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Review

Review

Hormone Therapy in Menopause: Concepts, Controversies, and Approach to Treatment

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Abbreviations: BMD, bone mineral density; CAC, carotid artery calcium; cBHT, compounded bioidentical hormone therapy; CEEs, conjugated equine estrogens; CGHFBC, Collaborative Group on Hormonal Factors in Breast Cancer; CHD, coronary heart disease; CIMT, carotid artery intima-media thickness; COC, combined oral contraceptive; CVD, cardiovascular disease; DHEA, dehydroepiandrosterone; DVT, deep vein thrombosis; E_2, estradiol; E-alone, estrogen-alone trial; EEs, esterified estrogens; ELITE, Early vs Late Intervention Trial with Estradiol; EPT, estrogen and progestin therapy; ER, estrogen receptor; FDA, US Food and Drug Administration; FMP, final menstrual period; GSM, genitourinary syndrome of menopause; HDL-C, high-density lipoprotein cholesterol; HERS, Heart and Estrogen-progestin Replacement Study; HR, hazard ratio; HT, hormone therapy; IUD, intrauterine device; KEEPS, Kronos Early Prevention Study; LDL-C, low-density lipoprotein cholesterol; LNG, levonorgestrel; MP, micronized progesterone; MPA, medroxyprogesterone acetate; NAMS, North American Menopause Society; NETA, norethindrone acetate; NK3R, neurokinin 3 receptor; PE, pulmonary embolism; PEPI, Postmenopausal Estrogen/Progestin Interventions; POI, primary ovarian insufficiency; RCT, randomized controlled trial; SERM, selective estrogen receptor modulator; SSRI, selective serotonin reuptake inhibitor; TSEC, tissue-selective estrogen complex; VMS, vasomotor symptoms; VTE, venous thromboembolism; WHI, Women's Health Initiative.

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Abstract

Hormone therapy (HT) is an effective treatment for menopausal symptoms, including vasomotor symptoms and genitourinary syndrome of menopause. Randomized trials also demonstrate positive effects on bone health, and age-stratified analyses indicate more favorable effects on coronary heart disease and all-cause mortality in younger women (close proximity to menopause) than in women more than a decade past menopause. In the absence of contraindications or other major comorbidities, recently menopausal women with moderate or severe symptoms are appropriate candidates for HT. The Women's Health Initiative (WHI) hormone therapy trials—estrogen and progestin trial and the estrogen-alone trial—clarified the benefits and risks of HT, including how the results differed by age. A key lesson from the WHI trials, which was unfortunately lost in the posttrial cacophony, was that the risk:benefit ratio and safety profile of HT differed markedly by clinical characteristics of the participants, especially age, time since menopause, and comorbidity status. In the present review of the WHI and other recent

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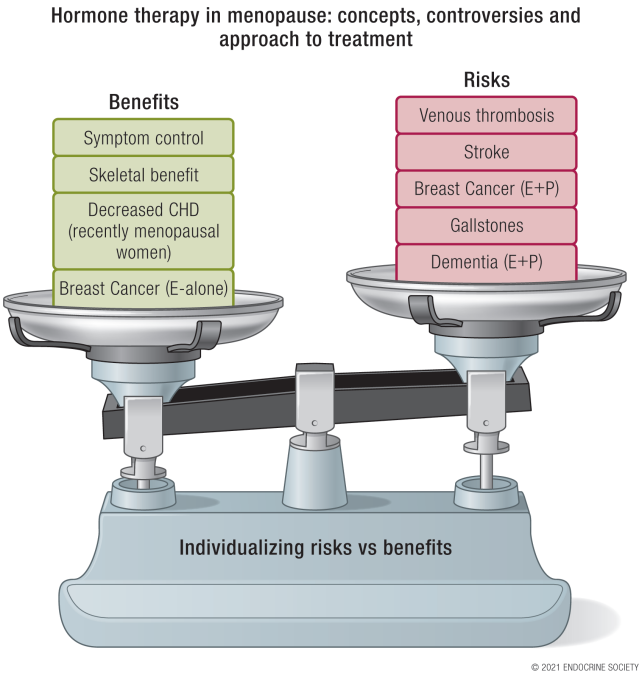
HT trials, we aim to provide readers with an improved understanding of the importance of the timing of HT initiation, type and route of administration, and of patient-specific considerations that should be weighed when prescribing HT.

Key Words: menopause, hormone therapy, timing hypothesis

Graphical Abstract



ESSENTIAL POINTS

- The effects of menopausal hormone therapy vary based on clinical factors (age, time since menopause, and comorbidity status) and by hormone therapy type, dose, and route of administration
- In healthy women less than 10 years since menopause onset, or younger than 60 years, hormone therapy is a safe, effective treatment option for menopausal symptoms; the benefits extend beyond the control of vasomotor symptoms and genitourinary syndrome of menopause to include reductions in risk of fracture and type 2 diabetes
- Transdermal estrogens avoid first-pass hepatic metabolism, and available studies have not found an increased risk of venous thrombosis; for postmenopausal women with risk factors for cardiovascular disease or who are obese, the transdermal route of hormone therapy is preferred
- Secondary analysis of the Women's Health Initiative (WHI) trials found that younger women within 10 years of menopause did not have an increased risk of coronary heart disease or all-cause mortality
- Breast cancer risk was significantly reduced in the WHI estrogen-alone trial; conjugated equine estrogen formulations contain more than 10 estrogens that can have differential actions on the target tissue, which may in part explain the reduction in breast cancer
- Breast cancer risk may be influenced by choice of progestogen in hormone therapy regimens; the tissue selective estrogen complex allows for beneficial effects of estrogens without the need for a progestogen to counteract estrogen's effects on the endometrium, thereby avoiding the potential negative effect of progestogens on the breast
- For those experiencing loss of ovarian function at an earlier age than the average population norms, consideration for initiation of hormone therapy is advisable not only to mitigate the symptoms resulting from hypoestrogenism, but also to prevent the long-term health consequences associated with premature onset of estrogen insufficiency

The use of hormone therapy (HT) in menopausal women has, in recent decades, been one of the most contentious topics in women's health. A plethora of observational data had suggested that HT was not only effective against common menopausal symptoms such as hot flushes and night sweats, but also offered benefit against chronic disorders such as osteoporosis, coronary artery disease, dementia, and even all-cause mortality (1-4). However, as randomized trials of HT were conducted, some of the previously purported long-term health benefits of HT were called into question. The Women's Health Initiative (WHI) primary prevention hormone trials, by demonstrating HT-related risks in older postmenopausal women, led to a seismic shift in menopause management, and a prescribing pattern that shifted considerably in the years following the WHI HT trials (5, 6). Prior to these randomized clinical trials, observational studies consistently demonstrated lower rates of coronary heart disease (CHD) and all-cause mortality among women using HT, compared to nonusers. As such, HT was initially heralded for use in the prevention of CHD and other chronic diseases, in addition to treatment of menopausal symptoms. However, the large-scale WHI trials, conducted in postmenopausal women across a broad age range (50-79 years, mean age 63) did not confirm the cardiovascular and all-cause mortality benefits that had previously been suggested by observational studies. On the contrary, although benefits for fracture reduction were confirmed, HT was found to increase the risk of stroke and venous thromboembolic disease. For CHD and breast cancer, the results varied by formulation. Subsequent analyses of the WHI indicated that the trial findings for CHD and all-cause mortality were influenced by age or time since menopause, with more favorable results in younger than older women (especially for the estrogen-alone trial [E-alone]). Given that most postmenopausal women in observational studies began HT early in menopause, the age-stratified results from the WHI trials helped to reconcile results from these different sources of evidence.

As we discuss in the present review, recent data from the WHI and other randomized trials have provided insights into the role of age, timing of HT initiation, formulation and route of administration, and assessment of comorbidities when considering prescribing HT for menopausal women.

Menopausal Hormone Therapy: Indications for Treatment

Management of Menopausal Symptoms

HT remains the most effective treatment option available for the management of menopausal vasomotor symptoms (VMS) and the genitourinary syndrome of menopause (GSM) (7-9). Both conditions are highly prevalent in postmenopausal women, affecting 80% and 50%, respectively, and adversely affecting health and quality of life. HT is approved by the US Food and Drug Administration (FDA) for both of these indications, as well as for prevention of bone loss, and treatment of premature hypoestrogenism. In a metanalysis of RCTs in aging women (on average age 50 years), it was found that both oral conjugated equine estrogens (CEEs) or transdermal estradiol (E_2) (with or without the addition of a progestin) were effective in ameliorating hot flashes, reducing symptoms by 70% to 95% (10). For the treatment of GSM, a systematic review found that vaginal estrogen products were the most effective form of treatment for genitourinary symptoms, with superiority over vaginal lubricants and moisturizers (11). Clinical management guidelines, available HT formulations, and alternative treatment options are discussed in the following sections. Ongoing debate about the benefit:risk profile of HT when used to prevent osteoporosis, another FDA-approved indication for HT, are also addressed in detail.

Menopausal Hormone Therapy: Observational Studies and Clinical Trials

Observational Studies of Hormone Therapy and Cardiovascular Risk

Cardiovascular disease (CVD) risk increases for women following menopause, and the loss of ovarian estrogen has been postulated to contribute to this risk. In observational studies, decreased CHD risk was nearly consistently demonstrated in postmenopausal women using HT compared to nonusers of HT (3, 12-48). This seemed plausible because of the low risk of CHD in premenopausal compared to postmenopausal women and the findings from small-scale RCTs indicating that estrogens increase high-density lipoprotein cholesterol (HDL-C) and decrease low-density lipoprotein cholesterol (LDL-C), thus potentially slowing the risk of atherosclerosis (49). In the large-scale Nurses' Health Study, estrogen therapy (ET) at doses of 0.3 mg or 0.625 mg of CEEs was associated with reduced risk for CHD, even after adjusting for physical activity, diet, and other lifestyle and medical factors; the same held true for combined estrogen and progestin therapy (EPT) (50). Meta-analyses of observational studies demonstrated 40% to 50% reductions in CHD comparing HT users to nonusers (51) (see subsequent sections). Observational studies showed inconsistent results for HT and stroke, with an increased risk found in the Nurses' Health Study (52) and in the General Practice Research Database (53), but a reduced risk in several other studies (56, 60-64). The overall supportive evidence for cardioprotection from HT

in observational studies led to increasing prescription rates for these hormones (54-57) and generated hypotheses for testing in randomized trials of HT and CVD outcomes.

The Women's Health Initiative Hormone Trials

The 2 WHI randomized controlled trials (RCTs) of HT (funded by the US National Institutes of Health) were designed to examine the effects of HT on the prevention of CHD and other chronic diseases in postmenopausal women across a broad range of midlife and older age groups (5, 6). The WHI-E + P trial compared the effects of continuous combined estrogen-progestin regimen (0.625 mg of CEE and 2.5 mg of medroxyprogesterone acetate [MPA] daily) vs placebo in 16 608 postmenopausal women (aged 50-79 years; mean age 63.3 years) with an intact uterus. The WHI-E-alone trial assessed the effects of CEE (0.625 mg daily) therapy (ET) alone or placebo in postmenopausal women lacking a uterus (had previously undergone hysterectomy for noncancerous reasons) (58, 59). The WHI-E + P trial was discontinued after 5.6 years of intervention (3 years earlier than planned) because of evidence of net harm from HT exceeding a predetermined threshold, and in the absence of evidence of benefit for CHD, the primary end point). Increased risks of breast cancer, stroke, deep vein thrombosis (DVT) and pulmonary embolism (PE)—in the absence of coronary benefit—led to the premature termination of the WHI-E + P trial despite significant reductions in incident fractures and colon cancer. Subsequent analyses showed a complex matrix of benefits and risks (Table 1).

