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## POSITION STATEMENT

# The 2017 hormone therapy position statement of The North American Menopause Society

**Abstract**

The 2017 Hormone Therapy Position Statement of The North American Menopause Society (NAMS) updates the 2012 Hormone Therapy Position Statement of The North American Menopause Society and identifies future research needs. An Advisory Panel of clinicians and researchers expert in the field of women's health and menopause was recruited by NAMS to review the 2012 Position Statement, evaluate new literature, assess the evidence, and reach consensus on recommendations, using the level of evidence to identify the strength of recommendations and the quality of the evidence. The Panel's recommendations were reviewed and approved by the NAMS Board of Trustees.

Hormone therapy (HT) remains the most effective treatment for vasomotor symptoms (VMS) and the genitourinary syndrome of menopause (GSM) and has been shown to prevent bone loss and fracture. The risks of HT differ depending on type, dose, duration of use, route of administration, timing of initiation, and whether a progestogen is used. Treatment should be individualized to identify the most appropriate HT type, dose, formulation, route of administration, and duration of use, using the best available evidence to maximize benefits and minimize risks, with periodic reevaluation of the benefits and risks of continuing or discontinuing HT.

For women aged younger than 60 years or who are within 10 years of menopause onset and have no contraindications, the benefit-risk ratio is most favorable for treatment of bothersome VMS and for those at elevated risk for bone loss or fracture. For women who initiate HT more than 10 or 20 years from menopause onset or are aged 60 years or older, the benefit-risk ratio appears less favorable because of the greater absolute risks of coronary heart disease, stroke, venous thromboembolism, and dementia. Longer durations of therapy should be for documented indications such as persistent VMS or bone loss, with shared decision making and periodic reevaluation. For bothersome GSM symptoms not relieved with over-the-counter therapies and without indications for use of systemic HT, low-dose vaginal estrogen therapy or other therapies are recommended.

***Key Words:*** Breast cancer – Cardiovascular disease – Cognition – Estrogen – Hormone therapy – Menopause – Position Statement – Vaginal atrophy – Vasomotor symptoms

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The 2017 Hormone Therapy Position Statement of The North American Menopause Society (NAMS) provides evidence-based and current best clinical practice recommendations for the use of hormone therapy (HT) for the treatment of menopause-related symptoms and reviews the effects of HT on various health conditions at different stages of a woman's life.

The availability of new clinical trial data prompted the NAMS Board of Trustees to update the NAMS 2012 Hormone Therapy Position Statement. The new data include findings from long-term randomized, clinical trials (RCTs) and observational studies related to 1) the effects of HT during and after its use and 2) detailed analyses stratified by age and time since menopause onset. NAMS convened an Advisory Panel of clinicians and researchers expert in the field of women's health and menopause to provide recommendations for this updated Position Statement.

The term *hormone therapy* is used to encompass estrogen therapy (ET) and estrogen-progestogen therapy (EPT) when outcomes are not specific to one or the other treatment, although whenever possible the different effects of ET, EPT, and estrogen-receptor (ER) agonists or antagonists are included. Key to initiating or continuing HT in an individual woman is an understanding of the benefits and risks of age at initiation or time since menopause, specific formulations or types of HT, the duration of therapy, the need for monitoring during therapy, potential risks of continuation, and the need for shared decision making.

The use of HT is considered for different cultural or minority populations of women, including those with surgical menopause, early menopause, or primary ovarian insufficiency (POI) and for women aged older than 65 years.

These statements do not represent codified practice standards as defined by regulating bodies or insurance agencies.

## METHODS

An Advisory Panel of clinicians and researchers expert in the field of women's health and menopause were enlisted to review the NAMS 2012 Hormone Therapy Position Statement (www.menopause.org/PSHT12.pdf), evaluate the literature published subsequently, and conduct an evidence-based analysis, with the goal of reaching consensus on recommendations.

NAMS acknowledges that no single trial's findings can be extrapolated to all women. The Women's Health Initiative (WHI) is the only large, long-term RCT of HT in women aged 50 to 79 years, and its findings were given prominent consideration. However, the WHI employed just one route of administration (oral), one formulation of estrogen (conjugated equine estrogens [CEE], 0.625 mg), and only one progestogen (medroxyprogesterone acetate [MPA], 2.5 mg), with limited enrollment of women with bothersome vasomotor symptoms (VMS; hot flashes, night sweats) who were aged younger than 60 years or who were fewer than 10 years from menopause onset—the group of women for whom HT is primarily indicated. In general, the Panel gave greater consideration to findings from larger RCTs or meta-analyses of larger RCTs and reviewed additional published analyses of the WHI findings; newer outcomes from smaller RCTs; longitudinal observational studies; and additional meta-analyses.

