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POSITION STATEMENT

Estrogen and progestogen use in peri- and postmenopausal women: September 2003 position statement of The North American Menopause Society

The termination of the estrogen-progestogen trial of the Women's Health Initiative (WHI) study in July 2002 was a milestone in the history of postmenopausal hormone therapy. In response, The North American Menopause Society (NAMS) convened an expert Hormone Therapy (HT) Advisory Panel to prepare a report on hormone therapy. After approval from the 2001-2002 NAMS Board of Trustees, the report was released in October 2002 (*Menopause* 2003;10:6-12).

Due to the subsequent influx of new clinical trial data regarding postmenopausal hormone therapy, the NAMS Board of Trustees convened a second HT Advisory Panel to develop another report. The overall objective was to present clinical recommendations for use of hormone therapy in peri- and postmenopausal women. As with the previous analysis, all relevant evidence was considered. After approval from the 2002-2003 NAMS Board of Trustees, this position statement was released on September 17, 2003.

Panel Members

The 2003 HT Advisory Panel was composed of acknowledged clinical and research experts (both NAMS members and nonmembers) from relevant areas of menopause-related health care, including investigators from the WHI and other key trials. All Panel members provided disclosure of interests during the past 2 years (presented at the end of the paper).

NAMS is grateful to the following individuals who served on the Panel, advising the NAMS Board of Trustees.

Panel Chair: Wulf H. Utian, MD, PhD, FACOG – Arthur H. Bill Professor Emeritus of Reproductive Biology and Obstetrics and Gynecology, Case Western Reserve University School of Medicine; Consultant in Gynecology, The Cleveland Clinic Foundation; President, Rapid Medical Research Inc, Cleveland, OH; NAMS Executive Director and Honorary Founding President, NAMS President 1989-1992, NAMS Board of Trustees 1989-Present.

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Meir J. Stampfer, MD, DrPH – Professor of Epidemiology and Nutrition, 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, WHI, and WHIMS Investigator, Chair, WHI Steering Committee.

Nancy Fugate Woods, PhD, RN, FAAN – Dean, School of Nursing, Professor, Family and Child Nursing, University of Washington, Seattle, WA; NAMS President 1999-2000, NAMS Board of Trustees 1997-2002; WHI Investigator.

Methodology

The 2003 Panel utilized the 2002 Hormone Therapy Advisory Panel report as a starting point. A two-part set of clinical questions was developed by the Panel. The first set related to items for which complete agreement was previously reached; the second set related to areas of previous nonconsensus. Each Panelist completed the questionnaire on a blinded basis (ie, unaware of the responses of the other Panelists). The responses were collated in the NAMS Central Office, again into two lists: those with consensus and those without. All responses were distributed to the entire Panel.

The Panel reviewed all of the responses by telephone conference call in an attempt to reach consensus. Further development of the report through multiple drafts was conducted through the internet. The clinical recommendations indicate where consensus was achieved as well as where opinions differed. The latter clearly indicates some of the areas needing future research.

The primary clinical question was to differentiate the risk-benefit ratio of postmenopausal estrogen therapy (ET) and estrogen-progestogen therapy (EPT) for both disease prevention and treatment of specific menopause-related symptoms. The Panel recognized that a woman's willingness to accept certain risks of HT will vary when therapy is used to treat existing symptoms as opposed to long-term use to prevent a future problem. Moreover, recognition had to be given to the fact that prevalence of disease outcomes is dependent on age. That is, HT is more likely to be acceptable for symptom reduction when therapy is planned to be short-term in a population that is younger with lower prevalence of risk outcomes. In contrast, the absolute risks of either use in older women or long-term therapy may make HT less acceptable. The Panel was required to take these issues into consideration when developing its recommendations.

This position statement focuses on the use of government-approved prescription ET/EPT products available in the United States and Canada, not custom ET/EPT preparations, selective estrogen-receptor modulators (SERMs), or hormones available without a prescription (including phytoestrogens).

Key references used in reaching these recommendations are listed at the end of this report. This is not a complete reference list, but it includes the most significant recent randomized, controlled clinical trials, meta-analyses, and review articles. The level of evidence indicated for each study is based on a grading system that evaluates the scientific rigor of the study design, as developed by the US Preventive Services Task Force. A synopsis of the levels is presented at the end of the reference list.