The WHI E-alone trial included 10 739 women (aged 50-79 years; mean age 63.6) and was stopped 1 year early (after 6.8 years) because of an increased risk of stroke and the absence of benefit for CHD. As in the E + P trial, increased risks of stroke, DVT, and PE were noted. However, unlike the E + P trial, there were no observed increases in risk of CHD or breast cancer with the use of E-alone (for E + P, hazard ratio [HR] was 1.18 [95% CI, 0.95-1.45] and HR 1.24 [95% CI, 1.01-1.53], respectively; for E-alone, HR was 0.94 [95% CI, 0.78-1.14] and 0.79 [95% CI, 0.61-1.02], respectively), and results for all-cause mortality were neutral in both trials. Similar to the E + P trial, significant decreases in fracture risk were seen with E-alone, compared to placebo (see Table 1). Improvements in self-reported VMS and sleep were similar to what was seen in the E + P trial (6).

Analyses following discontinuation of the WHI HT trials identified HT-related increases in the risk of dementia in the E + P and the pooled E + P and E-alone trials (not with E-alone), nonsignificant increases in the risk of ovarian and lung cancer in the E + P trial (60, 61), increased urinary incontinence and gallbladder disease both in E + P and E-alone trials, and reductions in risk of type 2 diabetes in hormone users in both trials (62, 63).

Women's Health Initiative Hormone Trials—Postintervention and Cumulative Follow-up

Although the WHI hormone trials were stopped early, participants have had continued follow-up following the end of hormone interventions (62). The risk for CHD was determined to be neutral both in the postintervention and 13-year cumulative follow-up periods of the E + P trial and E-alone trials (62). Invasive breast cancer risk remained significantly elevated in the postintervention and cumulative follow-up period of the E + P trial, with a decline in the risk over time since EPT cessation (64). Interestingly, in the E-alone trial, the reduced risk of invasive breast cancer in hormone users achieved statistical significance during cumulative follow-up (62). Results for stroke, PE, DVT, and colorectal cancer remained neutral after 13 years of cumulative follow-up in both hormone trials, and for all-cause mortality, results were neutral at all follow-up time points in both trials (62, 63). The risk reduction in fractures was attenuated during the postintervention period for both trials, although the positive effects of HT persisted over the 13-year cumulative follow-up for the E + P trial. Dementia risk was neutral in postmenopausal women aged 50 to 55 years at random assignment during the postintervention follow-up. In addition, the decreased rate of diabetes in HT users was no longer evident following discontinuation of HT, while urinary incontinence symptoms were still elevated in women assigned to HT in both trials. Risks of gallbladder disease showed persistent elevations in the E + P trial but became neutral in the E-alone trial (62).

Several of the adverse findings from the WHI HT trials in the overall cohort (intervention and cumulative follow-up) were unexpected and inconsistent with earlier observational data. Before investigating factors that may explain the inconsistencies between WHI findings and prior observational data, it is important to examine the results of other major RCTs that assessed HT and health outcomes.

Hormone Therapy: Secondary Prevention Trials

The Heart and Estrogen-progestin Replacement Study (HERS) was a randomized, placebo-controlled trial designed to determine if EPT (CEEs + MPA) treatment reduced CHD in women with existing coronary disease (62, 65). The 4-year secondary prevention trial included 2763 women, who were on average age 66.7 years. While there was no difference in the risk of CHD (myocardial infarctions or coronary deaths) in the intervention compared to placebo groups, a 50% increased risk of CHD during the first year of the intervention was found. An increased risk of venous thrombotic events

Table 1. Women's Health Initiative estrogen-progestin and estrogen-alone trials, intervention phase[a] (62, 63)

	Estrogen + progestin	Estrogen alone
Outcome	HR (95% CI)	HR (95% CI)
CVD		
Coronary heart disease[b]	1.18 (0.95-1.45)	0.94 (0.78-1.14)
Myocardial infarction	1.24 (0.98-1.56)	0.97 (0.79-1.21)
Coronary revascularization[c]	0.95 (0.78-1.16)	1.00 (0.83-1.19)
Stroke	1.37 (1.07-1.76)	1.35 (1.07-1.70)
Pulmonary embolism	1.98 (1.36-2.87)	1.35 (0.89-2.05)
Deep vein thrombosis	1.87 (1.37-2.54)	1.48 (1.06-2.07)
Cardiovascular mortality	1.08 (0.78-1.48)	1.01 (0.78-1.31)
All cardiovascular events[d]	1.13 (1.02-1.25)	1.11 (1.01-1.22)
Cancer		
Breast cancer	1.24 (1.01-1.53)	0.79 (0.61-1.02)
Colorectal cancer	0.62 (0.43-0.89)	1.15 (0.81-1.64)
Endometrial cancer	0.83 (0.49-1.40)	NA
Cancer mortality	1.10 (0.86-1.42)	0.96 (0.75-1.22)
All cancer types[e]	1.02 (0.91-1.15)	0.93 (0.81-1.07)
Other outcomes		
Hip fracture	0.67 (0.47-0.95)	0.67 (0.46-0.96)
All fracture	0.76 (0.69-0.83)	0.72 (0.64-0.80)
Diabetes	0.81 (0.70-0.94)	0.86 (0.76-0.98)
Gallbladder disease	1.57 (1.36-1.80)	1.55 (1.34-1.79)
Probable dementia[f]	2.01 (1.19-3.42)	1.47 (0.85-2.52)
Other (non-CVD, noncancer) mortality[g]	0.59 (0.39-0.90)	1.34 (0.93-1.94)
All-cause mortality	0.97 (0.81-1.16)	1.03 (0.88-1.21)
Global index[h]	1.12 (1.02-1.24)	1.03 (0.93-1.13)

Abbreviations: CVD, cardiovascular disease; HR, hazard ratio; NA, not applicable (because of hysterectomy).
[a]Median length of randomized treatment was 5.6 years for estrogen-progestin and 7.2 years for estrogen alone.
[b]Coronary heart disease is defined as nonfatal myocardial infarction or coronary death.
[c]Coronary revascularization is defined as coronary artery bypass grafting or percutaneous coronary intervention.
[d]"All cardiovascular events" is a composite outcome of myocardial infarction, stroke, coronary revascularization, angina, heart failure, carotid artery disease, peripheral vascular disease, venous thromboembolism (pulmonary embolism, deep vein thrombosis), and cardiovascular mortality.
[e]All cancer types except nonmelanoma skin cancer.
[f]Probable dementia was assessed in women aged 65 years and older.
[g]Other (non-CVD, noncancer) mortality is a composite outcome of dementia mortality, chronic obstructive pulmonary disease (COPD) mortality, accident and injury mortality, and other mortality of known cause not due to CVD, cancer, dementia, COPD, or accident or injury.
[h]Global index is a composite outcome of coronary heart disease, stroke, pulmonary embolism, breast cancer, colorectal cancer, endometrial cancer (in the estrogen-progestin trial), hip fracture, and all-cause mortality.

was also observed. In HERS II, HERS participants underwent an open-label, 2.7-year mean follow-up after stopping HT; rates of coronary events in the HT group were not significantly different from those in the placebo group (66).

The Estrogen Replacement and Atherosclerosis trial examined cardiovascular effects of CEEs alone or CEE + MPA compared to placebo in postmenopausal women (309 participants, average age 65.8 years) with known coronary artery disease. While this 3-year trial found improvements in lipid biomarkers with use of HT compared to placebo (decrease in levels of LDL-C and increase in HDL-C levels), there was no difference in atherosclerosis progression across treatment groups (67).

The Women's Estrogen-progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial (WELL-HART) examined the ability of daily oral E_2 alone or oral E_2 plus sequential MPA to slow atherosclerosis progression compared to placebo in 226 postmenopausal women with an average age of 63.5 years. There was no difference in atherosclerosis progression among the 3 groups (68).

Three additional secondary prevention randomized trials failed to identify any decrease in CHD with the use of menopausal HT (69-71).

Elucidating the Divergent Findings on Hormone Therapy and Cardiovascular Disease in Randomized Controlled Trials vs Observational Studies

Results of RCTs differed from observational data in terms of CHD effects of HT. While the bulk of observational

data suggested that HT offered cardioprotection and was associated with a reduced risk of CHD, to the surprise of many, these assumptions were not supported by the primary and secondary prevention trials discussed earlier. However, it is important to recognize that in observational studies women initiating HT were younger and closer to menopause onset, as they began HT in early menopause primarily for managing hot flashes and other vasomotor symptoms. Indeed, in the Postmenopausal Estrogen/Progestin Interventions (PEPI) randomized clinical trial, in which enrolled women were on average age 56 years, the effects of HT on CVD biomarkers tended to be favorable. The PEPI trials assessed the effects of ET, EPT (with cyclic vs continuous MPA or cyclic micronized progesterone) or placebo on several CVD risk factors (HDL, fibrinogen, insulin, and systolic blood pressure) (72). The 3-year trial included 875 healthy postmenopausal women aged 45 to 64 years. The study found that E-alone resulted in the greatest increases in HDL-C and decreases in LDL-C, although all HT regimens favorably affected these biomarkers when compared to placebo; triglyceride levels increased in all hormone intervention groups compared to placebo. Fibrinogen levels were not elevated in the HT groups but were mildly elevated in the placebo group. Insulin levels did not differ across treatment or placebo groups, and there was no difference in blood pressure levels. It is important to recognize, however, that because different progestogens were used, this alone could have affected CVD outcomes. Thromboembolic disease, and breast cancer, though not primary outcomes, were assessed as adverse events; there was no difference in these adverse events across groups, but statistical power was limited (72).

In the decades following the WHI hormone trials, we have learned much about the relevance of age, and time since onset of menopause and of aging-related comorbidities as determinants of cardiovascular effects of HT; population differences in these critical modulators may contribute to the discrepant cardiovascular effects of HT reported in RCTs and observational studies, as discussed further in the subsequent section.

Meta-Analyses of Randomized Controlled Trials of Hormone Therapy in Relation to Cardiovascular Disease, Venous Thromboembolism, Breast Cancer, Fracture, and All-Cause Mortality

Coronary heart disease/cardiovascular disease/venous thromboembolism

Following the publication of the WHI results, there was a sharp decline in prescription rates and use of HT. However, in a meta-analysis of 23 trials (including 39 049 women), the effects of HT on CHD varied by the woman's age and/or time since onset of menopause. In the meta-analysis, HT initiated less than 10 years from the onset of menopause was associated with a 32% reduction of CHD, whereas HT initiated 10 or more years since menopause onset did not reduce risk (73). Additionally, a separate meta-analysis found no association between HT and cardiac death or stroke (74). Venous thromboembolism (VTE) risk was increased in postmenopausal women using oral HT (ET or EPT); however, there was no significant excess risk in women using nonoral HT (75).

Breast cancer

In a meta-analysis of 58 studies conducted by the Collaborative Group on Hormonal Factors in Breast Cancer (CGHFBC), there was an increased risk of breast cancer in HT users, particularly EPT users, which equated to a 6% to 10% increase per 5 years of HT use (76). The risk was also increased for ever-users of EPT. In a separate meta-analysis, which included 2 RCTs, EPT was again found to confer a greater increased risk of breast cancer when compared to ET (77). In a meta-analysis including 12 RCTs, there was an increase in breast cancer mortality in EPT users; however, there was no increase in breast cancer risk with ET use alone (78). Importantly, in the WHI E-alone trial, breast cancer risk was decreased (79) with long-term follow-up. Though not assessed by the CGHFBC, nor the prior-mentioned meta-analysis, the E3N French Cohort Study also found different relative risks (RRs) of breast cancer based on HT type and years of use. In EPT users, the RR of breast cancer for 2 to 5 years of hormone use was 1.59 (95% CI, 1.39-1.95) (80). In ET users, the RR of breast cancer for 2 to 5 years of hormone use was 1.13 (95% CI, 0.70-1.8) (80). However, a major limitation of the CGHFBC (and other prior studies) was the lack of assessment of the effect of underlying breast cancer risk on attributable risk (81). As such, the CGHFBC data was recently reassessed, taking into consideration the effect of underlying risk of breast cancer on attributable risk (81). To do so, women were divided into low (1.5%), intermediate (3%), and high (6%) underlying risk of breast cancer over 5 years. Using this approach, the attributable risk in EPT users for 5 to 9 years was 12, 42, and 85 per 1000 in each respective group (81). The attributable risk in ET users was lower—4.8, 9.9, and 19 per 1000 in each respective group (81). These results highlight the importance of examining the innate risk of breast cancer for each woman, as for those with low underlying risk, the overall risk of breast cancer with use of hormone therapy is lower than that predicted from other studies (including the CGHFBC). Last, it is equally important to recognize that many of the analyzed studies were observational studies with the potential

for differential surveillance (ie, mammographic screening) for breast cancer in HT users and nonusers, and as such the potential for residual confounding by other factors.

