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Managing Menopause by Combining Evidence with Clinical Judgment

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Abstract

In the United States, nearly 10 million women are currently in the menopause transition and 2.25 million women are 51 years of age, which is the average age of menopause.¹ Approximately 75% of these women will experience vasomotor symptoms such as hot flashes and night sweats.² Menopause hormone therapy (HT) remains the most effective treatment for menopausal symptoms, but the decision to use HT is complex and requires balancing the benefits and risks for the individual patient. The decision also requires clinical judgment and shared decision making with the patient. In this review, we discuss the current guidelines for HT use, the benefits and risks for the individual patient and a novel algorithm and clinical decision support tool for menopausal symptom management that facilitates shared decision making between clinician and patient.

Introduction

Many women and some physicians remain reluctant to use and prescribe HT for menopause due to the concerns about an increased risk of heart disease and breast cancer. Overall, the Women's Health Initiative (WHI) clinical trials found an unfavorable balance of the benefits and risks of HT when used for chronic disease prevention among women aged 50–79, especially for combination estrogen plus progestin, due primarily to increased risk of venous thrombosis, cardiovascular disease (CVD), and breast cancer. The WHI clinical trials were randomized double-blinded placebo control trials to determine if HT could prevent chronic diseases, specifically cardiovascular disease. Over 27,000 women were enrolled in the estrogen and progestin (E+P trial, which tested oral conjugated equine estrogens [CEE] plus medroxyprogesterone acetate [MPA]) or the estrogen-alone (E-alone trial, which tested oral CEE alone), based on hysterectomy status. By design, the age range spanned early-to-late postmenopausal years (mean, 63 years) and women with severe vasomotor symptoms requiring treatment were excluded. The trials were stopped early due to increased risk of CVD and breast cancer in the E+P trial and increased risk of stroke in the E-alone trial.

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Subsequent analyses of the WHI have revealed lower absolute risks and attributable risks of adverse outcomes when menopausal HT was initiated in younger women (aged 50 to 59 years). (Figure 1) The use of hormones closer to the onset of menopause (within 10 years) demonstrated a trend toward lower risk of coronary heart disease compared to women who began therapy further from menopause (> 20 years) for both the E-alone and E+P trials (Figure 2).³ From these and other findings, the “timing hypothesis” was developed suggesting that there may be less risk and possible coronary heart disease benefit when HT is initiated closer to the time of menopause, whereas starting HT further from menopause may be harmful.

Most recently two smaller clinical trials using surrogate CVD outcomes, carotid intimal media thickness (CIMT) and coronary artery calcification (CAC), evaluated the use of HT closer to the time of menopause. Both the Kronos Early Estrogen Prevention Study [KEEPS] (n=720) and the Early Versus Late Intervention Trial with Estradiol [ELITE] (n=504) provided further evidence that starting HT closer to menopause onset did not increase surrogate markers for CVD and may be safe in early menopause, while the ELITE trial also demonstrated that there was a beneficial effect on atherosclerosis progression (as assessed by CIMT) when HT was started within 6 years of menopause onset.

Current Menopause Guidelines

Guidelines have evolved over the past 15 years, with the pendulum swinging from what was once treatment directed at chronic disease prevention to treatment primarily for menopausal symptom management. Current guidelines focus on the timing of HT initiation and the type and route of delivery of estrogen with respect to specific risk factors. The risks of HT differ depending on type, dose, duration of use, route of delivery and whether the formulation is combination estrogen plus progestogen or estrogen-alone. Overall, HT is considered appropriate for the treatment of vasomotor symptoms when initiated in early menopause among women who are considered to be at low cardiovascular risk and have no personal history of breast cancer.