The position statement was reviewed and approved by the NAMS 2002-2003 Board of Trustees.

Recommendations for Clinical Practice: Areas of Consensus

The Panel agreed on the following clinical recommendations for postmenopausal hormone therapy:

- A strong recommendation was made for uniform and consistent terminology for menopause-related therapies, as indicated below:

ET	estrogen therapy
EPT	combined estrogen-progestogen therapy
HT	hormone therapy (encompassing both ET and EPT)
CC-EPT	continuous-combined estrogen-progestogen therapy (daily administration of both estrogen and progestogen)

CS-EPT	continuous-sequential estrogen-progestogen therapy (estrogen daily, with progestogen added on a set sequence)
systemic ET/EPT	preparations of ET or EPT that have a systemic, not solely vaginal, effect
local ET	preparations of ET that have a predominantly vaginal, not systemic, effect
progestogen	encompassing both progesterone and progestin

- Treatment of moderate to severe menopause symptoms (ie, vasomotor symptoms, sleep disruption from vasomotor symptoms) remains the primary indication for systemic ET and EPT. Every systemic ET/EPT product is government approved for this indication.
- Every systemic and local ET/EPT product is government approved for treating moderate to severe symptoms of vulvar and vaginal atrophy, such as vaginal dryness, dyspareunia, and atrophic vaginitis. When hormones are considered solely for this indication, local ET is generally recommended.
- The primary menopause-related indication for progestogen use is endometrial protection from unopposed ET. For all women with an intact uterus who are using estrogen therapy, clinicians are advised to prescribe adequate progestogen, in either a CC-EPT or CS-EPT regimen. Women without a uterus should not be prescribed a progestogen.
- Some women with an intact uterus who choose EPT may experience undesirable side effects from the progestogen component. However, there is insufficient evidence regarding long-term endometrial safety to recommend use of long-cycle progestogen (ie, progestogen every 3-6 months for 12-14 days), a progestin-containing intrauterine device (IUD), or low-dose estrogen without progestogen as an alternative to standard EPT regimens. If utilizing any of these approaches, closer surveillance of the endometrium is recommended, pending more definitive research.
- No EPT regimen should be used for primary or secondary prevention of coronary heart disease (CHD) or stroke.
- The effect of ET on CHD and stroke is not yet clear. ET does not have a significant effect on stroke risk in postmenopausal women with known ischemic cerebrovascular disease, but for healthy older women, effects of ET on stroke risk are not clear. However, unless confirming data become available, ET should not be used for primary or secondary prevention of these conditions.
- Breast cancer risk is increased with ET and, to a greater extent, EPT use beyond 5 years. Progestogen appears to contribute substantially to that adverse effect. EPT and, to a lesser extent, ET increase breast cell proliferation, breast pain, and mammographic density. HT may impede the diagnostic interpretation of mammograms. One recent observational study suggests that the increase in incidence of breast cancer with oral, transdermal, and implanted estrogens varies little between specific estrogens and progestogens or their doses, or between continuous and sequential regimens. The observational data also suggest that breast cancer incidence may begin to increase slightly with less than 5 years HT use. Observational data from one study suggest that HT use may be associated with increased breast cancer mortality, but insufficient data exist to determine whether ET or EPT, or duration of use of ET or EPT, is associated with any increase in mortality.
- There is definitive evidence for EPT efficacy in reducing risk for postmenopausal osteoporosis fracture. There is, to date, no comparable evidence for ET. Many EPT and ET products are government approved for prevention of postmenopausal osteoporosis (ie, loss of bone mineral density) through long-term treatment. Because of the potential risks associated with HT, for women who require drug therapy for osteoporosis risk reduction (including women at high risk of fracture in the next 5-10 years), alternatives to HT should also be considered, weighing the risks and benefits of each. Recognition should be given to the fact that there are no published data on osteoporosis drug use beyond 7 years.
- Initiating EPT after age 65 cannot be recommended for primary prevention of dementia as it increases the risk of dementia during the ensuing 5 years in this population. The evidence is insufficient to either support or refute the efficacy or harm of ET/EPT for primary prevention of dementia when therapy is initiated during the menopause transition or early postmenopause. However, given other adverse events that may be expected to accrue during long-term HT use, it is by no means clear that theoretical dementia benefits would outweigh known risks. HT does not appear to convey direct benefit or harm for secondary prevention (ie, symptomatic treatment) of dementia due to Alzheimer's disease.