Bone health

In the WHI E + P and E-alone trials, the interventions reduced the risk of hip fracture by approximately one-third (62). In a metanalysis of RCTs assessing fracture risk in women using oral CEEs, transdermal, or oral E_2 (with or without the addition of a progestin) there was a 20% to 37% reduced risk of hip, vertebral, and total fracture (82). While both CEE and E2 were effective at reducing total fracture risk, E_2 resulted in a slightly greater decrease in risk (82). There was some attenuation of protection following cessation of HT, as well as a more pronounced reduced risk of fracture in those using HT before age 60 years; importantly, there was no increased risk of rebound fractures (82, 83).

All-Cause mortality

Use of HT and effect on mortality has also been assessed in a meta-analysis and systematic review of 43 RCTs that demonstrated that HT does not affect risk of death from all causes (74). A Bayesian meta-analysis of 19 RCTs and 8 observational studies of HT in younger postmenopausal women (mean age < 60 years) demonstrated a 25% reduction in mortality in women taking HT compared to placebo (84). As will be discussed in subsequent sections of this review, age at HT initiation is an important factor to consider when balancing risks and benefits of HT use in postmenopausal women.

Evidence for or Against the "Timing Hypothesis"

In Animal Models

The timing hypothesis was first proposed by Thomas Clarkson in the 1990s (85). Using a cynomolgus monkey model, he found that initiating CEE immediately after bilateral ovariectomy resulted in a 70% reduction in coronary atherosclerosis, when compared to ovariectomized monkeys receiving placebo (86, 87). Conversely, monkeys that did not initiate treatment until 2 years following bilateral oophorectomy (the equivalent of > 6 years in humans) did not have a reduction in coronary atherosclerosis; estrogen did not cause plaque regression (86, 87). Nonhuman primates represent an ideal animal model for studying menopause because they have a more than 90% average genetic coding sequence identical to humans (88, 89). In addition, they experience surgical menopause after ovariectomy and respond to ET in a manner similar to that of women (88, 89). With respect to cognitive function, several monkey models have been used to study the potential neuroprotective effects of HT based on timing of initiation. When ovariectomized monkeys are given HT within 6 months of oophorectomy, cognition improves; however, HT given 2 or more years following oophorectomy does not improve cognition (90). Human studies (as discussed later) have demonstrated similar findings. The mechanism by which early initiation of estrogen has favorable cardiovascular and neurological effects is felt to relate to its ability to play an anti-inflammatory/protective role only prior to an inflammatory insult, and prior to a prolonged hypoestrogenic state. For example, arteries from younger women/women without significant plaque buildup are able to respond favorably to exogenous estrogen production—with increased vasodilatory capacity and decreased inflammatory activity. Similarly, exogenous estrogen administration prior to the onset of cognitive dysfunction (ie, closer to the onset of menopause) has an anti-inflammatory/neuroprotective effect. However, with age and following long periods of estrogen deprivation, cardiac and brain function is adversely affected by estrogen administration. In blood vessels, there is increased vasoconstriction and potential for plaque disruption in vessels following delayed exposure to E_2, and in the brain there is inability to mediate an anti-inflammatory response, with some data supporting a paradoxical effect of estrogen-mediated inflammation (91-93).

In clinical trials—by age group and time since menopause

Subsequent analyses of the WHI trials—stratifying HT use by age and time since menopause—as well as a review of newer studies have provided additional clarity on HT use related risks in postmenopausal women. The "timing hypothesis" postulates that the timing of HT initiation in relation to time since the final menstrual period (FMP) differentially affects clinical outcomes. Thus, the more proximate the timing of initiation of HT to the FMP (within 5 years of menopause onset), the more likely that HT will confer organ-specific protection (eg, cardioprotection or neuroprotection). Conversely, HT-related risks are amplified when HT is introduced in older menopausal women who are remote from menopause onset (more than 10 years since FMP) (9, 94). A secondary analysis of the WHI trial by age group (50-59, 60-69, 70-79 years at baseline) found that women in the 50 to 59 age group did not have an increased risk of CHD with HT (95-97) (Table 2, Figure 1). On the contrary, women in this age group had a protective effect with CEEs alone, and no significant effect with EPT, and a statistically significantly reduced risk for total mortality in the two HT trials pooled (95, 96). Furthermore, in a 10-year follow-up of these younger postmenopausal

women in the ET arm of the WHI, there was a significantly reduced risk of myocardial infarction and CHD, and total mortality was also in the direction of risk reduction (see Table 2, Figure 1) (97, 98). Conversely, in women who were more than 20 years from the time of menopause at the time of random assignment to ET or EPT, use of HT was associated with a significantly increased risk of CHD (see Table 2) (95). As previously mentioned, subsequent metanalyses have also demonstrated reduced risk of CHD in women initiating HT within 10 years of menopause onset.

The Kronos Early Prevention Study (KEEPS) was a randomized, double-blind, placebo-controlled trial that examined the effects of early initiation of oral or transdermal estrogen on subclinical atherosclerosis progression (99). KEEPS participants were 6 to 36 months from their FMP, aged 42 to 58 years, with no prior CVD events, a carotid artery calcium (CAC) less than 50 Agatston units, and no prior estrogen or lipid therapy exposure in the last 90 days. Participants were randomly assigned to receive 0.45 mg oral CEEs or transdermal E_2 50 µg per day vs placebo; those assigned to HT also received 200 mg oral progesterone for 12 days of each month during the 4-year intervention. The primary study end point was an annual change in ultrasound measured carotid artery intima-media thickness (CIMT), and secondary end points were changes in markers of CVD risk (including CAC scores). While there was a mean CIMT increase of 0.0007 mm per year, this was similar across all 3 intervention groups. There was also no significant difference in the CAC scores among the 3 groups (100). Interestingly, an ancillary study examined the effects of HT on cardiac adipose deposition and relationship of cardiac fat with CIMT in KEEPS. Oral CEE use was significantly associated with less CIMT progression per increase in pericardial adipose deposition, whereas transdermal E_2 was not (100). Lastly, oral CEE use was associated with decreased LDL-C and increased HDL-C; and there was a neutral effect of HT on blood pressure indices. Overall, KEEPS results suggested that HT use was not associated with atherosclerosis progression in younger menopausal women. Although the timing hypothesis was not supported by KEEPS data, the study design may not have been optimally suited to address the timing hypothesis given minimal CIMT progression in any group due to the young age and the relatively healthy state of the participants and the short duration of the trial.

Almost contemporaneous with KEEPS was the Early vs Late Intervention Trial with Estradiol (ELITE), which directly tested the "timing hypothesis" and compared the development/progression of atherosclerosis following earlier vs late initiation of HT in relation to menopause onset (101). Postmenopausal women were stratified by years since menopause—less than 6 years (early, average age 55 years) or greater than 10 years (late, average age 65 years)—and were randomly assigned to oral E_2 (1 mg daily), plus vaginal progesterone gel (45 mg for 10 days per month in women with a uterus) or placebo. The primary outcome was rate of change in CIMT, with a secondary outcome of change in CAC score. In the early postmenopausal group, 5 years of oral E_2 with/without vaginal progesterone had a slower increase in CIMT compared to placebo (P value = .008). In the late menopause group, there was no difference in CIMT progression compared to placebo (P for interaction by time since menopause onset = .007). There were no differences in CAC measurements for the early or late menopause group, or the placebo group. These results differed from KEEPS; however, differences in dose and estrogen formulation may explain the different outcomes (and of note women in KEEPS had been menopausal for only 1.8 years on average and had minimal CIMT progression). Overall, the evidence suggests that, while HT does not reduce the risk of cardiac disease/events in the secondary prevention setting or in late menopause, earlier initiation (with respect to time since menopause and age younger than 60) may provide cardioprotective effects (as seen in meta-analyses of RCTs of HT and in the ELITE trial, but not in KEEPS). Both KEEPS and ELITE established safety of short-term use of HT in otherwise healthy women.

There were no significant differences in the results for invasive breast cancer when WHI hormone trial data were stratified by age or time since menopause (see Table 2, Fig. 1) (62). There were also no modifying effects of these variables on the risk for stroke or PE, although there were fewer strokes and PEs in younger postmenopausal women (see Table 2, Fig. 1) (62, 63). There were more adverse outcomes of CEEs alone for colorectal cancer in women aged 70 to 79 years (23 cases with CEE use compared to 13 with placebo), but there were no modifying effects of age on this outcome in the EP trial (63). Hip fracture hazard ratios (HRs) were lower in women who were greater than 10 years since menopause onset. HRs for all-cause mortality were more favorable in younger compared to older menopausal women; a trend by age was significant for the E trial and a trend was noted for time since menopause for both trials (62, 63). Venous thrombosis and PE risks with HT did not differ by age or time since menopause. There was a trend toward decreased total cancer mortality with CEEs alone in women younger than 60 years and increased total cancer mortality in women older than 70; there was no modifying effect of age or time since menopause in the EP arm (see Table 2, Fig. 1) (63). Effects of HT on diabetes or gallbladder disease risk did not differ appreciably by age or time since menopause (62).

The Women's Health Initiative Memory Study assessed the effects of HT on cognition and dementia risk. An increased risk of dementia was noted in HT users both in

Table 2. Health outcomes in the Women's Health Initiative estrogen-progestin and estrogen-alone trials, according to age at study entry, intervention phase[a] (62)

	Estrogen + progestin		Estrogen alone	
Outcome	HR (95% CI)	*P*, trend by age	HR (95% CI)	*P*, trend by age
CVD				
Coronary heart disease[b]				
50-59 y	1.34 (0.82-2.19)	.81	0.60 (0.35-1.04)	.08
60-69 y	1.01 (0.73-1.39)		0.95 (0.72-1.24)	
70-79 y	1.31 (0.93-1.84)		1.09 (0.80-1.49)	
Myocardial infarction				
50-59 y	1.32 (0.77-2.25)	.55	0.55 (0.31-1.00)	.02
60-69 y	1.05 (0.74-1.47)		0.95 (0.69-1.30)	
70-79 y	1.46 (1.00-2.15)		1.24 (0.88-1.75)	
Coronary revascularization[c]				
50-59 y	1.03 (0.63-1.68)	.67	0.56 (0.35-0.88)	.06
60-69 y	0.85 (0.64-1.13)		1.13 (0.88-1.46)	
70-79 y	1.08 (0.77-1.51)		1.07 (0.79-1.43)	
Stroke				
50-59 y	1.51 (0.81-–2.82)	.50	0.99 (0.53-1.85)	.77
60-69 y	1.45 (1.00-2.11)		1.55 (1.10-2.16)	
70-79 y	1.22 (0.84-1.79)		1.29 (0.90-1.86)	
Pulmonary embolism				
50-59 y	2.05 (0.89-4.71)	.61	1.53 (0.63-3.75)	.28
60-69 y	1.69 (1.01-2.85)		1.72 (0.94-3.14)	
70-79 y	2.54 (1.27-5.09)		0.85 (0.39-1.84)	
Cancer				
Breast cancer				
50-59 y	1.21 (0.81-1.80)	.68	0.82 (0.50-1.34)	.89
60-69 y	1.20 (0.89-1.62)		0.73 (0.51-1.07)	
70-79 y	1.37 (0.90-2.07)		0.86 (0.52-1.43)	
Colorectal cancer				
50-59 y	0.79 (0.29-2.18)	.66	0.71 (0.30-1.67)	.02
60-69 y	0.61 (0.37-0.99)		0.88 (0.53-1.47)	
70-79 y	0.58 (0.31-1.08)		2.24 (1.16-4.30)	
Cancer mortality				
50-59 y	0.71 (0.38-1.33)	.37	0.78 (0.43-1.40)	.06
60-69 y	1.26 (0.88-1.80)		0.77 (0.53-1.12)	
70-79 y	1.13 (0.73-1.75)		1.34 (0.90-1.97)	
All cancer[d]				
50-59 y	0.97 (0.76-1.23)	.77	0.89 (0.66-1.19)	.39
60-69 y	1.11 (0.93-1.31)		0.89 (0.73-1.08)	
70-79 y	0.94 (0.75-1.17)		1.04 (0.81-1.33)	
Other outcomes				
All fracture				
50-59 y	0.82 (0.68-1.00)	.83	0.90 (0.72-1.11)	.33
60-69 y	0.70 (0.61-0.81)		0.63 (0.53-0.75)	
70-79 y	0.79 (0.66-0.95)		0.71 (0.58-0.87)	
Diabetes				
50-59 y	0.85 (0.66-1.09)	.10	0.83 (0.67-1.04)	.99
60-69 y	0.61 (0.49-0.77)		0.91 (0.76-1.09)	
70-79 y	1.35 (0.98-1.88)		0.82 (0.62-1.07)	
Other (non-CVD, noncancer) mortality[e]				
50-59 y	0.53 (0.22-1.27)	.65	0.51 (0.20-1.26)	.002
60-69 y	0.55 (0.27-1.13)		1.15 (0.65-2.03)	
70-79 y	0.67 (0.35-1.26)		2.59 (1.36-4.92)	

