

From The Endocrine Society's Research Affairs Core Committee
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POSTMENOPAUSAL HORMONE THERAPY: *Benefits vs. Risks*

AS WOMEN FACE MENOPAUSE, WHICH OCCURS ON AVERAGE AT AN AGE OF 51 YEARS,

many are challenged with symptoms that can disrupt their lives such as hot flashes, vaginal dryness, and a host of other physiological changes. Estrogen and progesterone hormone therapies have been used to alleviate these symptoms. The promise they seemed to offer for also combatting other disorders that strike after menopause, including osteoporosis, cognitive decline, and cardiovascular disease, fell under a cloud after studies pointed to unexpectedly harmful effects of the therapy. Further investigation of the data, especially from the important Women's Health Initiative, has deepened our understanding of this complex issue. This Tri-Point article incorporates viewpoints from a basic scientist, a clinical scientist, and a clinician, weighing the benefits and risks of such hormone treatment.



Presenting the basic scientist perspective is Judith Turgeon, Ph.D., professor of medicine in the division of endocrinology at the University of California Davis.



Presenting the clinical scientist perspective is JoAnn E. Manson, M.D., Dr.P.H., professor of medicine and women's health at Harvard Medical School and Brigham and Women's Hospital.



Presenting the clinician perspective is Cynthia A. Stuenkel, M.D., clinical professor of medicine in the division of endocrinology and metabolism at the University of California, San Diego.

ABBREVIATIONS IN THIS ARTICLE

27HC	=	27-hydroxycholesterol
CEE	=	conjugated equine estrogens
CHD	=	coronary heart disease
CVD	=	cardiovascular disease
E₂	=	17 β -estradiol
ER	=	estrogen receptor
ET	=	estrogen therapy
HT	=	hormone therapy
KEEPS	=	Kronos Early Estrogen Prevention Study
RCT	=	randomized clinical trial
VTE	=	venous thromboembolism
WHI	=	Women's Health Initiative

FROM THE BASIC SCIENTIST

- Hypoestrogenicity is associated with increased vulnerability to osteoporosis, CVD, and cerebrovascular stroke.
- Different estrogens can lead to distinctive biological activities.
- ET's action is dependent on formulation, dose, and delivery mode.
- Response to ET depends on age, genetics, inflammatory state, and timing relative to previous hormone exposure.

Women now live about half their adult lives beyond menopause. What, if any, are the consequences of prolonged hypoestrogenicity, given estradiol's pleiotropic actions in the cardiovascular and immune systems, in brain and bone, and in adipose tissue and metabolism? The observation that postmenopausal women are more vulnerable to osteoporosis, CVD, cerebrovascular stroke, and certain neurodegenerative diseases led to the HT hypothesis, which posited that treatment with ovarian hormones after menopause would decrease this susceptibility to age-related degenerative processes. Support came from several decades of clinical observational, retrospective, and prospective studies, and from basic cause-and-effect studies in cell and animal models.

Apparent Disconnect Between WHI Results and Basic and Clinical Research

The simplified view of the admixture of hypoestrogenicity, sex, and aging in vulnerability to certain diseases in recent years became complex with the publication of trials—RCTs—particularly the WHI, but the interest in re-evaluation has led to a refreshing wave of studies to clarify mechanistic bases for E_2 actions outside the reproductive system. Factors contributing to the apparent contradictions between recent RCTs and earlier studies relate to the type of HT used and the profile of the WHI participants: Their age at entry averaged 63, most had been without ET for more than a decade, and most were obese or overweight.¹ This profile has provided context for studies re-examining ET structure/function/concentration consequences and the interactions of estrogens, timing, and the inflammatory state.

Do All Estrogens Produce the Same Effect?