- The effects of HT on risk for breast cancer and osteoporotic fracture in symptomatic perimenopausal women have not been established in randomized clinical trials. The findings from trials in different populations (eg, WHI) should, therefore, be extrapolated with caution. There is, however, no evidence that symptomatic women differ from asymptomatic women in cancer or bone outcomes.
- Data from studies such as the WHI and the Heart and Estrogen/progestin Replacement Study (HERS) should be extrapolated only with caution to women younger than 50 years of age who initiate HT. WHI and HERS involved women aged 50 and over (with mean ages of 63 and 67, respectively), and HERS was conducted solely in women with known coronary artery disease. The data should not be extrapolated to women experiencing premature menopause (<40 years of age) and initiating HT at that time.
- Premature menopause and premature ovarian failure are conditions associated with earlier onset of osteoporosis and CHD, but there are no clear data as to whether ET or EPT will reduce morbidity or mortality from these conditions. The benefit-risk ratio may be more favorable for younger women.
- Use of ET and EPT should be limited to the shortest duration consistent with treatment goals, benefits, and risks for the individual woman, taking into account symptoms and domains (eg, sexuality, sleep) that may have an impact on quality of life.
- Lower-than-standard doses of ET and EPT should be considered (ie, daily doses of 0.3 mg conjugated estrogens tablet, 0.25-0.5 mg micronized 17β-estradiol tablet, 0.025 mg 17β-estradiol patch, or the equivalent). Many studies have demonstrated nearly equivalent vasomotor and vulvovaginal symptom relief and preservation of bone mineral density. Lower EPT doses are better tolerated and may or may not have a more positive safety profile than standard doses; however, lower doses have not been tested for outcomes (including endometrial safety) in long-term trials.
- Nonoral routes of administration of ET/EPT may offer advantages and disadvantages, but the long-term benefit-risk ratio has not been demonstrated. Differences would be related to the role of the first-pass hepatic effect, the hormone concentrations in the blood achieved by a given route, and the biologic activity of component ingredients. There is some evidence that transdermal 17β-estradiol does not increase the level of C-reactive protein, and also that it may be associated with lower risk of deep venous thrombosis than oral estrogen. A large observational study has shown similar increased risks for breast cancer with both oral and transdermal estrogens.
- Extended use of ET or EPT is acceptable under the following circumstances, provided the woman is well aware of risks and there is strict clinical supervision:
  - For the woman for whom, in her opinion, benefits of symptom relief outweigh risks, notably after failing an attempt to withdraw HT. Attempts should be made over time to reduce and cease HT.
  - For women with moderate to severe menopause symptoms who are at high risk for osteoporotic fracture. Attempts should be made over time to lower the dose or cease HT and introduce alternate bone-sparing therapy.
  - For prevention of osteoporosis in a high-risk woman when alternate therapies are not appropriate for that woman.
- Prior to consideration of any therapeutic regimen, including HT, all women should have a complete health evaluation, including a comprehensive history and physical examination. More specific examinations, such as bone densitometry, should be considered on a case-by-case basis.
- The Panel acknowledged that the absolute risks published thus far regarding ET/EPT are small (eg, the EPT arm of the WHI), as are the benefits for bone and reduction in colon cancer risk. For women younger than 50 or those at low risk for CHD, stroke, osteoporosis, breast cancer, or colon cancer, the absolute risk or benefit from EPT is likely to be smaller than demonstrated in WHI, although the relative risk may be similar. An individual risk profile is essential for every woman contemplating any regimen of EPT or ET. Women should be informed of known risks.