In 2015, the Endocrine Society released practice guidelines for the management and treatment of menopausal symptoms. Based on grading recommendations, the task force supported the use of HT in healthy women with bothersome menopausal symptoms, when started in early menopause (below 60 years of age or less than 10 years from menopause onset).⁴ The assessment of risk of breast cancer and cardiovascular risk was recommended in all women prior to initiating, as well as regular assessments for continued use of HT. The guidelines also recognized the increased risk of breast cancer during and after the use of estrogen plus progestogen therapy, thus recommending ongoing surveillance. For women at moderate risk of CVD, transdermal estradiol (rather than oral estrogen) was recommended as first line therapy; while women at increased risk for venous thromboembolism (VTE) or breast cancer were advised to avoid hormone therapy and use nonhormonal options.

In 2017, the American Association of Clinical Endocrinologists and the American College of Endocrinology updated their position statement on menopause.⁵ The new recommendations suggested that the use of transdermal estradiol may pose less of a

thrombotic risk than oral estrogen, findings that may be relevant to VTE, stroke, and coronary disease. The statement also recommended using micronized progesterone (as opposed to a synthetic progestin) when a progestogen is needed. Finally, consistent with other professional organizations, the statement did not endorse the use of custom compounded bioidentical HT.

Perhaps the most comprehensive published position statement is the 2017 hormone therapy position statement of The North American Menopause Society,⁶ updated from 2012. In this statement, experts evaluated HT use with respect to all major organ systems and the influence on health and quality of life. These guidelines no longer recommend “the lowest effective HT dose for the shortest duration of time” and instead suggest “appropriate” dose and duration, taking into account the balance of benefits and risks of HT and the timing of initiation. The statement also recognizes important distinctions between estrogen alone and estrogen with a progestogen. Departing from previous guidelines, the 2017 position statement affirms that there is no evidence to support routine discontinuation of HT at a specific age or after 65 years. The guideline also recognizes that the risk for breast cancer is not increased on E-alone; in contrast, there is an increase after 5-years of continuous E+P use, with the added attributable risk being 1 in 1000 women. To date, no guidelines support the use of HT for primary or secondary prevention of cardiovascular disease.

Benefits of HT: E+P and E-alone

The benefits of HT are summarized below and in Tables 1a and 1b.

Vasomotor Symptoms Menopausal HT in the form of both E+P and E-alone is associated with a 60–95% improvement in vasomotor symptoms, which is the primary FDA indication for systemic HT use. Symptom relief can occur as early as 2 weeks after initiating treatment, but may require more than 4 weeks for full benefit. **Bone Health** Another benefit of HT (E +P or E-alone) relates to bone health. There was a 33% reduction in fractures in the WHI in women randomized to HT compared to placebo. Estrogen is known to stimulate osteoblast activity, and promotes the formation of several growth factors, including transforming growth factor- β , insulin-like growth factor-1, and bone morphogenetic protein 6. Systemic estrogen (including both oral and transdermal formulations in various doses) have been FDA approved for the indication for osteoporosis prevention. **Urogenital atrophy** While not a health outcome directly assessed in the WHI clinical trials, both systemic estrogen as well as local intra-vaginal estrogen improve the physical changes of urogenital atrophy and reduce dyspareunia and other symptoms of the genitourinary syndrome of menopause.

Possible or Uncertain Benefits: E+P

Suggestive but inconclusive benefits of E+P are summarized below and in Table 1a.

Colorectal Cancer In the WHI, colorectal cancer incidence was reduced by 37% among women taking E+P, but colorectal cancer mortality was not reduced.⁷ **Coronary heart disease** When stratified by years since menopause, the WHI suggested a neutral association between E+P and myocardial infarction (MI) among women within 10 years of menopause onset, but increased risk in older women (p, trend for MI by time since menopause = 0.01).

No clear trend was observed by age group. The subsequent KEEPS trial found no association between E+P and a surrogate measure of CHD (atherosclerosis progression by carotid intimal media thickness [CIMT]). However, the ELITE trial, designed specifically to test the “timing hypothesis”, found a reduced rate of atherosclerosis progression by CIMT among women within 6 years of menopause onset but not among women >10 yrs past menopause (P for interaction = 0.007). **Type 2 Diabetes** E+P was associated with a lower risk of type 2 diabetes (16 fewer cases per 10,000 women per year in the E+P vs the placebo group). In the KEEPS trial, using serum glucose changes over time, transdermal estradiol but not oral estrogen was associated with favorable effects on glucose metabolism.