The 2017 Hormone Therapy Position Statement of The North American Menopause Society is based on material related to methodology, a review of key studies and evidence-based literature, and presentation and synthesis of evidence. It was written after this extensive review of the pertinent literature and includes key points identified during the review process. The resulting manuscript was submitted to and approved by the NAMS Board of Trustees.

A scientific background report supporting the 2017 Hormone Therapy Position Statement of The North American Menopause Society can be found online at www.menopause.org/docs/2017-scientific-background.

### Explaining hormone therapy risk

Clinicians caring for menopausal women should understand the basic concepts of relative risk (RR) and absolute risk in order to communicate the potential benefits and risks of HT and other therapies. Relative risk (risk ratio) is the ratio of event rates in two groups, whereas absolute risk (risk difference) is the difference in the event rates between two groups.[1]

Odds ratios (ORs; measure of association between exposure and outcome) or risk ratios of 2 and less in observational trials lack credibility and are difficult to interpret.[2] Therefore, these smaller risk ratios can have little clinical or public health importance, especially if outcomes are rare. In properly performed RCTs, smaller risk ratios may be interpreted as having greater credibility and relevance, but low risk ratios provide less assurance that biases, confounding, and other factors do not account for the findings (Table 1).[3]

### Key points

- Odds ratios or risk ratios less than 2 provide less assurance about the findings.
- Smaller risk ratios in RCTs have more credibility than in observational studies.

## FORMULATION, DOSING, ROUTE OF ADMINISTRATION, AND SAFETY

### Formulation

#### *Estrogens*

The estrogens most commonly prescribed are CEE, synthetic conjugated estrogens, micronized 17β-estradiol, and

**TABLE 1.** *Frequency of adverse drug reactions*

| | |
|---|---|
| Very common | $\geq$ 1/10 |
| Common (frequent) | $\geq$ 1/100 and $<$ 1/10 |
| Uncommon (infrequent) | $\geq$ 1/1,000 and $<$ 1/100 |
| Rare | $\geq$ 1/10,000 and $<$ 1/1,000 ($\leq$ 10/10,000 per year) |
| Very rare | $<$ 1/10,000 |

Council for International Organizations of Medical Sciences (CIOMS).[3.]

ethinyl estradiol. Conjugated equine estrogen, used in the WHI, is isolated from the urine of pregnant mares and comprised of estrone sulfate (weaker than estradiol) and mixtures of more than 10 minor components of different active forms of estrogens (weak estrogen agonists). Conjugated equine estrogens and estradiol are rapidly metabolized into weaker estrogens such as estrone. Thus, there may be differences in the types of concentrations of estrogens or interactions with ERs in different target tissues.

Meta-analysis of FDA-approved estrogen trials found no evidence of a significant difference in effectiveness between estradiol and CEE in treating VMS. Findings with regard to adverse events (AEs) were inconsistent,[4] despite more hepatic protein production with CEE.[5] However, there were differences in cognitive outcomes between types of estrogen and the brain serotonergic system, with estradiol providing more robust anxiolytic and antidepressant effects.[6,7]

### *Progestogen indication: need for endometrial protection*

Chronic unopposed endometrial exposure to estrogen increases the risk for endometrial hyperplasia or cancer.[8,9] The primary menopause-related indication for progestogen use is to prevent endometrial overgrowth and the increased risk of endometrial cancer during ET use. Progestins commonly used include MPA, norethindrone acetate, and native progesterone. Women with an intact uterus using systemic ET should receive adequate progestogen unless they are taking CEE combined with bazedoxifene.[10-12]

Progestogen dose *and* duration of use are important in ensuring endometrial protection. When adequate progestogen is combined with estrogen, the risk of endometrial neoplasia is not higher than in untreated women. In the WHI, use of continuous oral CEE + MPA daily was associated with a risk of endometrial cancer similar to placebo (hazard ratio [HR], 0.81; 95% confidence interval [CI], 0.48-1.36),[13] with significant reduction of risk after a median 13 years' cumulative follow-up.[14]

A higher incidence of breast cancer was seen in the WHI for CEE + MPA compared with placebo, but a reduced incidence with CEE alone (Figure 1).[14] Observational studies have suggested that the risk of breast cancer may be less with the use of micronized progesterone (MP) compared with synthetic progestogens,[15,16] but the bioavailability of oral and transdermal progesterone is poor.