Areas Where Insufficient or Conflicting Evidence Precludes Consensus

The Panel could not reach consensus on the following issues:

- *What are the currently acceptable definitions of "short-term" and "long-term" HT?* The Panel could not reach a consensus regarding definitions of these terms, agreeing that delineating specific time periods is arbitrary and that no uniform time can be broadly applied to all women. The Panel rec-

ognized that this question is an attempt to assign a "safe window" for HT. The dilemma is that current data suggest that the risk of breast cancer is significantly increased beyond 5 years use, with a lower elevation in risk before 5 years, whereas there is evidence of potential early CHD and thromboembolism risk within the first 2 years of use and conflicting evidence of early risk of ischemic stroke. Moreover, there are emerging data showing no association of early increase in CHD events in young (ie, average age 53), healthy postmenopausal women with HT during the first 2 years of treatment. However, deep venous thrombosis is slightly increased from an expected annualized rate of 0.3 per 1,000 to 0.9 per 1,000. It is therefore difficult to define any "safe window," and an individual risk-benefit profile needs to be considered for every woman considering commencement of HT.

- *Is HT associated with early risk of CHD?* Panelists were divided on the issue as to whether there is definitive evidence for early increased risk of CHD with HT. For women similar to participants in the EPT arm of WHI (average age 63 years; range from 50 to 79 years), the WHI data are the best estimate of early harm from EPT. The WHI demonstrated that EPT may increase the risk of CHD among generally healthy postmenopausal women during the first year after initiation of hormone use. There is also evidence that early harm within 2 years of use may not pertain to healthy menopausal women using ET/EPT for menopause symptom management.
- *How long should HT be prescribed for symptom relief?* No consensus could be reached, although a general guiding principle should be for the shortest time at the lowest possible dose. The Panel recognized that symptoms can recur when therapy is discontinued, independent of age and duration of HT use. Useful information regarding the consideration of reinstituting HT is anticipated from the terminated EPT arm of the WHI, as trial participants are being followed for outcomes after termination. The Panel agreed that the decision to reinstitute HT should be individualized based on severity of symptoms, current risk/benefit considerations, and the woman's preference. Reinstituting therapy at a lower dose may facilitate future attempts at discontinuing.
- *Is there a best way to discontinue HT?* Panelists were divided in their recommendations, including both abrupt therapy cessation and tapering the dose. Past history of severe symptoms may favor tapering, but no specific protocols could be recommended. Some gradually decrease the dose, while others lengthen the time between doses. Matrix transdermal HT patches can be trimmed to provide smaller doses. Current data are inadequate to suggest that one method is better than the other.
- *Is it possible to make general conclusions about all members of the estrogen and progestogen families?* The majority opinion was that it is not possible to extrapolate conclusions from the study of one compound directly to another. It was acknowledged that estrogen and progesterone agonists share some common features and effects, and the only way to establish definitively the net clinical outcome for any given agent (alone or in combination) is through randomized clinical trials. In the absence of clinical trial data for each estrogen and progestogen, the clinical trial results for one agent probably should be generalized to all agents within the same family, especially with regard to adverse effects.
- *Does a continuous-combined EPT regimen (CC-EPT) have an effect different from continuous estrogen with sequential progestogen (CS-EPT)?* There are some indications that continuous progestogen in the dosages administered in studies such as WHI and HERS may be related to these trials' adverse cardiovascular and breast outcomes, but conflicting data preclude a consensus.
- *Does HT enhance quality of life (QOL)?* There is a lack of consensus on the impact of HT on QOL. This has largely been due to a lack of agreement in the scientific community regarding how best to obtain an appropriate evaluation of QOL, including the domains to be incorporated into any survey instruments. There is consensus that validated instruments for determining the impact of HT, or indeed any menopause-related therapy, on QOL should be incorporated into future studies.

Need for Future Research

On the basis of this review, the Panelists identified the following areas requiring further research. Two overarching dimensions of the agenda are the following:

Further study of the positive and negative effects of hormone therapy and the mechanisms by which they occur:

- Long-term benefits/risks of ET.
- Long-term benefits/risks of estrogen and progestogen preparations, dosages, and regimens and routes