Table 2. Continued

Outcome	Estrogen + progestin		Estrogen alone	
	HR (95% CI)	*P*, trend by age	HR (95% CI)	*P*, trend by age
All-cause mortality				
50-59 y	0.67 (0.43-1.04)	.20	0.70 (0.46-1.09)	.04
60-69 y	1.07 (0.81-1.41)		1.01 (0.79-1.29)	
70-79 y	1.03 (0.78-1.36)		1.21 (0.95-1.56)	
Global index[f]				
50-59 y	1.12 (0.89-1.40)	> .99	0.84 (0.66-1.07)	.02
60-69 y	1.13 (0.97-1.31)		0.99 (0.85-1.15)	
70-79 y	1.12 (0.95-1.32)		1.17 (0.99-1.39)	

Abbreviations: CVD, cardiovascular disease; HR, hazard ratio.
[a]Median length of randomized treatment was 5.6 years for estrogen-progestin and 7.2 years for estrogen alone.
[b]Coronary heart disease is defined as nonfatal myocardial infarction or coronary death.
[c]Coronary revascularization is defined as coronary artery bypass grafting or percutaneous coronary intervention.
[d]All cancer types except for nonmelanoma skin cancer.
[e]Other (non-CVD, noncancer) mortality is a composite outcome of dementia mortality, chronic obstructive pulmonary disease (COPD) mortality, accident and injury mortality, and other mortality not due to CVD, cancer, dementia, COPD, or accident or injury. Age-specific effect estimates for these individual outcomes could not be computed because the numbers of events within age strata were small.
[f]Global index is a composite outcome of coronary heart disease, stroke, pulmonary embolism, breast cancer, colorectal cancer, endometrial cancer (in the estrogen-progestin trial), hip fracture, and mortality.

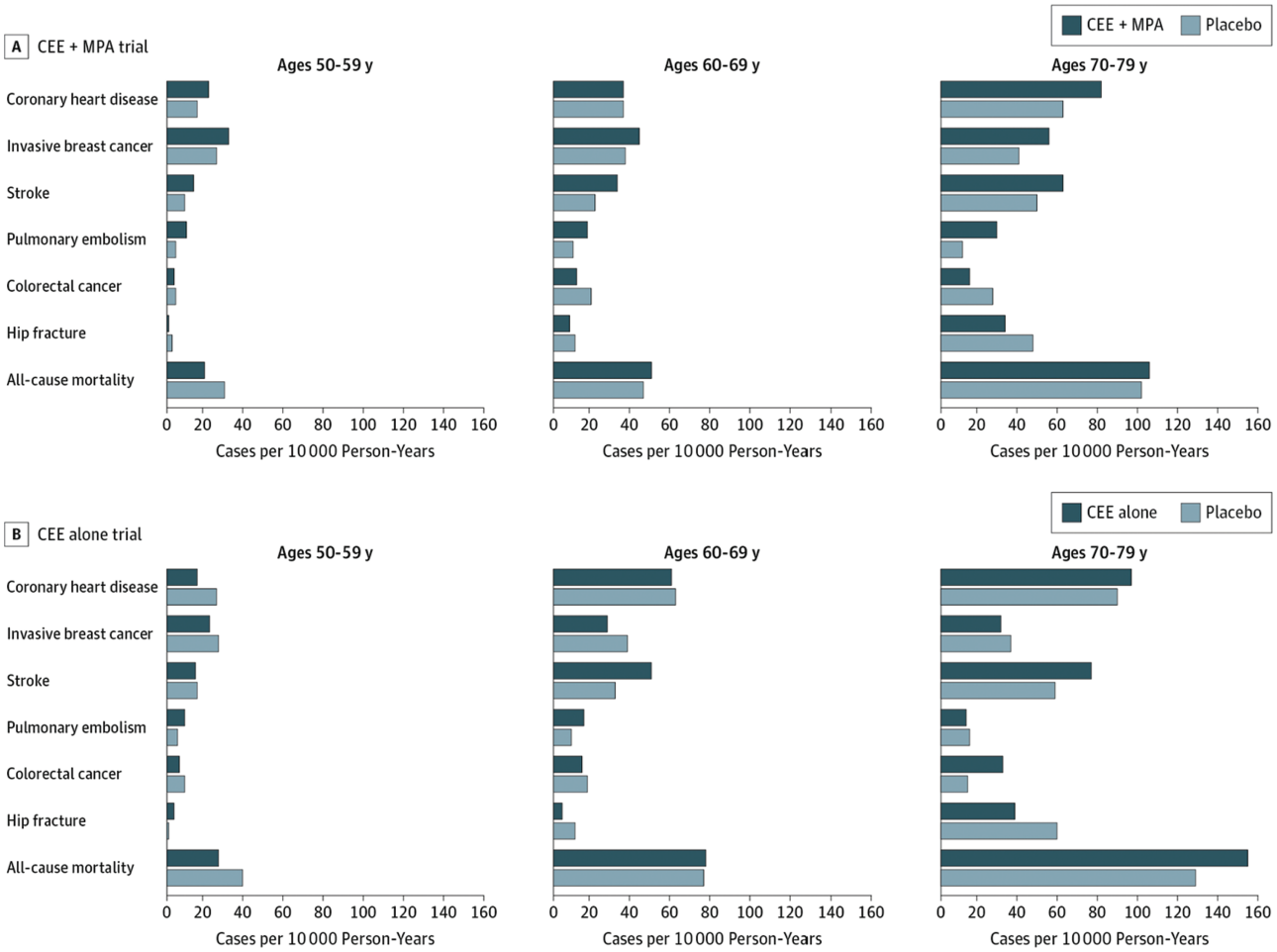


Figure 1. Absolute risks and risk differences for major health outcomes in the Women's Health Initiative estrogen-progestin and estrogen-alone trials, according to age at study entry, intervention phase (62). ‡Difference in estimated absolute excess risk (active minus placebo). Numbers may not add up precisely because of rounding error. CEE, conjugated equine estrogens; MPA, medroxyprogesterone acetate. Reproduced from Manson JE, et al. *JAMA*. 2013;310(13):1353-1368. Copyright© 2013 American Medical Association. All rights reserved.

the EP trial and the pooled EP plus E trials; use of HT had nonsignificant effects on risk of mild cognitive impairment (96, 102, 103). These trials were limited to women aged 65 years and older at random assignment. Women aged 50 to 55 at time of random assignment showed no increased risk of cognitive decline with HT compared to placebo, when assessed many years postintervention (104). In an ancillary study to KEEPS (Cognitive and Affective Study of KEEPS), however, no cognitive benefit was noted when HT was initiated proximate to FMP; reassuringly there were no deleterious effects of HT on cognitive function appreciated either. In addition to VMS, mood symptoms improved with oral CEEs (105). Similar to KEEPS, no cognitive benefit was noted in women randomly assigned to HT vs placebo in the ELITE trial, but there was also no harm to cognition (106).

Do Hormone Therapy Effects Differ by Formulation, Dose, or Route of Administration?

By Hormone Therapy Formulation

Estrogen formulations

Vasomotor symptoms. The available estrogen formulations for HT include CEEs, 17β- E_2, and esterified estrogens (EEs)—all forms are similarly effective in treating VMS (Table 3).

Cardiovascular system. Cardiovascular effects have not been demonstrably different with oral CEEs vs oral E_2 (107). In the WHI Observational Study, no differences were observed in CVD outcomes for women taking CEEs compared to oral E_2 (108). In a separate 6-year study, CEEs had a slightly higher risk of VTE compared to oral E_2 but

Table 3. Systemic hormone therapy formulations

Route and formulation	Available doses	Considerations
Oral formulations		
CEEs		
	0.3, 0.45 mg	Low dose
	0.625 mg	Standard dose
	0.9 mg, 1.25 mg	High dose
CEE + BZA	0.45 mg CEE/20 mg BZA	No need for addition of progestin in women with uteri
Esterified estrogen		
	0.3 mg	Low dose
	0.625 mg	Standard dose
	1.25 mg	High dose
Estradiol		
	0.5 mg	Low dose
	1 mg	Standard dose
	2 mg	High dose
Transdermal formulations		
Patch		
Estrogen-progestin	0.05 mg estradiol/0.14 or 0.25 mg norethindrone	Apply twice weekly
Estrogen-progestin	0.045 mg estradiol/0.015 mg levonorgestrel	Apply twice weekly
Estradiol	0.025 mg	Low dose
	0.05, 0.075 mg	Standard dose
	0.1 mg	High dose
		Apply twice weekly
Estradiol	0.025, 0.0375 mg	Low dose
	0.05, 0.06, 0.075 mg	Standard dose
	0.1 mg	High dose
		Apply weekly
Estradiol	0.014 mg	Lowest approved dose
		Apply weekly
Gel		
Estradiol	0.52, 0.75 mg	Per pump, daily
Estradiol	0.25, 0.5, 1 mg	Per pouch, daily
Spray		
Estradiol	1.53 mg	Per spray, daily

Abbreviations: BZA, bazedoxifene; CEE, conjugated equine estrogen.

there were no differences in myocardial infarction or ischemic stroke (109). Oral CEEs and E_2 promote hepatic effects, perhaps explaining the increased thrombotic risk with this orally administered formulation.

Fracture risk. In a systematic review and meta-analysis of RCTs of estrogen formulations and fracture risk, all were effective in reducing fracture risk (70). Also, no differences between formulation were observed in the WHI Observational Study (108).

Cognition. Neutral results for cognition were found for oral CEEs vs placebo and for oral E_2 vs placebo among recently menopausal women in the KEEPS and ELITE trials, respectively (110).

Breast health. With respect to breast cancer risk, it is important to recognize that CEE formulations contain more than 10 estrogens that can not only bind with differential affinity for the 2 estrogen receptor types (ERα and ERβ), but can also have differential actions on the target tissue, similar to selective estrogen receptor modulators (SERMs) (111-113). Certain estrogens in CEEs can activate ERβ, which serves to inhibit ERα-mediated cell proliferation (114, 115). Furthermore, in vitro studies have found that some of the estrogenic compounds in CEE act as partial estrogen agonists/antagonists, thus the differences in downstream signaling may allow CEEs to have effects different from E_2's purely stimulatory effects (116, 117). This may in part explain the results of the WHI E arm, which found a lower risk of breast cancer, whereas similar findings have not been demonstrated in studies using E_2 regimens (5, 72, 113, 118). A small case-control study assessing mammographic changes in women using oral or transdermal E_2 found no increase in mammographic density (119); no long-term RCTs of E2 and breast cancer have been conducted.