Micronized progesterone needs to be adequately dosed for endometrial protection.[17-19] Improperly formulated or

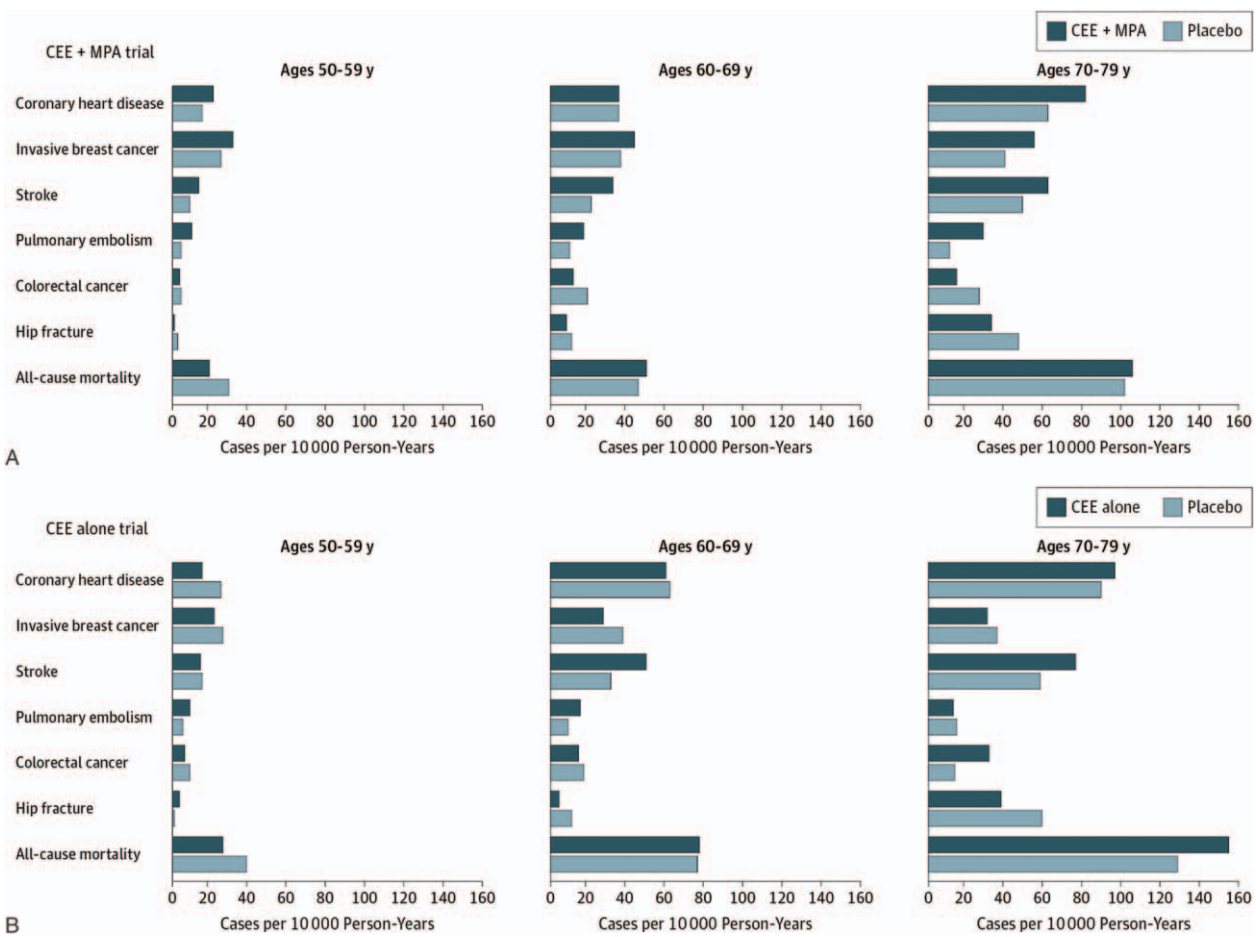


**FIG. 1.** Absolute risks of health outcomes by 10-year age groups in the Women's Health Initiative Hormone Therapy Trials during the intervention phase. CEE, conjugated equine estrogens; MPA, medroxyprogesterone acetate. From Manson et al.[14] Reproduced with permission of the American Medical Association ©American Medical Association. All rights reserved.

dosed or delivery issues with estrogen plus MP combinations have potentially serious health consequences, including increased risk of endometrial neoplasia.[20] In women using EPT, unscheduled bleeding occurring more than 6 months after initiation should be investigated.