of administration other than oral CEE and oral MPA.
- Long-term benefits/risks of lower-than-standard doses of ET and EPT expressed as disease outcomes.
- Mechanism for early harm from EPT, including pharmacogenomics, polymorphisms, and prothrombosis.
- Cause for increase in CHD, stroke, and breast cancer adverse events with EPT in order to better understand the pathophysiology of these events, identify potential new treatments and ways to prevent their occurrence, and to identify a subgroup for whom HT would be less toxic.
- Effects of endogenous levels of estradiol and/or estrone on benefit and/or risk.
- Mechanisms supporting the difference in benefits/risks of ET versus EPT.
- How to factor QOL issues into the benefit-risk profile for EPT/ET.
- The benefit-risk profile of CS-EPT compared with CC-EPT or other HT regimens.
- Endometrial effects from alternatives to standard progestogen regimens, such as a progestin-releasing intrauterine device or long-cycle progestogen regimens.
- Long-term effects of ET/EPT on Alzheimer's disease risk and other forms of dementia, particularly when therapy is initiated before age 65.
- Short- and long-term effects of ET/EPT on neuropsychiatric disorders, such as Parkinson's disease, depression, and schizophrenia.
- Long-term effects of ET/EPT on primary and secondary prevention and progression of ophthalmologic disorders, such as cataract and age-related macular degeneration.
- Health outcomes with ET/EPT for women experiencing early or premature menopause.
- Health outcomes with osteoporosis drugs over the long term (>10 years).
- The effects of ET/EPT on atheromatosis development/progression, especially if initiated immediately after menopause.
- Impact of HT on cardiovascular and brain risk/benefit when initiated at the time of menopause.
- Role of progestogens (eg, type, regimen) in breast cancer and cardiovascular risk.
- Efficacy of nonpharmacologic methods of managing hot flashes.
- The benefit-risk profile associated with an abrupt versus a tapering discontinuation of HT regimens.

Further study of the natural history of the menopause transition:

- Course of symptoms with spontaneous menopause versus course of symptoms after discontinuing HT.
- Incidence and course of chronic disease in women experiencing early or premature menopause.
- How women can best be identified for risk of deep venous thrombosis and pulmonary embolism, as well as hypercoagulability responsiveness to estrogens in general.
- Stricter evaluation of domains of QOL.

Panelist Disclosures

Chair, Wulf H. Utian, MD, PhD, FACOG – Industry consulting fees (Berlex, Eli Lilly, Endeavor, Pfizer, Roche, Warner Chilcott); direct industry lecture fees (none disclosed); industry research support (Amylin, 3M, Barr, Berlex, Bristol-Myers Squibb, Eli Lilly, Endeavor, Forest, Neurocrine Biosciences, Novartis, Novo Nordisk, Organon, Pfizer, Pharmacia, Procter & Gamble, Roche, Sepracor, Solvay, Wyeth, Yamanouchi). *Peter Collins, MD, FRP* – Industry consulting fees (Eli Lilly, Novartis, Pfizer); direct industry lecture fees (Akzo Nobel, Merck, Novartis, Novo Nordisk, Schering, Wyeth); industry research support (Eli Lilly, Protein Technologies, Merck). *Bruce Ettinger, MD, FACP* – Industry consulting fees (Berlex, Eli Lilly, Procter & Gamble, Tap); direct industry lecture fees (Berlex, Eli Lilly, Merck, Procter & Gamble, Tap); industry research support (Eli Lilly, Merck, Procter & Gamble). *J. Chris Gallagher, MD* – Industry consulting fees (Aventis, Endeavor, Pfizer, Roche, Wyeth); direct industry lecture fees (Aventis, Organon, Pfizer, Roche, Wyeth); industry research support (Endeavor, Organon, Pfizer, Roche, Wyeth). *Margery L.S. Gass, MD* – Industry consulting fees (Eli Lilly, GlaxoSmithKline, Merck, Procter & Gamble); direct industry lecture fees (Aventis); industry research support (Eli Lilly, GlaxoSmithKline, Merck, Pfizer, Procter & Gamble, Wyeth). *Morrie M. Gelfand, CM, MD* – Industry consulting fees (none disclosed); industry lecture fees (none disclosed); industry research support (Pfizer). *Victor W. Henderson, MD, MS* – Industry consulting fees (Wyeth); direct industry lecture fees (Wyeth); industry research support (none disclosed). *David M. Herrington, MD, MHS* – Industry consulting fees (none disclosed); direct industry lecture fees (Eli Lilly, Organon, Pfizer, Wyeth); industry research support (Eli Lilly, Pfizer). *Marian C. Limacher, MD* – Industry consulting fees (none disclosed); direct industry lecture fees (none dis-

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KEY REFERENCES

NAMS 2002 HT Advisory Panel Report

The North American Menopause Society. Amended report from the NAMS Advisory Panel on Postmenopausal Hormone Therapy. *Menopause* 2003;10:6-12. Level of evidence: III.