Estrogen actions are mediated through dimeric ER subtypes with distinct tissue-specific distribution, expression levels, and function. ERs modulate the activity of intracellular targets through the intercession of specific coregulators, which also have tissue-specific expression and regulation. The strategic point is that different ligands induce distinct conformational changes in each ER subtype, leading to differential recruitment of coregulators and ultimately causing distinct biological activities. This is the basis for selective ER modulators or SERMs. Most animal studies of estrogen's non-reproductive functions are based on parenterally administered E_2 , the gold-standard

estrogen in humans. The most common postmenopausal ET is oral Premarin (conjugated equine estrogens, CEE)—a mixture of at least 10 different estrogenic compounds with E_2 accounting for < 1%.^{2,3} CEE components produce unique ER conformations and differential coregulator recruitment and target gene profiles.³ For example, one CEE component was shown in humans to have agonist effects on central nervous system end points but little activity at expected E_2 hepatic and vascular targets.^{2,4}

In addition to complex pharmacology and different clinical outcomes of CEE components, the oral route causes high estrogen concentrations to be presented to hepatocytes (first-pass effect), with consequent dose-dependent alteration in production of several proteins, including hormone-binding globulins, and inflammatory, coagulation, and fibrinolysis markers. In contrast, transdermal E_2 administration has a relatively simple pharmacokinetic profile and no liver protein effects.^{5,6} In clinical studies, the benefits of transdermal E_2 on, e.g., cardiovascular end points, are consistent with extensive work in animal models.⁵ Highly anticipated are results from the KEEPS—an ongoing, multicenter, 5-year clinical trial to evaluate CEE effectiveness, transdermal E_2 , and placebo, using subclinical cardiovascular end points in postmenopausal women.⁷

Interactions of Estrogens, Timing, and the Inflammatory State

Multiple factors contribute to chronic inflammation, but visceral adiposity is a significant component. The menopause transition and lack of E_2 are associated with increases in visceral adiposity and waist circumference, which in turn are linked to insulin resistance, dyslipidemia, hypertension, and the inflammatory state.⁸ Inflammatory cytokines and acute-phase proteins, produced by visceral adipose in direct relation to its mass, can affect subclinical disease progression. A key point is that E_2 can lower cytokine production and mitigate the cellular response to pro-inflammatory cytokines.

Evidence from basic and clinical studies supports the conclusion that estrogen deficiency spurs the progression of certain chronic inflammatory diseases such as atherosclerosis. Whether ET can slow the progression depends on context. In the classic monkey model of diet-induced atherosclerosis, the timing of ET initiation was shown to be critical; delaying ET by an equivalent of 6 human years eliminated beneficial reductions in atherosclerosis.⁹ Multiple factors likely contribute to this. For example, if aging and/or disease have progressed in the absence of E_2 , a vascular microenvironment of cytokines can down-regulate or modify E_2 targets.¹⁰ Recently, researchers proposed that 27HC, an abundant cholesterol metabolite found in atherosclerotic plaque-associated macrophages, contributes to the loss of estrogen protection. 27HC is a competitive antagonist of ER action in the vasculature; when increased relative to E_2 , 27HC inhibits ER-mediated beneficial effects on nitric oxide synthesis and facilitates conditions that favor vascular disease progression.¹¹ Inflammation also plays a critical role in ischemic stroke, with increased central and peripheral pro-inflammatory cytokine production. In a mouse stroke model, E_2 has neuroprotective and anti-inflammatory (peripheral and central) actions that are disrupted after prolonged hypoestrogenicity.¹²

Although much work remains to be done, studies and dialogue between basic and clinical researchers have begun to resolve previously paradoxical results and put welcome limits on recent generalizations.

FROM THE CLINICAL SCIENTIST

- Biological differences between study populations may help reconcile divergent findings from observational studies and RCTs of HT.
- Evidence suggests that a woman's age and time since menopause influence her health outcomes on HT.
- Women at lowest risk of coronary events associated with HT are those near the menopause transition and those with favorable lipid profiles.
- After stopping estrogen+progestin in WHI, most of the benefits and risks of treatment dissipated quickly, but scientists have raised concerns about persistent cancer risks.