Endometrial cancer There was a 33% reduced risk for endometrial cancer for women in the E+P arm of WHI compared to placebo; this reduction in risk became statistically significant after the trial ended (RR 0.67 [95% CI, 0.49, 0.91]) at 13 years of cumulative follow-up.³

Possible Benefits or Uncertain Benefits: E-alone

Suggestive but inconclusive benefits of E-alone are summarized below and in Table 1b.

Breast cancer The risk of breast cancer was not increased in the E-alone trial of the WHI; rather, the HR was 0.79 (0.65–0.97), over 13 years of follow-up, with 7 fewer cases of breast cancer for every 10,000 women per year for E-alone compared to placebo.³ **Coronary Heart Disease** In the E-alone trial, the signals for reduced coronary risk in the younger women and differences by age group were stronger than in the E+P trial. For total MI, a statistically significant reduction in risk was observed in younger women (HR= 0.60; 95% CI, 0.39–0.91) over 13 years of cumulative follow-up, as well as a trend for increasing risk of MI with increasing age (p, trend by age = 0.007).³ **Type 2 Diabetes** Similar to the E+P trial, the E-alone trial also found a lower risk (14% decrease) in incidence of type 2 diabetes.³

Probable Increased Risk: E+P

Probable risks of E+P are summarized below and in Table 1a.

Coronary heart disease The WHI found an increase in CHD (defined as nonfatal MI or coronary death) among older women who were many years past menopause (>10 years), this was not observed in women starting HT within 10-years since menopause.⁸ For MI, specifically, a trend for increasing risk by increasing time since menopause was apparent (p for trend = 0.01).³ **Dementia** Findings from the WHI ancillary Memory Study, which included women aged 65 years and older, identified an increased risk of probable dementia in women randomized to E+P, and E+P did not reduce the risk of mild cognitive impairment.⁹ **Ovarian cancer** The risk of ovarian cancer was increased with longer duration (over 5-years) of use, with 1 excess case per 10,000 women per year observed in women who received HT compared to placebo.³

Probable Increased Risk: E-alone

Probable risks of E-alone are summarized below and in Table 1b.

Colorectal cancer Overall there was no increased risk of colorectal cancer in the WHI E-alone trials, however the results appeared to be modified by age.³ Younger women had no

elevation in risk, while women aged 70–79 years old had nearly a doubling in risk. **Dementia** A nonsignificant increase in the risk of probable dementia was observed with E-alone in the WHI memory trial for women >65 year of age. **Stroke** In the overall study population, there were 13 excess cases of ischemic stroke per 10,000 women per year using E-alone as compared to placebo.¹⁰ No increase in hemorrhagic stroke was observed.¹⁰

Definite Risk E+P and E-alone

Definite risks of each formulation of HT are summarized below and in Tables 1a and 1b.

Breast Cancer (E+P only) An increased risk of breast cancer was found during the WHI E+P trial after 4–5 years of continuous use. **Deep Vein Thrombosis** An increased risk of deep vein thrombosis was observed in the WHI E+P and E-alone trials. Observational studies have suggested that the increased thrombosis risk may be due to oral estrogen's first pass liver metabolism, which creates a prothrombotic state, as opposed to transdermal estrogens. The differences in thrombosis risk according to route of estrogen delivery have not been conclusively tested in randomized clinical trials. **Pulmonary Embolism** As with venous thrombosis, there was an increased risk of pulmonary embolism in both trials. Pulmonary embolism accounts for one third of the excess potentially fatal events associated with HT use in several trials.¹¹ **Endometrial Cancer (E-alone, unopposed)** Endometrial cancer is increased in women with an intact uterus who received unopposed estrogen.¹² **Gallbladder disease** There was an increased risk of gallbladder disease with both E+P and E-alone.