Hormone Effects on Menopause Symptoms and QOL

Heart and Estrogen/progestin Replacement Study (HERS)

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. Level of evidence: I.

Heart and Estrogen/progestin Replacement Study follow-up (HERS II)

Barnabei VM, Grady D, Stovall DW, et al. Menopausal symptoms in older women and the effects of treatment with hormone therapy. *Obstet Gynecol* 2002;100:1209-1218. Level of evidence: I.

Women's Health Initiative (WHI)

Hays J, Ockene JK, Brunner RL, et al, for the Women's Health Initiative Investigators. Effects of estrogen plus progestin on health-related quality of life. *N Engl J Med* 2003;348:1839-1854. Level of evidence: I.

Other Studies

Utian WH, Janata JW, Kingsberg SA, Schluchter M, Hamilton JC. The Utian Quality of Life (UQOL) Scale: development and validation of an instrument to quantify quality of life through and beyond menopause. *Menopause* 2002;9:402-410. Level of evidence: II-3.

Review Articles

MacLennan A, Lester S, Moore V. Oral oestrogen replacement therapy versus placebo for hot flushes (Cochrane Review). *Cochrane Database Syst Rev* 2001;1:CD002978. Level of evidence: III.

Effects of Low-Dose Hormones

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

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. Level of evidence: I.

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. Level of evidence: I.

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. Level of evidence: I.

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. Level of evidence: I.

Other Studies

Brynhildsen J, Hammar M. Low dose transdermal estradiol/norethisterone acetate treatment over 2 years does not cause endometrial proliferation in postmenopausal women. *Menopause* 2002;9:137-144. Level of evidence: I.

Hashimoto M, Miyao M, Akishita M, et al. Effects of long-term and reduced-dose hormone replacement therapy on endothelial function and intima-media thickness in postmenopausal women. *Menopause* 2002;9:58-64. Level of evidence: II-1.

Prestwood KM, Kenny AM, Kleppinger A, Kulldorff M. Ultralow-dose micronized 17β-estradiol and bone density and bone metabolism in older women: a randomized controlled trial. *JAMA* 2003;290:1042-1048. Level of evidence: I.

Speroff L, Whitcomb RW, Kempfert NJ, Boyd RA, Paulissen JB, Rowan JP. Efficacy and local tolerance of a low-dose, 7-day matrix estradiol transdermal system in the treatment of menopausal vasomotor symptoms. *Obstet Gynecol* 1996;88:587-592. Level of evidence: I.

Utian WH, Burry KA, Archer DF, et al. Efficacy and safety of low, standard, and high dosages of an estradiol transdermal system (Esclim) compared with placebo on vasomotor symptoms in highly symptomatic menopausal patients: the Esclim Study Group. *Am J Obstet Gynecol* 1999;181:71-79. Level of evidence: I.

Progestogen Added to ET

Review Articles

The North American Menopause Society. Role of progestogen in hormone therapy for postmenopausal women: position statement of The North American Menopause Society. *Menopause* 2003;10:113-132. Level of evidence: III.

Hormone Effects on CHD and Stroke

EStrogen and THromboEmbolism Risk (ESTHER) study

Scarabin P-Y, Oger E, Plu-Bureau G, for the EStrogen and THromboEmbolism Risk (ESTHER) Study Group. Differential association of oral and transdermal oestrogen-replacement therapy with venous thromboembolism risk. *Lancet* 2003;362:428-432. Level of evidence: II-2.

Estrogen in the Prevention of Atherosclerosis Trial (EPAT)

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. Level of evidence: I.

Estrogen in the Prevention of Reinfarction Trial (ESPRIT)

Cherry N, Gilmour K, Hannaford P, et al, for The ESPRIT team. Oestrogen therapy for prevention of reinfarction in postmenopausal women: a randomised placebo controlled trial. *Lancet* 2002;360:2001-2008. Level of evidence: I.

Estrogen Replacement and Atherosclerosis trial (ERA)

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. Level of evidence: I.

Heart and Estrogen/progestin Replacement Study (HERS)

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. Level of evidence: I.

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. Level of evidence: I.