Emerging evidence suggests that a woman's age, time since menopause onset, and underlying risk factor profile strongly influence her benefit-to-risk ratio on menopausal HT.¹⁻⁴ HT has a net beneficial effect for some women and a net harmful effect for others; decision making must be individualized. Newly menopausal women—who are more likely to have vasomotor symptoms or other indications for HT, low baseline risks of CVD and other chronic diseases, and low *absolute* risks of adverse events attributable to HT—tend to be better candidates than women distant from menopause onset.⁴⁻⁶ Recent clinical studies have clarified which clinical factors best inform decision making and have helped to reconcile divergent research findings.

Understanding Discrepancies Between Observational Studies and RCTs

Observational studies suggested a 40%–50% lower risk of CHD among current users of HT compared with nonusers, whereas the WHI and other randomized trials have observed either neutral or increased CHD risk with HT.^{7, 8} Although observational studies have likely overestimated HT's benefits due to confounding and selection biases, major differences in the study populations may have also contributed to the discrepancies. In observational studies, most HT users initiate treatment within 2–3 years of menopause onset.^{1, 7} In contrast, in the WHI, the mean age of study participants was 63 and the mean time since menopause was more than 12 years.^{3, 8}

The timing of HT initiation appears to influence its association with CHD. Estrogen might have a beneficial or neutral effect on the heart if started in early menopause, when the arterial endothelium is likely to be relatively healthy, but a harmful effect if started in late menopause, when advanced atherosclerosis may be present.^{1, 6, 9} In combined analyses of the WHI estrogen-alone and estrogen+progestin (E+P) trials, women who were less than 10 years since menopause had a 24% *reduced* risk of heart disease with HT, women 10–19 years

past menopause had a 10% *increased* risk, and women 20 years or more past menopause had a 28% *increased* risk (P for trend = .02).³ All-cause mortality rates and total attributable risks with HT also appeared more favorable in younger than older women.³ A meta-analysis of randomized trials found that HT was associated with 30%–40% reductions in CHD and all-cause mortality in trials with predominantly younger women, but no reduction in trials with predominantly older participants.⁴

Biological Mechanisms Relevant to the Timing Hypothesis and Route of Hormone Delivery

Estrogen has complex biological effects, including both beneficial and harmful effects on cardiovascular biomarkers.^{1, 9} Women with a healthy and responsive endothelium may benefit most from estrogen's favorable effects on endothelial function, nitric oxide production, and blood vessel elasticity, whereas the prothrombotic and plaque-destabilizing effects of estrogen may disproportionately affect women with advanced atherosclerosis.^{1, 9} Studies in nonhuman primates also indicate that HT's coronary effects depend on vasculature health.¹⁰ Some adverse effects of estrogen may be mitigated by non-oral routes of delivery. Transdermal E_2 is less likely than oral estrogen to raise triglycerides and thrombotic/inflammatory markers, and may be less likely to raise the risk of VTE and gallbladder disease, but more research is needed.^{5, 6}

Other Relevant Findings

Women with favorable lipid profiles at WHI enrollment had better CHD outcomes on HT than women with dyslipidemias. For example, women with LDL-cholesterol/HDL-cholesterol ratios < 2.5 trended toward CHD risk reduction on HT, but women with ratios > 2.5 had evidence for risk elevation (P for interaction = .02).¹¹ These findings are consistent with the hypothesis that women at lower CVD risk tend to have more favorable coronary outcomes on HT. Other biomarkers and genetic factors have not been particularly helpful for risk stratification. WHI E+P trial findings post-stopping suggested that fracture benefits tended to dissipate soon after treatment cessation.¹² Although VTE and other CVD risks also appeared to abate promptly, concerns have been raised about a residual increase in breast cancer risk and a trend toward rising rates of lung and total cancer and all-cause mortality.¹² Thus, the post-stopping findings further support the need for guidelines to avoid long-duration HT and to limit use to treating menopausal symptoms rather than chronic disease prevention.