All-Cause Mortality in the E+P and E-Alone Trials

In view of the complex matrix of benefits and risks of HT, all-cause mortality is an important summary measure representing the net effect of HT on serious and life-threatening health conditions. Neither formulation was associated with an increase or decrease in risk of all-cause, cardiovascular, or cancer mortality in the overall cohort (aged 50–79) during the intervention or cumulative follow-up phases. However, differences were apparent by age group during the intervention phase. The HRs for all-cause mortality in the two trials (pooled) during the intervention phase were 0.69 (95% CI, 0.51–0.94) for women ages 50–59, 1.04 (95% CI, 0.87–1.25) for ages 60–69, and 1.13 (95% CI, 0.94–1.36) for ages 70–79 (p-value for trend = 0.01) The trends by age in the pooled trials were attenuated during cumulative follow-up (HRs, 0.89, 0.98, 1.03; p-value for trend = 0.06).⁷

Clinical Consideration

Symptomatic women with bothersome vasomotor symptoms and seeking treatment in early menopause (within 10 years of menopause onset) tend to have the most favorable benefit: risk profile on HT. While guidelines help shape clinical decision making with respect to specific disease risk, it is important to assess patients based on risk stratification to maximize health after menopause. Shared decision making with the patient is important, as some women will be receptive to HT and others will prefer nonhormonal options. Lifestyle modifications should be encouraged, including daily physical activity and weight bearing exercises. Women's health screenings, particularly mammography and clinical breast

examination, should be current prior to initiating HT. Women should also be screened for depression, tobacco use, alcohol consumption and domestic violence.

Menopause Algorithm

To personalize medicine in a digital era, the North American Menopause Society has developed an evidence-based algorithm and app called “MenoPro” (available for iOS and Android devices) for both clinicians and patients to tailor menopause treatment decision making.¹³ The MenoPro algorithm allows for a step-by-step risk factor evaluation to determine who may be an appropriate candidate for HT versus non-hormonal options. The questions also address whether a woman is interested in using HT and if she has tried behavioral and lifestyle medications for her symptoms for at least 3 months. Once the algorithm determines that a woman is free of contraindications to HT (such as a personal history of venous thrombosis or breast cancer), the decision is based primarily on years since menopause and the calculated 10-year atherosclerotic cardiovascular disease¹⁴ (ASCVD) risk score, as well as the patient’s personal preferences. (see Table 2) As with other algorithms in medicine, this application should be used as a clinical decision support tool, but it does not replace clinical judgment.

For women who have a moderate risk for cardiovascular disease with an ASCVD between 5–10%, the use of transdermal (rather than oral) estradiol is recommended. Transdermal estrogen formulations bypass first-pass hepatic metabolism, resulting in lower production of prothrombotic factors, triglycerides, and inflammatory markers such as C-reactive protein compared to oral regimens.¹⁵ There is observational study evidence that transdermal estrogen may be associated with lower risk of stroke than oral estrogen.¹⁶

Clinical Vignette Recommendations

Ms. B is within 10-years of menopause and having moderate-to-severe vasomotor symptoms. She has a history of dyslipidemia and no significant personal or family history of breast disease. Based on her physical exam and laboratory findings, her calculated ASCVD risk score is moderate at 5.2%. Given this, and the absence of clinical contraindications, she would be a candidate for HT. She was receptive to HT treatment. Due to her CVD risk factors, the recommended formulation would be transdermal (rather than oral) estrogen with a progestogen. The risks of hormone therapy were discussed with the patient, including the increased risk of breast cancer after five years of combined hormone therapy use. The risks of cardiovascular disease increase with age and are low in otherwise healthy women who are within ten years of menopause. Benefits include treatment of moderate to severe vasomotor symptoms, treatment of urogenital atrophy, and prevention of postmenopausal osteoporosis. If genitourinary symptoms were the only indication for treatment, low-dose vaginal estrogen (non-systemic therapy) would be recommended.