Progestogen formulations

Cardiovascular system. Progestogens, owing to their varied structures and steroid receptor binding affinity, can have differential effects on target tissues. The most common progestogen formulations include micronized progesterone (MP), MPA, and norethindrone acetate (NETA). Additional progestogens are available worldwide and are listed in Table 4. From a CVD risk perspective, an ideal progestogen is one that does not counteract the positive effects of estrogens on lipids. In a review assessing various progestogens effects on cardiovascular markers, progestogens without androgenic effects (progesterone and 19-norprogesterone derivatives) did not counteract estrogen's beneficial effects on the lipid profile; conversely, progestogens with androgenic activity (19-nortestoterone derivates and MPA) can blunt some of the beneficial effects on lipids (120, 121). In the PEPI trial, women randomly assigned to CEEs or CEEs/MP had an increase in HDL that was significantly higher than in women randomly assigned to CEEs/MPA (72). However, there was no difference in the magnitude of lowering of LDL among the 3 HT groups. HT regimens using NETA have not shown any adverse effect on lipid parameters (122). Furthermore, in studies assessing arterial vasodilatory response to HT, vasodilation induced by estrogens was not attenuated by the addition of MPA or NETA (123, 124). Drospirenone, a third-generation progestin that possesses both antiandrogenic and antimineralocorticoid properties, may confer benefits against CVD risk. In an RCT of hypertensive postmenopausal women, significant improvements in systolic blood pressure were noted with the addition of drospirenone to estrogen-based HT (125). The addition of progestogens to estrogen HT did not increase VTE risk for MP or NETA (ie, nortestosterone derivatives); VTE risk is, however, increased with the inclusion of pregnane derivatives (ie, MPA) and norpregnane derivative progestogens (nomegestrol acetate and promegestone) in the HT regimen (126, 127). Norpregnane derivatives are not available in the United States.

Breast safety. Breast cancer risk may be influenced by the choice of progestogen in the HT regimen. The WHI E + P trial data demonstrated an increased risk of breast cancer with the continuous combined regimen of CEEs plus MPA. In a review of 8 randomized (estrogen-alone or estrogen-progestogen) trials, the risk of breast cancer was increased with the use of estrogen-progestin (MPA or gestodene) HT, compared to a decreased risk with E-alone (128). The trials consisted of the WHI E-alone and E + P trials, as well as secondary prevention trials, in which breast cancer was a secondary outcome. Several observational studies have also demonstrated an increased risk of breast cancer with synthetic progestins, but not with MP (129-131). In the E3N French Cohort Study, breast cancer risk was not increased with MP or dydrogesterone, but was consistently increased with E combined with medrogestone, chlormadinone acetate, promegestone, nomegestrol, NETA, and MPA (118). Similar findings were seen with MPA and NETA use in a separate observational study (132). While these observational studies provide helpful insights, it is difficult to draw definitive conclusions from these types of studies, especially since subsequent analysis of the E3N French Cohort study noted an increased risk of breast cancer, even with MP, when used for more than 6 years' duration. Notably, the high rate of changes in HT regimens over time made it difficult to clearly tease out individualized risk differences of MP from dydrogesterone formulations (133, 134). Following the differential results of the E and EP trials of the WHI, additional research has aimed to obtain a better understanding of how the different progestogens affect breast cancer risk. Laboratory research has shown that E plus progestogen treatment results in an increase in

Table 4. Progestogen formulations

Progestogen class	Formulation	Comparable dose	Dosing regimens
Oral			
Progesterone	MP	100 mg (when used as single tab of 1 mg E_2/100 mg MP, no peanut oil in tablet)	Daily, sequential
		200 mg	
		300 mg (VMS)	
21-Carbon derivatives	Medroxyprogesterone	2.5 mg	Daily
	Acetate	5 mg	Sequential
		10 mg for VMS	
	Megesterol acetate	5 mg	Daily
		20 mg for VMS	
	Cyproterone acetate	1 mg	Daily, sequential
	Dydrogesterone	10 mg	Daily, sequential
	Chormadinone acetate	5-10 mg	Daily, sequential
	Medrogestone	10 mg	Daily, sequential
19-Norpregnanes	Trimegestone	0.0625-0.5 mg	Daily, sequential
	Promegestone	0.5 mg	Daily, sequential
	Nomegestrol	5 mg	Daily, sequential
	Nomegestrol acetate	3.75–5 mg	Daily, sequential
19-Nortestosterone	Norethindrone	0.35 mg	Daily
		0.7 mg	Sequential
Ethinylated	Norethindrone acetate	1 mg	Daily, sequential
Nonethinylated	Levonorgestrel	0.075 mg	Daily, sequential
		52 mg	5-7 y
		19.5 mg	5 y
		13.5 mg	3 y
	Desogestrel	0.15 mg	Daily, sequential
	Norgestrimate	0.09 mg	Daily, sequential
	Gestodene	0.2 mg	Daily, sequential
	Dienogest	2 mg	Daily, sequential
Spironolactone derivative	Drosperinone	2 mg	Daily, sequential
Vaginal			
Progesterone off-label use	4% gel	45 mg	Twice weekly, every other day, sequential
	Suppository	100 mg	Twice weekly, every other day, sequential
Intrauterine			
Levonorgestrel off-label use	Intrauterine device	52 mg	5-7 y
		19.5 mg	5 y
		13.5 mg	3 y

Abbreviations: E_2, estradiol; MP, micronized progesterone; VMS, vasomotor symptoms.

breast cell proliferation to a magnitude that is greater than with E alone. In vitro studies using normal human breast cells found that treatment with E_2 plus MPA did not affect cellular proliferation, but did reduce cell apoptosis; E_2 plus natural progesterone blocked E_2-mediated proliferative effects and increased the number of apoptotic cells (135). In a separate study, breast explant tissue from postmenopausal women were exposed to MPA at concentrations similar to that of HT, and breast cell proliferation was uninhibited (136). Similar findings were recapitulated in a primate postovariectomy model—E_2 plus MPA resulted in breast cell proliferation, whereas treatment with E_2 plus natural progesterone did not (137). It is important to emphasize, however, that despite the breast cancer risk noted in the EP arm of WHI, the time frame of the study was too brief to support de novo breast cancer development (94). As the cancer risk ultimately dissipated with time since stopping HT, it is more likely that EPT acted on indolent, subclinical

breast cancer by accelerating growth of preexisting cancerous cells (96). This is further supported by the fact that there were no more in situ lesions in the EP group compared to placebo in the WHI trials (102). With respect to the levonorgestrel (LNG) intrauterine device (IUD), there has been no increased risk of recurrence in women with a history of breast cancer using the progestin-containing IUD, although additional research is needed (138-140)

Cognition risk. Studies on the effects of progestogens on cognition are limited. One small RCT found that CEEs alone did not affect cognitive test scores, CEEs/MPA decreased delayed verbal memory scores, and CEEs/MP significantly improved working memory (141). In KEEPS and ELITE, micronized progesterone added to estrogen was associated with neutral effects on cognition (105, 142).While progesterone is a neuroactive steroid, its potential for clinically relevant neuroprotective effects requires further research (143).

Fracture. In the WHI HT trials, CEEs plus MPA and CEEs alone similarly reduced hip fracture risk by one-third (62, 63, 98). MPA and NETA alone both have been shown to prevent bone resorption in postmenopausal women. Other progestogen formulations have been studied for effects on bone mineral density (BMD) but have not been tested in large RCTs for fracture reduction.

Endometrial safety. Because unopposed estrogens in postmenopausal women increase the risk of endometrial hyperplasia/cancer, a progestogen is indicated in women with a uterus. Progestogens reduce endometrial hyperplasia and endometrial cancer, as demonstrated in the PEPI trial (using MPA, NETA, and MP) and WHI (using continuous MPA) (5, 72). In the WHI E + P trial, continuous combined CEE plus MPA was associated with a significantly reduced risk of endometrial cancer in long-term follow-up (62, 63, 144). There has previously been concern that MP may not be as effective at protecting the endometrium—in the European Prospective Investigation Into Cancer and Nutrition study, there were more cases of endometrial cancer in those using MP and nortestosterone derivates; however, doses of HT were not specified (145). The PEPI trial and systematic review using MP doses of 200 mg per day demonstrated endometrial protection, emphasizing the importance of dosing in providing adequate endometrial protection (146).

The LNG IUDs are an alternative method for endometrial protection in women taking estrogen-based HT who are sensitive to the bothersome systemic side effects of progestogens, although this is considered off-label use (147-151). See Table 4.

By dose of estrogen or progestogen

Hormone dose is relevant to the magnitude of benefit as well as HT-related risk—the higher the dose, the greater the benefit against common menopausal symptoms, albeit at the expense of greater risk, particularly for VTE. The dose of E in an HT regimen should be the lowest effective dose needed for the menopausal symptoms being treated; the progestogen dose should be one that provides adequate endometrial protection in postmenopausal women with a uterus. The initial standard oral doses of various E formulations are 0.625 mg of CEEs, 1 to 2 mg of E_2, and 0.625 mg EE; the standard transdermal E_2 dose is 50 µg. It is important to recognize that the rationale for dosing regimens is based on biological end points/clinical symptom improvement. For example, to achieve a 75% to 80% reduction in hot flashes, standard doses of estrogens are needed (152). In several trials, lower doses of estrogens reduce hot flashes by 65% (twice as effective than placebo) although the time needed to achieve this rate was 8 to 12 weeks, compared to 4 weeks for standard doses (153). However, the lower doses of estrogen are associated with fewer unwanted side effects (50% lower rates of irregular bleeding and less breast tenderness) (153). In addition, when lower doses of estrogen are prescribed, less progestogen can be used. In appropriately selected individuals, MPA in daily doses as low as 1.5 mg, or in intermittent doses as infrequent as an only twice-yearly regimen of 10 mg for 14 days, has been shown to be both safe and associated with less breakthrough bleeding (154, 155). The rationale is that endometrial proliferation by estrogen is dose related—low-dose estrogens produce about 50% less endometrial growth as the standard doses (156). With respect to other clinical effects and varying doses of estrogens, there have been several studies assessing the effect of different dosing regimens of unopposed estrogens on the endometrium, cardiovascular markers, bone, and on serum levels of E_2 (157). In a 2-year prospective study using low (0.3 mg), standard (0.625 mg), and high (1.25 mg) doses of esterified estrogens and calcium 1000 mg/day compared to placebo in women also taking calcium, the aforementioned parameters were assessed. Endometrial hyperplasia/thickened endometrium was a cause of termination of estrogen therapy only in women using standard and high-dose EE (157). Lipid levels were significantly favorable (decreased LDL and increased HDL) across all 3 doses of EE (157). BMD was also increased across all 3 doses at the lumbar spine, total hip, and whole body. Perhaps not surprisingly, E_2 levels decreased in the placebo group. In the low-, medium-, and high-dose treatment groups, E_2 levels were 24 to 28 pg/mL, 40 to 43 pg/mL, and 58 to 64 pg/mL, respectively (157).

In a randomized, double blind, placebo-controlled trial using 600 mg calcium/day with CEEs at 0.3 mg, 0.45 mg, or 0.625 mg with or without MPA at 1.5 mg (with CEEs 0.3 mg and 0.45 mg) or 2.5 mg (with CEEs 0.45 mg and 0.625 mg), similar findings with respect to

the endometrium, lipid profile, and improvements in BMD were seen across all regimens compared to placebo (154, 158-160). Importantly, VMS were relieved at all doses (though greater with increasing doses of CEEs) and breakthrough bleeding was less frequent with the lower-dose regimens (158, 160).

In studies assessing the effects of low-dose transdermal E_2 administration, hot flashes were relieved at all doses (161); however, the ultra-low dose (0.014 mg) improved hot flashes less when compared to the low dose (41% decrease in VMS) (162, 163). In addition, favorable lipid effects (decreased total cholesterol and LDL) remain notable with low-dose transdermal E_2 administration (162).

When assessing risks/concerns related to higher doses of estrogen, much of the rationale for avoiding higher doses of estrogen comes from literature on cardiovascular outcomes with various estrogen doses. Low- and standard-dose CEEs had a similar reduced risk of coronary events, while the risk (including risk of stroke) was increased with higher doses (47, 164). VTE risk is also dose dependent. The use of CEEs or EE at 0.3, 0.625, and 1.25 mg are associated with an RR of VTE of 2.1, 3.1, and 6.9 ,respectively (165). Transdermal estrogens, because they avoid first-pass metabolism, allow for lower doses of estrogen to be used for management of menopausal symptoms. Overall, while the lowest effective dose is recommended, in those with inadequate relief of symptoms with lower doses, consideration should be given to increasing to standard dose regimens to alleviate clinical symptoms.