Hulley S, Grady D, Bush T, et al, for the Heart and Estrogen/progestin Replacement Study (HERS) Research Group. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* 1998;280:605-613. Level of evidence: I.

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. Level of evidence: I.

Heart and Estrogen/progestin Replacement Study follow-up (HERS II)

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. Level of evidence: I.

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. Level of evidence: I.

Vittinghoff E, Shlipak MG, Varosy PD, et al, for the Heart and Estrogen/progestin Replacement Study research group. Risk factors and secondary prevention in women with heart disease: the Heart and Estrogen/progestin Replacement Study. *Ann Intern Med* 2003;138:81-89. Level of evidence: I.

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. Level of evidence: II-2.

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. Level of evidence: II-2.

Papworth HRT Atherosclerosis study (PHASE)

Clarke SC, Kelleher J, Lloyd-Jones H, Slack M, Schofiel PM. A study of hormone replacement therapy in postmenopausal women with ischaemic heart disease: the Papworth HRT atherosclerosis study. *Br J Obstet Gynaecol* 2002;109:1056-1062. Level of evidence: I.

Postmenopausal Estrogen/Progestin Interventions study (PEPI)

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. Level of evidence: I.

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 in: *JAMA* 1995;274:1676]. *JAMA* 1995;273:199-208. Level of evidence: I.

Women's Angiographic Vitamin and Estrogen (WAVE) trial

Waters DD, Alderman EL, Hsia J, et al. Effects of hormone replacement therapy and antioxidant vitamin supplements on coronary atherosclerosis in postmenopausal women: a randomized controlled trial. *JAMA* 2002;288:2432-2440. Level of evidence: I.

Women's Estrogen for Stroke Trial (WEST)

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

Women's Estrogen-Progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial (WELLHART)

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. Level of evidence: I.

Women's Health Initiative (WHI)

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. Level of evidence: I.

Wassertheil-Smoller S, Hendrix SL, Limacher M, et al, for the WHI Investigators. Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. *JAMA* 2003;289:2673-2684. Level of evidence: I.

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. Level of evidence: I.

Other Studies

Angerer P, Kothny W, Störk S, von Schacky C. Hormone replacement therapy and distensibility of carotid arteries in postmenopausal women: a randomized, controlled trial. *J Am Coll Cardiol* 2000;36:1786-1796. Level of evidence: I.

Angerer P, Störk S, Kothny W, Schmitt P, von Schacky C. Effect of oral postmenopausal hormone replacement on progression of atherosclerosis: a randomized, controlled trial. *Arterioscler Thromb Vasc Biol* 2001;21:262-268. Level of evidence: I.

Lobo RA, Pickar JH. Evaluation of cardiovascular-event rates with hormone replacement therapy in healthy postmenopausal women [abstract]. *Obstet Gynecol* 2003;101:95S. [*Arch Intern Med* Full text in press.] Level of evidence: I.

Hormone Effects on the Skeleton

Heart and Estrogen/progestin Replacement Study follow-up (HERS II)

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. Level of evidence: I.

Postmenopausal Estrogen/Progestin Interventions study (PEPI)

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. Level of evidence: I.

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. Level of evidence: I.

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. Level of evidence: I.

Women's Health Initiative (WHI)

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. Level of evidence: I.

Other Studies

Gallagher JC, Rapuri PB, Haynatzki G, Detter JR. Effect of discontinuation of estrogen, calcitriol, and the combination of both on bone density and bone markers. *J Clin Endocrinol Metab* 2002;87:4914-4923. Level of evidence: I.

Greenspan SL, Emkey RD, Bone HG, et al. Significant differential effects of alendronate, estrogen, or combination therapy on the rate of bone loss after discontinuation of treatment of postmenopausal osteoporosis: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2002;137:875-883. Level of evidence: I.

Review Articles

Delmas PD. Treatment of postmenopausal osteoporosis. *Lancet* 2002;359:2018-2026. Level of evidence: III.

The North American Menopause Society. Management of postmenopausal osteoporosis: position statement of The North American Menopause Society. *Menopause* 2002;9:84-101. Level of evidence: III.

Hormone Effects on the Brain

Cache County Study

Zandi PP, Carlson MC, Plassman BL, et al, for the Cache County Memory Study Investigators. Hormone replacement therapy and incidence of Alzheimer disease in older women: the Cache County Study. *JAMA* 2002;288:2123-2129. Level of evidence: II-3.