### Tissue-selective estrogen complex

Bazedoxifene, a selective ER modulator (SERM; estrogen agonist or antagonist), has been combined with CEE to form a tissue-selective estrogen complex. The combination provides endometrial protection without the need for a progestogen.[21]

### Dosing

#### *Estrogen therapy*

The therapeutic goal should be to use the most appropriate, often lowest, effective dose of systemic ET consistent with treatment goals. The appropriate dose of progestogen is added to provide endometrial protection if a woman has a uterus, unless CEE is combined with bazedoxifene.

#### *Progestogen therapy*

Progestogen dosing-regimen options that provide for endometrial safety are dependent on the potency of the progestogen and vary with the estrogen dose. Different types and doses of progestogens, routes of administration, and types of regimen (sequential or continuous-combined) may have different health outcomes.[22]

### Routes of administration

Systemic estrogens can be prescribed as oral drugs; transdermal patches, sprays, and gels; or as vaginal rings. Low-dose vaginal estrogen is available as a cream, tablet, ring, and in some countries, a pessary. Progestogens are available as oral drugs, combination patches with estrogen, intrauterine systems, injectables, and vaginal gels or tablets.

Nonoral routes of administration (transdermal, vaginal, and intrauterine systems) may offer potential advantages because nonoral routes bypass the first-pass hepatic effect; however, there are no head-to-head RCTs to validate this supposition.

### Safety considerations

Contraindications for HT include unexplained vaginal bleeding, severe active liver disease, prior estrogen-sensitive breast or endometrial cancer, coronary heart disease (CHD), stroke, dementia, personal history or inherited high risk of thromboembolic disease, porphyria cutanea tarda, or hypertriglyceridemia, with concern that endometriosis might reactivate, migraine headaches may worsen, or leiomyomas may grow.

More common AEs include nausea, bloating, weight gain, fluid retention, mood swings (progestogen-related), breakthrough bleeding, headaches, and breast tenderness.

Potential risks of HT initiated in women aged younger than 60 years or who are within 10 years of menopause onset include the possible risk of breast cancer with combined EPT, endometrial hyperplasia and cancer if estrogen is unopposed or inadequately opposed, venous thromboembolism (VTE), and biliary issues. Additional risks across ages include myocardial infarction (MI), stroke, and dementia.

### Key points

- Different HTs, even within the same HT class, may have different effects on target organs, potentially allowing options to minimize risk.
- The appropriate, often lowest, effective dose of systemic ET consistent with treatment goals that provides benefits and minimizes risks for the individual woman should be the therapeutic goal.
- The appropriate formulation, dose, and route of administration of progestogen is needed to counter the proliferative effects of systemic estrogen on the endometrium.
- Formulation, dose, and route of administration for HT should be determined individually and reassessed periodically.
- Potential risks of HT for women aged younger than 60 years or who are within 10 years of menopause onset include the rare risk of breast cancer with combined EPT, endometrial hyperplasia and cancer with inadequately opposed estrogen, VTE, and biliary issues. Additional risks across ages include MI, stroke, and dementia.

## FDA-APPROVED INDICATIONS

### Vasomotor symptoms

Hormone therapy has been shown in double-blind RCTs to relieve hot flashes[23] and is approved as first-line therapy for relief of menopause symptoms in appropriate candidates.

### Prevention of bone loss

Hormone therapy has been shown in double-blind RCTs to prevent bone loss, and in the WHI, to reduce fractures in postmenopausal women.[24,25]

### Premature hypoestrogenism

Hormone therapy is approved for women with hypogonadism, POI, or premature surgical menopause without contraindications, with health benefits for menopause symptoms, prevention of bone loss, cognition and mood issues, and in observational studies, heart disease.[26-31]

### Genitourinary symptoms

Hormone therapy has been shown in RCTs to effectively restore genitourinary tract anatomy, increase superficial vaginal cells, reduce vaginal pH, and treat symptoms of vulvovaginal atrophy (VVA).[32]

### Key point

- Hormone therapy is approved by FDA for four indications: bothersome VMS; prevention of bone loss; hypoestrogenism caused by hypogonadism, castration, or POI; and genitourinary symptoms.