As mentioned earlier, lower doses of HT are available and are listed in Table 3. In a review of randomized trials, although lower doses of CEE, E_2, and EE were effective at treating VMS, low-dose CEEs plus MPA tended to be more effective than low-dose CEEs alone (166). It also worth reiterating that while HT is not indicated for primary prevention of CVD, it is reassuring to note that low-dose E therapy is effective at increasing HDL and decreasing LDL (166). Continuous combined regimens of low-dose E plus progestogen allow for amenorrhea/low breakthrough bleeding risk, and maintain the reduced risk of endometrial hyperplasia/cancer (167). Breast cancer risk was not significantly different by estrogen dose, although RCT data are lacking (168).

The doses of various progestogens that have been shown to offer adequate endometrial protection in postmenopausal E users with a uterus are listed in Table 5. Progestogens can be administered continuously or sequentially (12-14 days per month); transdermal combined E + P patches are considered daily continuous regimens. Of note, the recommended dose of progestogen is higher in sequential compared to continuous E + P regimens; for example, if norethindrone is administered sequentially, the dose is 0.7 mg, compared to daily dose of 0.35 mg when administered as a continuous regimen. Oral MPA at 10 mg, MP at 300 mg, or megestrol acetate at 20 mg daily are also effective at treating VMS, although long-term safety data are not available (169-171).

Table 5. Hormone therapy formulations for symptoms of genitourinary syndrome of menopause

Vaginal		
Estradiol tablet	10 mcg	Daily for 2 wk, followed by twice weekly
Estradiol suppository	4 mcg 10 mcg	Per suppository, daily followed by twice weekly
Prasterone suppository	6.5 mg	Daily
Estradiol ring	7.5 mcg 0.05 mg 0.1 mg	Per 3 mo Standard dose High dose Per 3 mo Progestogen required because of systemic levels
Oral		
Ospemiphene tablet	60 mg	Daily

By route of administration

Oral vs transdermal

Cardiometabolic biomarkers. Oral and transdermal estrogens reduce total cholesterol and LDL-C. The KEEPS RCT compared oral CEEs with transdermal E_2 and found no adverse effects of transdermal E_2 or CEEs on cardiovascular parameters (100), although women with preexisting CVD were excluded from the trial. Oral CEEs were associated with lowering of LDL-C and insulin resistance, and increase in HDL-C, triglycerides, and C-reactive protein levels compared to placebo; transdermal E_2 reduced total cholesterol, lowered insulin resistance, and triglyceride levels compared to placebo (162, 172-176). Despite these differences, in an ancillary study of KEEPS, endothelial function did not differ between regimens, and overall in younger postmenopausal women the elevated C-reactive protein levels do not appear to be clinically relevant (94, 100).

Venous thromboembolism. Risk of venous thrombosis is different between oral vs transdermal estrogen. Because oral estrogens undergo first-pass hepatic metabolism, there is activation of the coagulation system, and an increased risk of VTE (177, 178). Transdermal estrogens avoid first-pass hepatic metabolism, and available studies have not found an increased risk of venous thrombosis. While an observational study noted no increased risk of cerebral vascular accidents with low-dose transdermal E_2 (53), no

large-scale RCTS have assessed transdermal E_2 use and VTE risk (75).

Breast cancer. While no RCT has compared effects of oral vs transdermal estrogens effect on breast cancer risk, observational studies (using predominantly E_2) have found no significant difference in breast cancer risk by E route of administration (118, 179).

Fracture. Oral and transdermal formulations both are effective for fracture prevention (180), without appreciable differences by regimen.

Cognition and mood. No clear difference in HT's effects on cognition has been demonstrated by route of administration (105, 181, 182). While studies on the effect of HT on mood are limited, there do appear to be improvements in mood with HT. However, HT should not be considered a primary treatment for mood disorders (183-186). Interestingly, in a subset of women in KEEPS at the Mayo Clinic, those in the transdermal E_2-arm with the apoliprotein *e*4 allele (associated with increased risk of Alzheimer disease) had reduced β-amyloid deposition (105, 187); however, there was no difference between oral CEEs and transdermal E_2on cognition in KEEPs.

Sexual function. The effect of route of estrogen administration on sexual function was also assessed in a (separate) ancillary study of KEEPS. Although both routes were associated with improvement in vaginal dryness and dyspareunia, only transdermal E_2 was associated with significant improved sexual function (ie, libido and sexual satisfaction) (188). The lack of effect of transdermal E_2 on sex hormone–binding globulin levels (as compared with increased levels with oral estrogens) results in increased free testosterone, likely explaining the improvement in sexual function (94). Oral and transdermal formulations of estrogens both are effective for treatment of VMS.

Progestogen route of administration. Progestogens can be administered in combination with estrogens in a transdermal patch and are able to provide endometrial protection. Transdermal cream application of progestogens, however, is not effective given the lack of adequate systemic levels achieved; its use is not FDA approved, nor is its use advised (189-196). Lastly, as mentioned earlier, oral progestogens—unlike vaginal progesterone—are effective for VMS.

For women on systemic estrogen therapy, vaginal progesterone gel (used off-label) can be administered every other day, twice weekly, or sequentially, although there are no long-term studies on endometrial protection in the latter regimen (197, 198). Administration of a vaginal progesterone insert (used off-label) every other day is effective, without an increased risk of endometrial hyperplasia (199).

There are also 3 available progestin-based IUDs, each with different doses of LNG—52 mg, 19.5 mg, and 13.5 mg (200). The LNG devices are effective at preventing endometrial hyperplasia/cancer, and the localized intrauterine effect of the device may avoid the bothersome side effects of oral and transdermal progestogens (201, 202). In premenopausal women, the amenorrhea rates at 3 years of use vary by dose of LNG—70% with 52 mg, 20% with 19.5 mg, and 12% with 13.5 mg (203, 204). In menopausal women also using ET, the incidence of bleeding/spotting was 1.8% to 4%, and endometrial biopsies at 6, 9, or 12 months noted a suppressed endometrium (148, 149, 205-207).

Vaginal estrogen

Low-dose vaginal estrogen is the most effective treatment available for GSM (153, 208). GSM is the term used to describe signs/symptoms resulting from estrogen deficiency of the genitourinary tract (209). Vaginal estrogen can be administered as a ring, tablet, suppository, or cream, all with equal effectiveness (see Table 5) (94). Creams are more readily absorbed in atrophic vaginal mucosa; however, as the mucosa matures, absorption decreases (210-214). For all formulations, systemic absorption is low; however, as most studies were no longer than 2 years, it is difficult to draw definitive conclusions regarding long-term endometrial safety (208, 215-221). In general the addition of a progestogen is not indicated with low-dose vaginal estrogen therapy; however, vaginal bleeding or spotting on low-dose vaginal estrogen therapy requires an evaluation (9). There is also a vaginal E_2 ring that is a standard dose HT (Femring; Estradiol acetate vaginal ring). The ring relieves genitourinary symptoms as well as VMS; it likely also improves bone health. Given the systemic levels with this formulation, a progestogen is indicated in postmenopausal women with a uterus (222, 223).

Selective estrogen receptor modulators

As their name implies, SERMs are able to exert agonist or antagonist actions on the ER in various estrogen-target tissues. Raloxifene is a SERM that is of proven efficacy in the prevention of osteoporosis-related spine fractures; it is neutral on the endometrium and holds chemoprophylactic efficacy against breast cancer risk (224-227). Raloxifene also has favorable effects on lipids, and does not modify CHD events/risks (228, 229). Raloxifene does have a VTE risk similar to that of oral estrogens, and unlike E, can lead to an increased incidence of hot flushes (94). There have not

been any reported adverse effects of raloxifene on cognitive function. Given its ER agonist/antagonist functions, it is perhaps not surprising that postmenopausal women using raloxifene had an almost 80% reduction in ER-positive breast cancers (230, 231). At this time raloxifene is approved for use in preventing osteoporosis-related spinal fractures and breast cancer prevention in women with osteoporosis and those at high risk of breast cancer; however, it does not reduce hip or wrist fractures. For women deemed at elevated risk for hip fracture, bisphosphonates or other fracture-reducing medications should be considered (94).

Ospemifene is a SERM that has been approved for the treatment of vulvovaginal atrophy (232) (see Table 4). Ospemifene acts as an ER agonist at the level of the urogenital tissues, reducing symptoms of dyspareunia, as well as improves urge incontinence, and sexual function (232, 233). Although in a preclinical model ospemifene also suppressed breast cancer development, human studies, including RCTs, are needed for definitive evidence of breast cancer prevention. Like raloxifene, hot flashes can worsen in women using ospemifene. In addition, VTE risk is increased with ospemifene, likely with a similar risk profile to oral ET and other SERMs (233).

A tissue-selective estrogen complex (TSEC) builds on pairing an estrogen with a SERM so that the estrogenic component offers benefit against menopausal symptoms whereas the SERM component, by acting as an antiestrogen, negates the proliferative effects of E on the endometrium and/or breast. Furthermore, both the E and SERM components hold antiresorptive effects on the skeleton. The only TSEC approved for menopause management in women with a uterus is a combination of bazedoxifene (BZA, a SERM) and CEEs (see Table 3); the 2 components of the formulation allow for the beneficial effects of estrogens (for VMS, lipid profile, vaginal atrophy, bone), without the need for a progestin to counteract estrogen's effects on the endometrium, thereby avoiding the potential negative effect of progestogens on the breast. BZA is unique in that when combined with CEE, it does not stimulate the endometrium (BZA is a potent ER antagonist at the level of the endometrium). In addition, when combined with CEEs, BZA does not increase breast density or tenderness (234, 235). Furthermore, in vitro studies on breast cancer cells have found that BZA blocks estrogen-mediated cell proliferation and has apoptotic effects (117). In a pilot study assessing BZA/CEEs use in women at high risk of breast cancer, favorable effects on breast cancer risk biomarkers were found (236). While further prospective trials are warranted for BZA/CEE use in breast cancer prevention, at this time the TSEC represents a novel treatment option for VMS management while also having positive effects on the bone and genitourinary tissue, without the need for a progestin to protect the endometrium (237-242).

Bioidentical hormones

Despite subsequent analyses of the initial publication of the WHI Trials demonstrating safety of HT in those younger than 60 years or less than 10 years since menopause, there remained an increased interest in compounded bioidentical hormone therapy (cBHT) (243). A common misconception with cBHT is that bioidentical hormones equate to "natural" or are structurally identical to endogenous hormones. However, bioidentical hormones still require biochemical synthesis, and with cBHT, the potency can vary considerably—with some samples being subpotent or superpotent (244). The latter is particularly concerning because rates of endometrial cancer increased by 10% when FDA-approved HT use decreased but cBHT use increased (245). While FDA-approved HT requires that HT options undergo randomized, placebo-controlled studies to demonstrate safety and efficacy, cBHT does not require the same rigorous assessment given the lack of FDA oversight. Recently, the National Academies of Science, Engineering, and Medicine provided recommendations regarding the clinical utility of cBHT (246). They provided 6 key recommendations in their report—"The Clinical Utility of Compounded Bioidentical Hormone Therapy: A Review of Safety, Effectiveness, and Use." Their key message is that cBHT use should be restricted to those with a documented allergy to an active pharmaceutical ingredient in an FDA-approved HT formulation (247). In addition, they recommend that compounders provide standardized content information, warnings for potential adverse effects and health risks, and note that the preparation is not FDA approved (247). They also noted the need for compounders to include financial disclosures of prescribers, pharmacists, and pharmacies, and to provide guidance on reporting adverse events (247). These recommendations are in line with recommendations from the North American Menopause Society (NAMS), American College of Obstetrics and Gynecology, and the American Society of Reproductive Medicine (9, 248).