Conclusions and Clinical Implications

Available evidence suggests that the timing of HT initiation in relation to the menopause transition and the patient's symptoms and vascular health influence the benefit-to-risk ratio for treatment. In general, HT use is best limited to fewer than 5 years (unless a woman has undergone premature menopause), because breast cancer risk increases with longer use, especially for combination E+P. Additional research on the benefits and risks of HT in recently menopausal women, as in the KEEPS, Early Versus Late Intervention Trial With Estradiol (ELITE), and other trials, will help to inform future decision making.^{1, 6}

FROM THE CLINICIAN

- HT remains the most effective means of treating hot flashes; using the “lowest dose for shortest time” adage makes deciding when to stop therapy a challenge.
- Short-term risks of HT in relatively young, recently postmenopausal women are low; in the WHI, risks with estrogen alone were less than with combined therapy.
- Lower estrogen doses reduce both vasomotor and vaginal symptoms; in observational studies associated risks were reduced.
- Transdermal therapies have fewer metabolic consequences than oral preparations and may be a more appropriate choice for some women.

In response to the WHI,¹ clinicians appropriately tempered enthusiasm for HT for prevention, but, because of concerns with risks, use for symptoms also declined. For the vast majority of healthy, recently postmenopausal women, the benefits of short-term HT for relief of vasomotor symptoms exceed risks.²⁻⁴ In the WHI,⁵ women taking HT reported relief of hot flashes, night sweats, and vaginal dryness, as well as improvement in joint pain and stiffness and general aches and pains—benefits consistent with current U.S. Food and Drug Administration indications. Fracture reduction is also an indication for HT if a woman is at risk for osteoporosis and other available therapies have not been tolerated or effective.

Approach to the Patient

The first step in considering HT is to establish safety. Contraindications include the possibility of pregnancy, undiagnosed vaginal bleeding, estrogen-sensitive cancers, history of stroke or myocardial infarction in the past year, history of blood clots, and active liver disease. As noted, a fasting lipid panel might help establish CHD risk. If triglycerides exceed 250 mg/dL, consider transdermal E₂ and monitor triglyceride levels carefully.

The benefits and risks of HT should be viewed in the context of an individual woman's overall health status. Presenting risk in absolute terms rather than relative risk is more effective.⁴ Because of higher cardiovascular risks, women aged more than 60 years should be cautioned not to initiate HT.⁶ In those more distant from menopause, persistent vasomotor symptoms should alert clinicians to evaluate risks of CHD.⁶

Lower Doses as Effective

Lower doses (CEE 0.3 mg daily or estradiol 14–25 µg transdermal patch equivalent)—half the dose used in the WHI—effectively reduce hot flashes. Maximal benefit requires 2–3 months of therapy. With lower doses, side effects of breast tenderness and vaginal bleeding occur less frequently. In the Nurses' Health Study, risks of stroke⁷ and gallbladder disease⁸ were reduced. Younger women with surgical menopause might require higher doses for adequate symptom relief.

Choice of Estrogen Preparation

Oral therapies are most commonly prescribed for vasomotor symptom relief and have been studied most extensively. Transdermal therapies include patches, gels, mists, and emulsions. These preparations avoid first-pass metabolism by the liver, resulting in less effect on blood pressure, triglycerides, glucose, C-reactive protein, clotting factors, and sex hormone-binding globulin. In observational studies, fewer blood clots⁹ and fewer cardiac events¹⁰ occurred in women taking transdermal therapy. For women with hypertension, dyslipidemia, diabetes (in the absence of known vascular disease), or obesity, transdermal therapies are probably a safer choice.³

For women with symptoms limited to vaginal dryness, painful intercourse, or recurrent urinary tract infection, local vaginal therapy (creams, tablets, or vaginal rings) is appropriate.⁴ After 2 weeks of daily administration (effective with lower doses than previously used), most women can titrate therapy to maintain relief—often reducing application to once or twice weekly.

Concurrent Progestogen Therapy

In women with a uterus, concurrent progestogen therapy protects the endometrium from estrogen-induced proliferation.⁴ Lower doses are adequate with lower doses of estrogen. In an effort to reduce total progestogen exposure (and possible attendant vascular and breast risks), alternative schedules (e.g., every 3 months) and routes (e.g., vaginally with progesterone gel or levonorgestrel-releasing intrauterine systems) of administration are being evaluated, but are not yet approved. For women intolerant of progestogens, annual endometrial monitoring with ultrasound or endometrial sampling is appropriate. Progestogen therapy is not recommended with vaginal estrogens.