## COMPOUNDED HORMONES

Government-approved bioidentical (similar to endogenous) HT, including estradiol, estrone, and MP, are regulated and monitored for purity and efficacy, sold with package inserts with extensive product information (based on RCTs), and may include black-box warnings for AEs. Compounded hormone therapies are prepared by a compounding pharmacist using a provider's prescription and may combine multiple hormones (estradiol, estrone, estriol, dehydroepiandrosterone [DHEA], testosterone, progesterone), use untested, unapproved combinations or formulations, or be administered in nonstandard (untested) routes such as subdermal implants, pellets, or troches.[33-36]

Compounded HT has been prescribed or dosed on the basis of salivary hormone testing; however, salivary testing for HT is considered unreliable because of differences in hormone pharmacokinetics and absorption, diurnal variation, and interindividual and intraindividual variability.[37-39]

Prescribers should only consider compounded HT if women cannot tolerate a government-approved therapy for reasons such as allergies to ingredients or for a dose or formulation not currently available in government-approved therapies. With interim guidance on compounding safety and quality control from FDA, quality control of compounded HT may improve.[40]

### Key points

- Compounded bioidentical HT presents safety concerns such as minimal government regulation and monitoring, overdosing or underdosing, presence of impurities or lack of sterility, lack of scientific efficacy and safety data, and lack of a label outlining risks.
- Salivary hormone testing to determine dosing is unreliable.
- Prescribers of compounded bioidentical HT should document the medical indication for compounded HT over government-approved therapies, such as allergy or the need for dosing or a formulation not available in FDA-approved products.

## MENOPAUSE SYMPTOMS: BENEFITS AND RISKS

### Vasomotor symptoms

Vasomotor symptoms are associated with diminished sleep quality, irritability, difficulty concentrating, reduced quality of life (QOL),[41] and poorer health status.[42] Vasomotor symptoms persisted on average 7.4 years in the Study of Women's Health Across the Nation[43] and appear to be linked to cardiovascular (CV), bone, and cognitive risks.[44-48] Compared with placebo, estrogen alone or combined with a progestogen was found to reduce weekly symptom frequency by 75% (95% CI, 64.3-82.3) and significantly reduce symptom severity (OR, 0.13; 95% CI, 0.07-0.23),[23] with no other pharmacologic or alternative therapy found to provide more relief.

Although the lowest-dose approved estradiol weekly patch (0.014 mg/d) appears effective in treating VMS,[49] it is approved for prevention of osteoporosis but not vasomotor relief. Lower doses may have lower risks for VTE[50] and may reduce AEs such as breast tenderness or unscheduled vaginal bleeding.[51,52] Lower doses of HT (oral CEE 0.3 mg; oral 17β-estradiol $\leq$ 0.5 mg; or estradiol patch 0.025 mg) may take 6 to 8 weeks to provide adequate symptom relief.

Progestogen formulations have been found to be effective in treating VMS,[53,54] studied with MPA 10 mg per day,[55] oral megestrol acetate 20 mg,[56] and MP 300 mg,[54] but no long-term studies have addressed the safety of progestogen-only treatment on menopause symptoms.

Vasomotor symptoms return in approximately 50% of women when HT is discontinued.[57,58] There is no consensus about whether stopping ''cold turkey'' or tapering is preferable.

### Sleep disturbances

A 2015 literature review found that HT in the form of low-dose estrogen or progestogen could improve chronic insomnia in menopausal women, with 14 of the 23 studies reviewed showing positive results,[59] but data are conflicting about the link between VMS at menopause and objective polysomnographic measures of sleep.[60] Oral progesterone has mildly sedating effects, reducing wakefulness without affecting daytime cognitive functions, possibly through a GABA-agonistic effect.[61]

### The genitourinary syndrome of menopause (vaginal symptoms)

The genitourinary syndrome of menopause (GSM) includes the signs and symptoms associated with postmenopause-related estrogen deficiency involving changes to the labia, vagina, urethra, and bladder and includes VVA.[62] Symptoms may include genital dryness, burning, and irritation; sexual symptoms of diminished lubrication and pain; and urinary symptoms of urgency, dysuria, and recurrent urinary tract infections (UTIs). Estrogen therapy is the most effective treatment for GSM.[32,63,64]

