stresses the need for individual discussions and use of the lowest effective dose for the shortest duration. It also increases the need for improved mammographic detection with hormone-induced increases in breast density.

JoAnn V. Pinkerton, MD
Director, Midlife Health Center
Associate Professor of Obstetrics
and Gynecology
University of Virginia Health
Sciences System
Charlottesville, VA

Richard Santen, MD
Professor of Endocrinology
University of Virginia Health Center
Charlottesville, Virginia

Paroxetine shows some efficacy in reducing hot flashes

Stearns V, Beebe KL, Iyengar M, Dube E. Paroxetine controlled release in the treatment of menopausal hot flashes: a randomized controlled trial. *JAMA* 2003;289:2827-2834.

Controlled-release paroxetine HCl (Paxil), a selective serotonin-reuptake inhibitor, is effective in reducing menopause-related hot flashes, according to this randomized, double-blind, placebo-controlled, parallel-group trial. A total of 165 postmenopausal women older than age 18 (mean age range, 54-55) were enrolled. Women with signs of cancer or those receiving chemotherapy or radiation therapy were excluded. Participants received either placebo or a controlled-release formulation of paroxetine at a dose of either 12.5 or 25 mg/day for 6 weeks. At study end, paroxetine recipients had mean reductions in hot flash frequency from baseline of 3.3 (from 7.1 to 3.8) and 3.2 (from 6.4 to 3.2) for the 12.5 and 25 mg/day doses, respectively. The reductions were statistically significant compared with placebo recipients (mean reduction, 1.8; from 6.6 to 4.8). Using percentages, paroxetine recipients had median hot flash reductions of 62.2% and 64.6%, respectively, compared with 37.8% for the placebo group.

Level I evidence

Comment. This was a poor patient population for evaluating a drug's efficacy in relieving vasomotor symptoms. The FDA guidance for industry regarding clinical evaluation of hormone therapy mandates that study participants have at least 7 to 8 moderate to severe hot flashes per day, or 50 to 60 per week at baseline. In this study, participants were experiencing only two or three hot flashes per day or at least 14 bothersome hot flashes per week, a very different population than currently recommended for hot flash studies. The authors' conclusion that controlled-release paroxetine may

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Laura McKeown, Managing Editor, at 732/282-0703
lmckeown@menopausemanagement.com



be an effective and acceptable alternative to hormones for hot flash therapy therefore is unjustified. This drug would be better tested in a head-to-head clinical trial against hormone therapy in which FDA guidance for hot flash trials is followed.

Wulf H. Utian, MD, PhD
Arthur H. Bill Professor Emeritus of
Reproductive Biology and Ob/Gyn
Case Western Reserve University
School of Medicine
Consultant in Women's Health
Cleveland Clinic Foundation
Executive Director
The North American
Menopause Society
Cleveland, OH

Comment. This trial is noteworthy in that it provides further data showing that newer antidepressants do alleviate hot flashes. There are now randomized, double-blinded, placebo-controlled trials demonstrating such effects for venlafaxine, fluoxetine, and paroxetine. Those trials primarily have been performed in women with a history of breast cancer. This current trial nicely demonstrates that the effects of these antidepressants on hot flashes are also applicable to women with hot flashes who do not have a history of breast cancer. This information is provided at a time when postmenopausal hormone therapy is out of favor, given the recent data from the WHI trial regarding the negative effects of hormone replacement therapy on breast cancer incidence and coronary artery disease.

Charles Loprinzi, MD
Chair, Medical Oncology
Mayo Clinic
Rochester, MN