Duration of Therapy

For most women, vasomotor symptoms typically last a few years. Women can be encouraged to try to taper therapy every 6–12 months to assess the tolerability of their symptoms. Symptoms will peak 8–12 weeks after discontinuing HT. Some women successfully taper therapy by reducing the dose gradually (progressively trimming their patch or reducing 1 day of oral therapy each week). Some women require a year to taper; others prefer to stop “cold turkey.” This is a personal preference; the best approach has not been established. Women should be informed that they have a 50/50 chance of hot flash symptoms resuming once they discontinue therapy.

When women in the WHI discontinued HT, cardiovascular risks (heart attack, stroke, and venous thromboembolic events) disappeared during 2.4 years of follow-up.¹¹ An increased risk in cancers, particularly lung cancer, was observed.¹¹ Breast cancer¹² risks appear to increase with longer (≥ 5 years) duration of combined HT in women who start soon after menopause. We await more information to help identify which women require additional surveillance after stopping HT. Hormone therapy should be discontinued if a vascular event or an estrogen-sensitive cancer arises.

Individualize Approach to Therapy

Consider each woman's desire for symptom relief, her risk tolerance, and consideration of concurrent medical conditions—all elements that contribute to an assessment of whether HT is beneficial or harmful for her.⁴ Be mindful of each woman's uniqueness and personal preferences. Stay apprised of new developments, and let your patients know that their decisions require ongoing reassessment and evaluation. ■

References:

Basic Scientist

1. Turgeon JL, McDonnell DP, Martin KA, Wise PM. Hormone therapy: physiological complexity belies therapeutic simplicity. *Science*, 2004;304:1269–1273.
2. Dey M, Lyttle CR, Pickar JH. Recent insights into the varying activity of estrogens. *Maturitas*, 2000;34:S25–S33.
3. Berrodin TJ, Chang KCN, Komm BS, Freedman LP, Nagpal S. Differential biochemical and cellular actions of Premarin estrogens: distinct pharmacology of bazedoxifene-conjugated estrogens combination. *Mol Endocrinol*, 2009;23:74–85.
4. Baracat E, Haidar M, Lopez FJ, Pickar J, Dey M, Negro-Vilar A. Estrogen activity and novel tissue selectivity of delta8,9-dehydroestrone sulfate in postmenopausal women. *J Clin Endocrinol Metab*, 1999;84:2020–2027.
5. L'Hermite M, Simoncini T, Fuller S, Genazzani AR. Could transdermal estradiol + progesterone be a safer postmenopausal HRT? A review. *Maturitas*, 2008;60:185–201.
6. Stanczyk FZ. Parenteral versus oral treatment of postmenopausal women with estrogen. *Menopause*, 2007;14:968–970.
7. Harman SM, Brinton EA, Cedars M, et al. KEEPS: the Kronos Early Estrogen Prevention Study. *Climacteric*, 2005;8:3–12.
8. Turgeon JL, Carr MC, Maki PM, Mendelsohn ME, Wise PM. Complex actions of sex steroids in adipose, the cardiovascular system, and brain: insights from basic science and clinical studies. *Endocr Rev*, 2006;27:575–605.
9. Mikkola TS, Clarkson TB. Estrogen replacement therapy, atherosclerosis, and vascular function. *Cardiovasc Res*, 2002;53:605–619.
10. Stice JP, Eiserich JP, Knowlton AA. Role of aging versus the loss of estrogens in the reduction in vascular function in female rats. *Endocrinology*, 2009;150:212–219.
11. Umetani M, Domoto H, Gormley AK, et al. 27-Hydroxycholesterol is an endogenous SERM that inhibits the cardiovascular effects of estrogen. *Nat Med*, 2007;13:1185–1192.
12. Suzuki S, Brown CM, Dela Cruz CD, Yang E, Bridwell DA, Wise PM. Timing of estrogen therapy after ovariectomy dictates the efficacy of its neuroprotective and antiinflammatory actions. *Proc Natl Acad Sci U S A*, 2007;104:6013–6018.