Clinical Guide for Treatment of Menopausal Symptoms

Assessment of Comorbid Conditions/ Contraindications to Hormone Therapy

Risk stratification

Meta-analyses and subgroup analyses of the WHI hormone trials bring to light another important concept regarding appropriateness of HT initiation: Careful assessment of

absolute contraindications and medical comorbidities is necessary prior to considering start of HT. The former include a personal history of CHD, VTE, stroke, transient ischemic attack, active liver disease, breast cancer, high-risk endometrial cancer, or unexplained vaginal bleeding (9). As previously discussed, variables including relatively young age (≤ 60 years) and or less than 10 years since menopause onset, are predictors of relative safety of HT in otherwise healthy menopausal women (97). In postmenopausal women with comorbidities such as CHD and those with a history of VTE, stroke, or transient ischemic attack, the risks of HT are greater; nonhormonal strategies should be considered as the first-line approach for the management of menopausal symptoms in such "at-risk" populations. In general, for women who are within 10 years of menopause and are deemed at low risk for CVD, HT can be safely considered (249). For those who are less than 10 years since menopause onset but with risk factors for CVD, if HT is considered for symptom control, a transdermal rather than oral route of HT should be considered (further discussed in the next section) (250). HT does not adversely affect glucose levels, and HT is not contraindicated in women with diabetes; however, careful assessment of associated comorbidities is warranted to minimize risks (176, 249, 251). For women who are considered high risk for VTE, such as obese women, or those who are smokers, if HT is being considered, then a transdermal route would be preferred given the higher risk of thrombosis with oral route of estrogen therapy (further discussed later) (94, 111, 112, 114, 115, 249). In light of the data discussed earlier, for women who are more than 10 years past FMP, nonhormonal approaches should be preferentially considered as the first-line approach even in those deemed at low or moderate risk for CVD (250). The Menopause Decision-Support Algorithm (and MenoPro mobile app: https://www.menopause.org/for-women/-i-menopro-i-mobile-app) is a clinical support tool developed in collaboration with the NAMS—it incorporates patient history to allow for risk stratification, and personalized care regarding HT use for a given patient (see Fig. 2) (252).

Available nonhormonal agents for those with contraindications to, or who prefer, nonhormonal therapy

When deciding on the use of HT for managing menopausal symptoms, it is important to take a thorough history and assess the patient for any contraindications to HT. In women with contraindications to HT or who wish to avoid HT, there are a number of nonhormonal alternative agents available for use. Paroxetine (a selective serotonin reuptake inhibitor, SSRI) is the only FDA-approved nonhormonal treatment available for managing hot flashes, at a dosage of 7.5 mg daily (253). While improvements in hot flashes are significantly greater than placebo, paroxetine is less effective than HT (253). As such, it should be reserved for women with contraindications to HT. Other SSRIs and selective norepinephrine reuptake inhibitors have also demonstrated reduction in VMS, although some have no greater effect than placebo (254). When choosing a nonhormonal regimen, consideration should be given to use the lowest effective dose to avoid the unwanted side effect of decreased libido, as well as potential nausea, constipation, and dry mouth (255). The following SSRIs (paroxetine, fluoxetine, sertraline) should specifically be avoided in women taking tamoxifen as an adjuvant therapy in the management of breast cancer because they can inhibit tamoxifen's active metabolite (256, 257). The antiseizure medications gabapentin and pregabalin also reduce VMS; however, side effects limit their use at high doses (258-260). Gabapentin and pregabalin both can cause drowsiness and dizziness; pregabalin can also decrease libido. In a randomized, placebo-controlled phase 2 trial, oxybutynin was also found to be more effective than placebo (73% vs 26%) at relieving moderate-to-severe VMS, with dry mouth being the most common side effect (261). As the neurokinin B/neurokinin 3 receptor (NK3R) signaling pathway has recently been implicated in the initiation of a hot flash, recent work has focused on blocking this pathway (262). In 2 randomized, placebo-controlled studies (using 2 different NK3R antagonists), it was found that these nonhormonal agents reduced hot flashes in symptomatic postmenopausal women by 45% (263, 264). While these results are promising, additional studies are needed to assess safety of NK3R antagonists.

Although GSM is best treated by low-dose vaginal estrogen, intravaginal dehydroepiandrosterone (DHEA), or ospemifene administration (208, 233, 265) (Table 5); however, alternative nonhormonal therapies include vaginal lubricants and moisturizers (266). Lubricants provide immediate, short-term relief of vaginal dryness and related pain during sex. There are no published studies on the irritation potential of various types of lubricants, so it is recommended that women first test on their skin prior to using intravaginally. If no skin irritation occurs, they can proceed with a given product (209). Moisturizers serve to hydrate dry mucosal tissue and, because they adhere to the vaginal lining, they can mimic normal vaginal secretions (266) and may be helpful for GSM (267, 268).

Treatment by Indication

Vasomotor symptoms, genitourinary syndrome of menopause, bone health, hypoestrogenism in perimenopausal women

In appropriately evaluated women who are deemed not to have an elevated risk of VTE, CVD, or breast cancer, HT

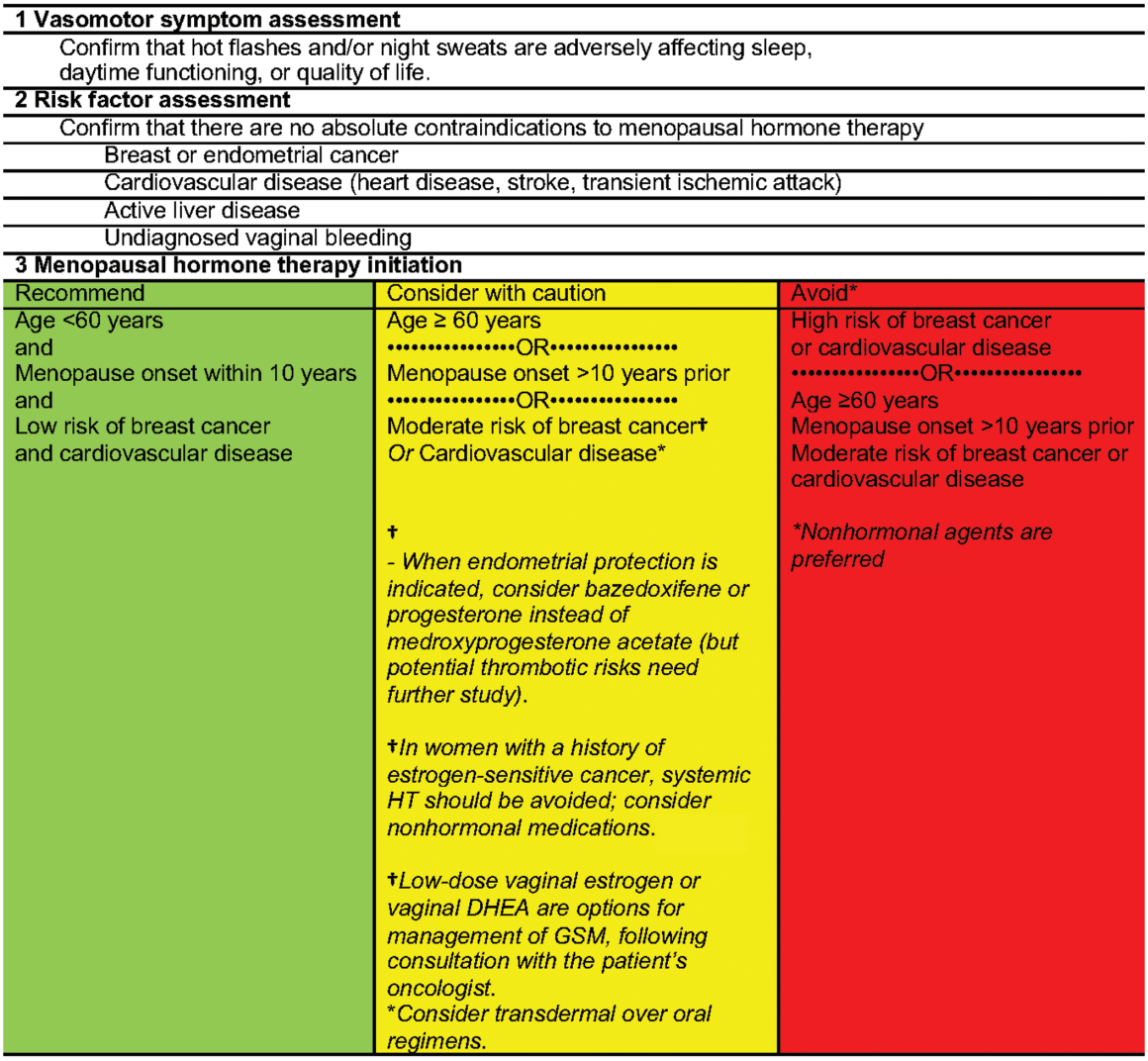


Figure 2. Approach to initiating menopausal hormone therapy (HT) (333). DHEA, dehydroepiandrosterone; GSM, genitourinary syndrome of menopause. Modified from Shifren JL, Crandall CJ, Manson JE. *JAMA*. 2019;**321**(24):2458-2459. Copyright© 2019 American Medical Association. All rights reserved.

(oral or transdermal route of E) is an effective and appropriate first-line management approach (with the addition of a progestogen in women with a uterus). As previously discussed, both standard and lower-dose hormone regimens are available; the lowest effective E dose needed for symptom relief is recommended. In those with VMS who are also burdened by GSM, the addition of low-dose vaginal estrogen, intravaginal DHEA (further discussion later), or ospemifene can be considered if focal symptoms persist despite improvement in VMS with systemic HT.

A variety of vaginal E formulations are available to address GSM (creams, tablets, rings). More recently, a synthetic DHEA (prasterone) vaginal suppository has been added to the therapeutic arsenal against GSM (see Table 5). In a randomized, placebo-controlled trial, daily 0.5% DHEA administered vaginally resulted in significant improvement in GSM symptoms without affecting the endometrium or liver (265, 269-271). The mechanism of action is believed to be due to local conversion of DHEA to estrogens in the vaginal epithelium (265, 272). There were minimal changes in systemic levels of DHEA, E_2, or testosterone. In a separate clinical trial comparing vaginal DHEA to vaginal estrogens, both were equally effective at improving vulvovaginal symptoms (265). Whether vaginally administered DHEA has any effect on the bone or breast is unknown.

HT has been shown in RCTs (including the WHI hormone trials) to effectively improve BMD and reduce fracture risk (273, 274). Some systemic E-alone, E plus P, or BZA/CEEs (TSEC) are approved for postmenopausal osteoporosis and fracture prevention (9). The ideal candidates for HT use for skeletal benefit are recently

menopausal women (within 10 years of FMP and younger than 60 years) who in addition to having an elevated lifetime risk for fracture, are also experiencing bothersome VMS, and have no contraindications to HT use. For older postmenopausal women or in those with contraindications to HT, a number of nonhormonal treatment options are available for fracture risk reduction and should be considered. These agents can be broadly classified under 2 categories: antiresorptive agents, which increase bone density by suppressing osteoclastic function and thereby decreasing bone resorption (bisphosphonates, SERMs, and denosumab), and bone-forming agents, which increase bone mass by stimulating osteoblastic function and thereby increasing bone formation (parathyroid hormone and its analogues are prototypes). Romosozumab, an inhibitor of sclerostin, represents a newer therapeutic class that offers a dual benefit by inhibiting bone resorption and stimulating bone formation (275). While HT is most effective for fracture prevention, a meta-analysis comparing RCTs using various pharmacological therapies for fracture prevention found that of available nonhormonal agents, teriparatide, abaloparatide, denosumab, romosozumab, and bisphosphonates were most effective at reducing fractures (276). As previously mentioned, raloxifene (a SERM) is effective only for the prevention of spine fractures. Calcium (1000-1200 mg in total from diet and/or supplements) and vitamin D (800-1000 IU) intake also help in fracture prevention (277-280). Nonestrogen treatments do not stimulate the breast or endometrium. The Menopause Decision-Support Algorithm (MenoPro) also helps guide treatment choice when HT is contraindicated (252).

For the younger perimenopausal population of women presenting with VMS who are seeking contraception and/or are experiencing irregular menses (with negative workup for other causes), low-dose combined oral contraceptives (COCs; 10-20 μg EE) can offer relief as well as ensure reliable contraception, provided there are no contraindications to the use of COCs (281). The decision to transition from COCs to HT should be an ongoing discussion with women, and usually can occur near the average age of menopause (around age 52 years), or based on individualized family reproductive history and personal profile.