Conclusion

Menopause HT remains the most effective treatment available for menopausal symptoms, and the decision to use HT requires balancing the benefits and risk of treatment for the

individual patient and shared decision making. The most established benefit of HT is the treatment of vasomotor symptoms as well as prevention of osteoporosis and fracture reduction. Estrogen with progestin modestly increases the risk of breast cancer.

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Clinical Vignette

Ms. B is a 54-year-old woman with a past medical history of dyslipidemia and hypothyroidism who presents with bothersome menopausal symptoms. Her last menstrual period was 2 years ago and she is having 5–8 hot flashes per day that often fog up her glasses, and 2–3 episodes of night sweats where she wakes up drenched. She has no past surgical history and no family history of breast cancer. A paternal grandfather died of heart disease in his 70's. Current medications include levothyroxine and a multivitamin. Her mammogram and pap smear are up-to-date and normal. She is asking about treatment options but is reluctant to use hormone therapy because she has heard that it increases the risk of breast cancer and heart disease.

Key Points

1. Menopausal hormone therapy (HT) remains the most effective treatment for menopausal symptoms, but the decision to use HT is complex and requires balancing of the benefits and risks for the individual patient
2. Hormone therapy is an appropriate option when initiated in symptomatic women < 60 years or within 10-years since menopause who are generally healthy and free of contraindications to HT.

Figure 1.

Benefits and Risks of the WHI E-alone and E+P trials in women 50 to 59 years of age. Risks and benefits are expressed as the difference in number of events (number in the hormone-therapy group minus the number in the placebo group) per 1000 women over 5 years

Figure 2.
Absolute risks of health outcomes by 10-year age groups in the Women's Health Initiative Hormone Therapy Trials

Table 1a

Risks vs Benefits of CEE+MPA use

Definite Benefit	Possible or Uncertain Benefit	Probably Increased Risk	Definite Risk
Vasomotor symptoms Osteoporosis Urogenital atrophy	Colorectal Cancer Coronary heart disease * Type 2 Diabetes Endometrial cancer †	Coronary heart disease ** Dementia ** Ovarian cancer † Stroke	Breast Cancer † Deep vein thrombosis Gallbladder disease Pulmonary embolism

* reduced risk or no effect in younger or recently menopausal women

** increased risk in older women

† long term use ≥ 5 years

CEE, conjugated equine estrogens, MPA, medroxyprogesterone acetate

Table 1b

Risks vs Benefits of CEE-alone

Definite Benefit	Possible or Uncertain Benefit	Probably Increase Risk	Definite Risk
Vasomotor symptoms Osteoporosis Urogenital atrophy	Breast cancer Coronary Heart Disease * Myocardial infarction * Type 2 Diabetes	Colorectal cancer ** Dementia ** Stroke	Deep vein thrombosis Endometrial cancer (unopposed) Gallbladder disease Pulmonary embolism

* reduced risk or no effect in younger or recently menopausal women

** increased risk in older women

CEE, conjugated equine estrogens

Table 2Algorithm for consideration of HT for menopausal symptoms¹³

ASCVD 10-Year Risk*	Years Since Menopause Onset		
	5	6 – 10	>10
Low (<5%)	HT OK	HT OK	Avoid HT
Moderate (5%–10%)	HT OK (Consider transdermal)	HT OK (Consider transdermal)	Avoid HT
High (>10%)	Avoid HT	Avoid HT	Avoid HT

* Atherosclerosis cardiovascular disease risk over 10 years (ACC/AHA Risk prediction score)¹⁴

Source: Manson JE, Ames JM, Shapiro M, et al. Algorithm and mobile app for menopausal symptom management and hormonal/non-hormonal therapy decision making: a clinical decision-support tool from The North American Menopause Society. *Menopause*. 2015;22(3):247–253.¹³