Low-dose vaginal estrogen preparations are effective and generally safe treatments for VVA[32,65] and include creams, tablets, and rings containing estradiol or CEE, available at doses that result in minimal systemic absorption.[64-66]

Because of the potential risk of small increases in circulating estrogens,[67] the decision to use low-dose vaginal ET in women with breast cancer should be made in conjunction with their oncologists.[68] This is particularly important for women on aromatase inhibitors (AIs) with suppressed plasma levels of estradiol,[69] although no increased risk was seen in an observational trial of survivors of breast cancer on tamoxifen or AI therapy with low-dose vaginal ET during 3.5 years' mean follow-up.[70]

A progestogen is generally not indicated when ET is administered vaginally for GSM at the recommended low doses, although clinical trial data supporting endometrial safety beyond 1 year are lacking.[66]

Nonestrogen therapies that improve vaginal VVA and are approved for relief of dyspareunia in postmenopausal women include ospemifene[71] and intravaginal DHEA.[72]

**Urinary tract symptoms (including pelvic floor disorders)**

Vaginal ET may improve incontinence by increasing the number of vessels around the periurethral and bladder neck region[73] and has been shown to reduce the frequency and amplitude of detrusor contractions to promote detrusor muscle relaxation.[74,75] Estrogen therapy, along with pelvic floor training, pessaries, or surgery, may improve synthesis of collagen and improve vaginal epithelium, but evidence for effectiveness for pelvic organ prolapse is lacking.[76]

Two large trials found that users of systemic HT (CEE 0.625 mg + MPA 2.5 mg) had an increased incidence of stress incontinence.[77,78] Increased incontinence was found in women using oral estrogen alone (RR, 1.32; 95% CI, 1.17-1.48) and in those using combined estrogen and progestogen (RR, 1.11; 95% CI, 1.04-1.18).[79] Vaginal estrogen use showed a decreased incidence of incontinence (RR, 0.74; 95% CI, 0.64-0.86) and overactive bladder, with one to two fewer voids in 24 hours and reduced frequency and urgency. A reduced risk of recurrent UTI with vaginal but not oral estrogen has been shown in RCTs.[80]

**Sexual function**

Systemic HT and low-dose vaginal ET provide effective treatment of VVA, improving sexual problems by increasing lubrication, blood flow, and sensation in vaginal tissues.[81] Studies have not found any significant effect of ET on sexual interest, arousal, and orgasmic response independent from its role in treating menopause symptoms.[82-84]

If systemic HT is needed and women have low libido, transdermal ET formulations may be preferred to oral, given increased sex hormone-binding globulin and reduced bioavailability of testosterone with oral ET.[81,85,86]

Conjugated equine estrogen combined with bazedoxifene relieves dyspareunia and improves VVA and some aspects of sexual function in postmenopausal women.[87-90]

**Key points**

***Vasomotor symptoms***

- Vasomotor symptoms may be caused by thermoregulatory dysfunction. They begin during perimenopause and may persist on average 7.4 years or longer, with ethnic differences. They affect QOL and appear to be linked to CV, bone, and brain health.
- Hormone therapy remains the gold standard for relief of VMS.
- Estrogen-alone therapy can be used for symptomatic women after hysterectomy.
- For symptomatic women with a uterus requesting HT, combination therapy protects against endometrial neoplasia, either with a progestogen or as a combination of CEE and bazedoxifene.
- For menopause symptom control, the lowest dose that offers relief should be used. Dosing and need for ongoing therapy for relief of menopause symptoms should be assessed periodically.
- Micronized progesterone 300 mg nightly significantly decreases VMS (hot flashes and night sweats) compared with placebo and improves sleep. Synthetic progestins have also shown benefit in studies. No long-term study results are available.

***Sleep disturbances***

- During the menopause transition, women with VMS are more likely to report reduced sleep.
- Hormone therapy improves sleep in women with bothersome nighttime VMS by reducing nighttime awakenings.

***The genitourinary syndrome of menopause (vaginal symptoms)***

- Low-dose vaginal estrogen preparations are effective and generally safe for the treatment of VVA, with minimal systemic absorption, and preferred over systemic therapies when ET is considered only for GSM.
- For women with breast cancer, low-dose vaginal estrogen should be considered and prescribed in consultation with their oncologists.
- Progestogen therapy is not needed with low-dose vaginal ET, but randomized trial data are lacking beyond 1 year; postmenopausal bleeding in women using low-dose vaginal ET must be thoroughly evaluated.
- Nonestrogen prescription therapies that improve VVA in postmenopausal women include ospemifene and intravaginal DHEA.