Heart and Estrogen/progestin Replacement Study follow-up (HERS II)

Grady D, Yaffe K, Kristof M, Lin F, Richards C, Barrett-Connor E. Effect of postmenopausal hormone therapy on cognitive function: the Heart and Estrogen/progestin Replacement Study. *Am J Med* 2002;113:543-548. Level of evidence: I.

Melbourne Women's Midlife Health Project

Henderson VW, Guthrie JR, Dudley EC, Burger HG, Dennerstein L. Estrogen exposures and memory at midlife: a population-based study of women. *Neurology* 2003;60:1369-1371. Level of evidence: II-2.

Women's Health Initiative Memory Study (WHIMS)

Rapp SR, Espeland MA, Shumaker SA, et al, for the WHIMS Investigators. Effect of estrogen plus progestin on global cognitive function in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA* 2003;289:2663-2672. Level of evidence: I.

Shumaker SA, Legault C, Thal L, et al, for the WHIMS Investigators. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA* 2003;289:2651-2662. Level of evidence: I.

Other Studies

den Heijer T, Geerlings MI, Hofman A, et al. Higher estrogen levels are not associated with larger hippocampi and better memory performance. *Arch Neurol* 2003;60:213-220. Level of evidence: II-2.

Thal LJ, Thomas RG, Mulnard R, Sano M, Grundman M, Schneider L. Estrogen levels do not correlate with improvement in cognition. *Arch Neurol* 2003;60:209-212. Level of evidence: II-2.

Hormone Effects on Breast Cancer

Heart and Estrogen/progestin Replacement Study follow-up (HERS II)

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 followup (HERS II). *JAMA* 2002;288:58-66. Level of evidence: I.

Million Women Study

Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2003;362:419-427. Level of evidence: II-2.

Postmenopausal Estrogen/Progestin Interventions study (PEPI)

Greendale GA, Reboussin BA, Sie A, et al. Effects of estrogen and estrogen-progestin on mammographic parenchymal density. Postmenopausal Estrogen/Progestin Interventions (PEPI) Investigators. *Ann Intern Med* 1999;130:262-269. Level of evidence: I.

Women's Health Initiative (WHI)

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. Level of evidence: I.

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. Level of evidence: I.

Other Studies

Li CI, Malone KE, Porter PL, et al. Relationship between long durations and different regimens of hormone therapy and risk of breast cancer. *JAMA* 2003;289:3254-3263. Level of evidence: II-2.

Olsson HL, Ingvar C, Bladström A. Hormone replacement therapy containing progestins and given continuously increases breast carcinoma risk in Sweden. *Cancer* 2003;97:1387-1392. Level of evidence: II-2.

Weiss LK, Burkman RT, Cushing-Hauger KL, et al. Hormone replacement therapy regimens and breast cancer risk. *Obstet Gynecol* 2002;100:1148-1158. Level of evidence: II-2.

Hormone Effects on Colon Cancer

Women's Health Initiative (WHI)

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. Level of evidence: I.

Other Studies

Grodstein F, Newcomb PA, Stampfer MJ. Postmenopausal hormone therapy and the risk of colorectal cancer: a review and meta-analysis. *Am J Med* 1999;106:574-582. Level of evidence: III.

MacLennan SC, MacLennan AH, Ryan P. Colorectal cancer and oestrogen replacement therapy: a meta-analysis of epidemiological studies. *Med J Aust* 1995;162:491-493. Level of evidence: III.

Nanda K, Bastian LA, Hasselblad V, Simel DL. Hormone replacement therapy and the risk of colorectal cancer: a meta-analysis. *Obstet Gynecol* 1999;93:880-888. Level of evidence: III.

Reviews

Grodstein F, Clarkson TB, Manson JE. Understanding the divergent data on postmenopausal hormone therapy. *New Engl J Med* 2003;348:645-650. Level of evidence: III.

Description of the levels of evidence*

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 analytic 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.

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*Preventive Services Task Force. *Guide to Clinician Preventive Services: Report of the US Preventive Services Task Force.* 2nd ed. Baltimore, MD: Williams & Wilkins; 1996.