Special Populations

Early menopause

Early menopause is defined as cessation of ovarian function between ages 40 and 45 years, whereas if this occurs before age 40, it is considered premature (282). Women experiencing early menopause (spontaneous or iatrogenic) face unique challenges consequent to unanticipated early ovarian estrogen loss. For those experiencing loss of ovarian function at an earlier age than the average population norms, consideration for initiation of HT is advisable not only to mitigate the symptoms resulting from hypoestrogenism, but also to prevent the long-term health consequences associated with premature onset of estrogen insufficiency. These health consequences include an increased lifetime risk of osteoporosis and fragility fractures, CVD, cognitive deficits, mood disorders, and increased all-cause mortality (283, 284). For this particular group of women, HT is highly recommended at least until the average age of natural menopause. For women with early menopause or primary ovarian insufficiency (POI), HT is correctly considered hormone replacement (285). Thus, HT dosing should be so that E_2 levels reach 100 pg/mL (attainable with consistent use of transdermal 0.1 mg E_2 patch, 0.1 mg vaginal ring, and with oral dose equivalents being daily 1.25 mg CEEs and 2 mg E_2), which is the usual serum level in premenopausal women (282). Estrogen replacement can be administered orally (as oral HT or COCs), transdermally, or vaginally, and should be individualized based on patient preference (286). In women with a uterus, the addition of a progestogen to estrogen regimen is indicated: 5 to 10 mg MPA, 200 mg natural MP, NETA 5 mg; alternatively, vaginal and intrauterine routes of progestogen administration—while off-label—can be used based on individualized needs and preferences (287). Progestogen inclusion in an HT regimen can be cyclical or continuous (287). Data on the efficacy and safety of off-label vaginal progesterone (gel or tablets) are primarily available for postmenopausal women (198, 199); although not as well studied in early menopause or POI populations, these are reasonable options for women who cannot tolerate oral progestogens and are hesitant to consider the progestin-containing IUD (287). While COCs can offer symptom relief (and contraception in those with POI), they are not ideal for reducing the risk of long-term health consequences of these conditions (184, 185).

Hysterectomy with bilateral oophorectomy

Similar to early menopause, bilateral oophorectomy (with or without concomitant hysterectomy) in premenopause or perimenopause renders women abruptly hypoestrogenic and severely symptomatic (282); surgically menopausal women often require HT to ensure quality of life, and depending on the age at time of removal of the ovaries, also to minimize long-term health consequences as discussed earlier. There are important differences to recognize with this particular group of early menopausal women. Surgically menopausal women experience an abrupt and profound drop in circulating levels of not only ovarian estrogens, but also ovarian androgens. While systemic estrogen therapy will treat symptoms resulting from hypoestrogenemia and

even prevent early onset GSM, women who experience hypoactive sexual desire following surgical menopause may benefit from the addition of androgen (testosterone) to ET (288). However, testosterone use is off-label because the long-term risks associated with use are unknown, and there are currently no approved formulations for women (289). In addition, testosterone therapy is contraindicated in women with breast or uterine cancer, CVD, or liver disease. Following hysterectomy, E-alone regimens suffice for the vast majority as there is no need to consider addition of a progestogen to E regimen in women with hysterectomy. The only exceptions are the surgically menopausal women for whom surgery was undertaken for the management of endometriosis for whom the addition of a progestogen to E regimen may be considered. While these women do not have a uterus, the progestogen serves to prevent potential stimulation/reactivation of endometriotic lesions, which may grow rapidly in response to estrogens (94, 282). Combination HT in endometriosis has been shown to result in a lower recurrence rate of endometriosis (290). Furthermore, in postmenopausal women with a past history of endometriosis, consideration should be given to adding a progestogen to estrogen-based therapy. While long-term data are lacking, experts often recommend estrogen plus progestogen-based therapy for at least a year following surgical menopause or natural menopause in these patients, followed by a trial of E-alone—with close follow-up for potential symptoms of endometriosis reactivation (282).

Women with a personal or family history of venous thromboembolism or other cardiovascular disease

In women with a personal history of idiopathic VTE, or family members with a history of VTE, an evaluation is warranted prior to considering HT (94). Laboratory assessment should include a complete blood count (malignancy), activated protein C resistance rate (factor V Leiden mutation), prothrombin G mutation (prothrombin gene mutation), protein S and C, and antithrombin III (antithrombin III mutation) (94). While a personal history of VTE is an absolute contraindication to HT, in rare cases of intractable VMS unresponsive to alternatives, a very low-dose transdermal E regimen may be considered, possibly concomitant with anticoagulation, but only after thorough counseling (94). Testing and counseling is best performed in conjunction with a hematologist, with whom a consideration of transdermal HT can be examined on an individualized basis for those with a personal or family history of VTE (94). Postmenopausal women with systemic lupus erythematosus who have stable disease without high antiphospholipid antibodies or renal disease can also consider transdermal HT in consultation with their rheumatologist (291, 292).

As previously discussed, risk stratification is helpful in determining whether CVD risk represents a contraindication to HT. The 10-year Atherosclerotic Cardiovascular Disease risk score and years since menopause (along with patient preferences) help determine if HT is an option, and which regimen (oral, transdermal, or vaginal) is preferred (293). Women without an elevated risk of CVD may be considered as candidates for HT (see Fig. 2)

Women with a prior history of estrogen-sensitive cancer/strong family history of cancer/*BRCA* positivity

In women with a prior history of early stage and surgically treated endometrial cancer, combined E plus progestogen HT can be used following consultation with their oncologist (9). A meta-analysis found that those with early-stage, low-grade, hormone receptor–negative endometrial cancer were not at a greater risk of recurrence when using HT (294-299); those with advanced disease should use nonhormonal treatment options for menopause (9). At this time, systemic HT is not recommended for women with a history of breast cancer (9). Several observational studies have not found an increased incidence of recurrent breast cancer in women using HT (300-317). Similarly, a randomized prospective trial and a separate prospective case-control study did not find an increased risk of recurrent breast cancer in HT users (316, 317). However, the HABITS (Hormone replacement therapy After Breast cancer— Is it Safe?) multicenter trial designed to compare breast cancer survivors treated with HT vs those treated with alternative therapies was discontinued early because of 26 new breast cancers in the HT group (compared to 7 in the non-HT group) (318). The HABITS trial was not without its limitations, yet given these results, it is important to be cautious regarding HT use in these patients (94). In those presenting with GSM, consideration of low-dose vaginal estrogen, in consultation with their oncologist, is a potential therapeutic option (224). Alternatively, vaginal DHEA can be considered despite the absence of clinical data in cancer survivors, given the purported mechanism of action (272). In women with a family history of breast cancer, HT does not affect the risk of subsequent breast cancer development (319). In addition, both arms of the WHI hormone trials found that HT use did not affect the risk of breast cancer in women with a family history of breast cancer (320, 321). In women who are *BRCA*1/2 positive, HT (including estrogen alone) has not negated the risk reduction in cancer following prophylactic bilateral oophorectomy in cohort studies (322, 323). In a case-control study of *BRCA*1-positive women using estrogen-alone or estrogen plus progestogen-based HT, there was no increased risk of breast cancer (324). While RCTs are limited, available evidence demonstrates the relative safety of HT

in women who are *BRCA* positive, although these women may benefit particularly from BZA/CEEs given the neutral effect of BZA on the breast (and blockage of breast cancer cell proliferation in vitro) (113, 117, 238).

In women with a history of ovarian cancer, an increased risk of cancer recurrence when using HT has not been found, although data come primarily from observational studies (325). There is concern that hormone-responsive ovarian cancers may reactivate, but studies are limited (9). HT use and cervical cancer has not been well studied; however, existing studies do not demonstrate an increased risk of cervical cancer or cervical cancer recurrence in postmenopausal women using HT (326-329). While data on lung cancer are limited, the overall data do not clearly support an increased risk with HT use (9, 60, 61).

Duration of Treatment and Importance of Shared Decision Making

The decision regarding duration of treatment and when to stop HT must be considered in the context of the individualized risk/benefit profile, as well as the personal preferences of the patient. It is not known if ongoing use of HT by women who initiated treatment early but are now older than 60 years carries the same risks as initiating HT in women older than 60 or those who are more than 10 years since menopause onset. When considering continued treatment, it is important to review the symptoms that led to HT initiation as well as consider any interval change in the individual woman's health status. For example, VMS can continue on average for 7 years (and for some beyond 10 years) (94). For otherwise healthy women with persistent VMS, continuing HT is a reasonable option provided counseling and shared decision making are taken into account; prescribers must remain vigilant about risk stratification and risk mitigation strategies such as switching from oral to transdermal E and lowering dosing regimens (330). In women at high risk for osteoporosis who also experience persistent VMS, HT may also be considered beyond age 65 years in select women who are deemed to remain at low risk for CVD despite advancing age (9). With discontinuation of HT, the beneficial effect on the skeleton dissipates; GSM and VMS can also reappear (9, 94). Therefore, the preferred approach to HT duration is to consistently assess symptoms and changes to patients' medical history so as to ensure that risks of continued therapy do not outweigh the benefits for each individual woman treated with HT (9, 94). The choice of transdermal estrogen with or without MP (depending on the presence or absence of a uterus) with periodic E dose reduction offers benefits of symptom control and long-term fracture risk reduction while minimizing some risks (such as VTE) and thus may be a safer strategy for long-term HT (96, 330).

Future Directions

It is important to recognize that while we have made significant advances in our understanding of the risk:benefit profiles of individualized menopausal hormone regimens, there is still much to be gained with respect to our understanding of the timing hypothesis on organ systems other than the cardiovascular system. Future studies can focus on studying the differential effects of routes of delivery of HT as well as how these therapies exert alternative effects based on when they are initiated. In addition, the development of more precise, nonhormonal therapies for the treatment of VMS is an important ongoing area of research; currently NK3R antagonists represent a promising class of therapeutics (262, 331). Another potential avenue of study is the consideration of ovarian function preservation through ovarian tissue cryopreservation and temporary restoration of premenopausal endocrinology with thawed ovarian tissue reimplantation; the identification of ovarian stem cells has allowed exploration of regenerative medicine, particularly in women experiencing POI (332-334). Such scientific contributions would certainly help advance the field of (menopausal) women's health.

Conclusion

Menopausal HT is one of the most effective treatments available to relieve menopausal symptoms. The benefits of HT extend beyond the control of VMS and GSM, including reductions in risk of fracture and type 2 diabetes. The risks of HT must be considered in the context of background risk attributable to advancing age and to existing comorbidities. In the absence of comorbidities (such as CVD, poorly controlled diabetes, and hypertension) and in the absence of risk factors for stroke (poorly controlled hypertension, smoking) and VTE (morbid obesity, clotting disorders), symptomatic yet healthy postmenopausal women who are younger than 60 years and/or within 10 years since menopause onset without contraindications are excellent candidates for HT. In otherwise healthy women who experience early or premature menopause, initiation of HT should be prioritized, even in the absence of bothersome symptoms given that in the absence of intervention, this patient population is at an elevated lifetime risk for a number of chronic disorders that can be mitigated with timely initiation of hormone replacement. Despite the plethora of data accrued over nearly 2 decades after the WHI HT trials, HT prescriptions and HT uptake have remained low; these practice patterns reflect a lingering concern on the part of clinicians as well as ongoing hesitation on the part of menopausal women regarding the safety of HT. The position statements on HT from the NAMS, the Endocrine Society, and other

professional organizations provide outstanding resources for multidisciplinary teams of providers caring for midlife and older women (including gynecologists, primary and family medicine practitioners, nurse practitioners, and others); it serves to guide prescribers in choosing safe and effective management approaches to menopausal symptoms. Websites such as www.menopause.org and the NAMS/MenoPro Clinical Decision Support tool provide accessible and highly useful information for patients and clinicians alike. Use of these and other resources will facilitate improved understanding and increasing comfort in judicious prescribing of HT. While it is important to understand potential risks associated with HT, it is equally important to recognize the benefits of treatment. For the vast majority of symptomatic women, the benefits of HT outweigh the risks. It is imperative that the choice of treatment be individualized and that patients share in the decision making.

Additional Information

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