***Urinary tract symptoms (including pelvic floor disorders)***

- Systemic HT does not improve urinary incontinence and may increase the incidence of stress urinary incontinence.
- Low-dose vaginal ET may provide benefit for urinary symptoms, including prevention of recurrent UTI, overactive bladder, and urge incontinence.
- Hormone therapy does not have FDA approval for any urinary health indication.

***Sexual function***

- Both systemic HT and low-dose vaginal estrogen increase lubrication, blood flow, and sensation of vaginal tissues.
- Systemic HT generally does not improve sexual function, sexual interest, arousal, or orgasmic response in women without menopause symptoms.
- If sexual function or libido are concerns in women with menopause symptoms, transdermal ET may be preferable over oral ET because of less effect on sex hormone-binding globulin and free testosterone levels.
- Low-dose vaginal ET improves sexual function in postmenopausal women with GSM (symptomatic VVA).
- Nonestrogen alternatives approved for dyspareunia include ospemifene and intravaginal DHEA.

## EARLY NATURAL MENOPAUSE AND PRIMARY OVARIAN INSUFFICIENCY

Women with early natural menopause and POI experience an extended period of time with loss of ovarian hormone activity compared with women experiencing normal menopause, with potential AEs of estradiol deficiency in all tissues. For women whose ovaries are retained at the time of hysterectomy, there is a two-fold increased risk of ovarian failure,[91] and 20% or more of these women may develop symptoms of diminished ovarian reserve within 1 year, with reduced antimüllerian hormone.[92] Health risks of early natural menopause

and POI may include persistent VMS, bone loss, VVA, mood changes, and increased risk of heart disease, dementia, stroke, Parkinson disease, ophthalmic disorders, and overall mortality.[26,28,93-95]

Women with POI have a higher risk of death from ischemic heart disease as well as from all causes compared with women who have a normal age of natural menopause,[27] which may be reflective of premature aging. They also have a higher risk of digestive tract cancer but a decreased risk of mortality from breast, uterine, and endometrial cancer.[94,96,97] Effective management may include appropriate doses of HT along with calcium, vitamin D, exercise, and screenings to detect medical issues. Although higher doses of HT appear to provide the best bone benefits,[29,98,99] oral contraceptives with an estrogen patch during the placebo week may be used if needed for psychological benefit in younger women.

**Key points**

- Women with early menopause and POI have health risks that may include persistent VMS, bone loss, VVA, mood changes, and increased risk of heart disease, dementia, stroke, Parkinson disease, ophthalmic disorders, and overall mortality.
- Results of the WHI studies in older women do not apply to women with early menopause, and observational evidence suggests benefit with HT taken to the average age of menopause.
- Hormone therapy such as transdermal estradiol in higher doses with adequate endometrial protection may be superior to oral contraceptive therapy to restore or maintain bone mineral density (BMD).

## OOPHORECTOMY IN PREMENOPAUSAL WOMEN

The surgical removal of both ovaries leads to a much more abrupt loss of ovarian steroids than does natural menopause and includes the loss of estrogen, progesterone, and testosterone.[100] Vasomotor symptoms as well as a variety of estrogen deficiency-related symptoms and diseases are more frequent and more severe after oophorectomy and can have a major effect on QOL[101,102] and potential AEs on the CV system, bone, mood, sexual health, and cognition, which have been shown in observational studies to be lessened by ET.[103]

Unless contraindications are present, ET is indicated for women who have had a bilateral oophorectomy and are hypoestrogenic to reduce the risk for VVA and dyspareunia[104] and osteoporosis,[105] with observational data suggesting benefit on atherosclerosis and CVD,[106] and cognitive decline and dementia[107]

**Key points**

- In women with early natural or surgical menopause or POI, early initiation of ET, with endometrial protection if the uterus is preserved, reduces risk for osteoporosis and related fractures, VVA, and dyspareunia, with benefit seen in observational studies for atherosclerosis and CVD, cognition, and dementia. Younger women may require higher doses for symptom relief or protection against bone loss.
- Ovarian conservation is recommended, if possible, when hysterectomy for benign indications is performed in premenopausal women at average risk for ovarian cancer.