Clinical Scientist

1. Manson JE, Bassuk SS, Harman SM, et al. Postmenopausal hormone therapy: new questions and the case for new clinical trials. *Menopause*, 2006;13:139–147.
2. Hsia J, Langer RD, Manson JE, et al. Conjugated equine estrogens and the risk of coronary heart disease: the Women's Health Initiative. *Arch Intern Med*, 2006;166:357–365.
3. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA*, 2007;297:1465–1477.
4. Salpeter SR, Walsh JM, Greyber E, Salpeter EE. Brief report: coronary heart disease events associated with hormone therapy in younger and older women. A meta-analysis. *J Gen Intern Med*, 2006;21:363–366.
5. Manson JE, Bassuk S. The menopause transition and postmenopausal hormone therapy. In: Fauci AS, Braunwald E, Kasper DL, et al. (eds). *Harrison's Principles of Internal Medicine*, 17th Edition. New York: McGraw-Hill, 2008:2334–2339.
6. Advisory Panel of the North American Menopause Society. Position Statement: estrogen and progestogen use in postmenopausal women. *Menopause*, 2008;15:584–602.
7. Grodstein F, Clarkson TB, Manson JE. Understanding the divergent data on postmenopausal hormone therapy. *N Engl J Med*, 2003;348:645–650.
8. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmeno-

- pausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA*, 2002;288:321–333.
9. Mendelsohn ME, Karas RH. Molecular and cellular basis of cardiovascular gender differences. *Science*, 2005;308:1583–1587.
10. Mikkola TS, Clarkson TB. Estrogen replacement therapy, atherosclerosis, and vascular function. *Cardiovasc Res*, 2002;53:605–619.
11. Bray PF, Larson JC, LaCroix AZ, et al. Usefulness of baseline lipids and C-reactive protein in women receiving menopausal hormone therapy as predictors of treatment-related coronary events. *Am J Cardiol*, 2008;101:1599–1605.
12. Heiss C, Wallace R, Anderson GL, et al. Health risks and benefits 3 years after stopping treatment with estrogen and progestin. *JAMA*, 2008;299:1036–1045.

Clinician

1. Writing Group for the Women's Health Initiative. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *JAMA*, 2002;288:321–333.
2. Grady D. Management of menopausal symptoms. *N Engl J Med*, 2006;355:2338–2347.
3. Ettinger B, Barrett-Connor E, Hoq LA, Vader JP, Dubois RW. When is it appropriate to prescribe postmenopausal hormone therapy? *Menopause*, 2006;13:404–410.
4. Estrogen and progestogen use in postmenopausal women: July 2008 position statement of the North American Menopause Society. *Menopause*, 2008;15:584–602.
5. Barnabei VM, Cochrane BB, Aragaki AK, et al. Menopausal symptoms and treatment-related effects of estrogen and progestin in the Women's Health Initiative. *Obstet Gynecol*, 2005;105:1063–1073.
6. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA*, 2007;297:1465–1477.
7. 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.
8. Grodstein F, Colditz GA, Stampfer MJ. Postmenopausal hormone use and cholecystectomy in a large prospective study. *Obstet Gynecol*, 1994;83:5–11.
9. Canonico M, Plu-Bureau G, Lowe GD, Scarabin PY. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. *BMJ*, 2008;336:1227–1231.
10. Lokkegaard E, Andreasen AH, Jacobsen RK, Nielsen LH, Agger C, Lidegaard Ø. Hormone therapy and risk of myocardial infarction: a national register study. *Eur Heart J*, 2008;29:2660–2668.
11. Heiss C, Wallace R, Anderson GL, et al. Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. *JAMA*, 2008;299:1036–1045.
12. Prentice RL, Chlebowski RT, Stefanick ML, et al. Estrogen plus progestin therapy and breast cancer in recently postmenopausal women. *Am J Epidemiol*, 2008;167:1207–1216.

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