## SKIN, HAIR, AND SPECIAL SENSES

Estrogen therapy may benefit wound healing through modifying inflammation, stimulating granulation tissue formation, and accelerating re-epithelialization. In studies, ET increased epidermal and dermal thickness, increased collagen and elastin content, and improved skin moisture, with fewer wrinkles.[108]

Hormone therapy appears to increase the risk of dry eye symptoms[109] but may decrease the risk of cataracts[110] and primary open-angle glaucoma.[111] Hormone therapy may play a role in hearing loss[112] and olfactory changes.[113] In small trials, HT appears to decrease dizziness or vertigo[114] and improve postural balance.[115]

**Key points**

- Estrogen therapy appears to have beneficial effects on skin thickness and elasticity and collagen when given at menopause.
- Changes in hair density and female pattern hair loss worsen after menopause, but no positive role has been identified for HT.
- Hormone therapy appears to increase the risk of dry eye symptoms but may decrease the risk of cataracts and primary open-angle glaucoma.
- Hormone therapy may play a role in hearing loss and olfactory changes.
- In small trials, HT appears to decrease dizziness or vertigo and improve postural balance.

## HORMONE THERAPY AND QUALITY OF LIFE

Women who are severely symptomatic at baseline in clinical trials show a significant improvement in health-related QOL and menopause-specific QOL with HT when validated QOL measurement instruments are used, whereas no significant improvement is seen in women without severe symptoms at baseline.[116]

**Key points**

- The effect of severe menopause symptoms on QOL may be substantial.
- Desire for improved QOL may cause women and providers to accept a greater degree of risk to obtain significant improvement.

## OSTEOPOROSIS

Standard-dose ET and HT prevent bone loss in postmenopausal women by inhibition of osteoclast-driven bone resorption and a reduced rate of bone remodeling.[117-120] Randomized, controlled trials and observational studies show that standard-dose HT reduces postmenopause osteoporotic fractures, including hip, spine, and all nonspine fractures, even in women without osteoporosis.[24,25,121-124]

In the WHI intervention phase, the CEE-alone and the CEE + MPA groups combined had statistically significant reduced hip fracture incidence of 33% ($P = 0.03$), with 6 fewer fractures per 10,000 person-years overall (Figure 1).[14,25,124]

Bone mineral density response to estrogen is dose related, with less protection from bone loss at lower doses, particularly for women aged younger than 40 years. Neither low-dose (oral CEE 0.3 mg; oral 17β-estradiol $\leq$ 0.5 mg; or estradiol patch 0.025 mg) nor ultralow-dose (estradiol patch 0.014 mg) therapy has been shown to reduce fracture risk, although no studies have been adequately powered for this endpoint. Bone protection dissipates rapidly after treatment discontinuation.[14,125-128]

Although persistent benefit was found with CEE + MPA for reduced fractures in the WHI cumulative data (intervention plus 13 years' follow-up),[14] postintervention data showed that after 5 years' discontinuation, residual benefit was seen for total fractures in the CEE-alone arm but no reduction in total or hip fractures with CEE + MPA, and no rebound fracture risk was found for either.[129] There are no prospective fracture studies comparing the efficacy of HT in preventing fractures with other approved pharmacologic therapies.

**Key points**

- Hormone therapy prevents bone loss in healthy postmenopausal women, with dose-related effects.
- Unless contraindicated, women with premature menopause who require prevention of bone loss are best served with HT or oral contraceptives (which are less effective than HT) rather than other bone-specific treatments until the average age of menopause, when treatment may be reassessed.
- Hormone therapy effectively prevents postmenopause osteoporosis and fractures, and some formulations of ET, EPT, and CEE combined with bazedoxifene are approved for this indication.
  - Women in the ET and EPT cohorts in the WHI intervention trial overall had significant reductions in hip fracture.
  - Bone protection dissipates rapidly after HT discontinuation, but no rebound in fracture risk has been found.
- For women with VMS aged younger than 60 years or who are within 10 years of menopause onset, HT (ET, EPT, or CEE combined with bazedoxifene) is probably the most appropriate bone-active therapy in the absence of contraindications.
- When alternate osteoporosis therapies are not appropriate or cause AEs, the extended use of HT is an option for women who are at high risk of osteoporotic fracture.
- The decision to stop HT should be made on the basis of extraskeletal benefits and risks.

## JOINT PAIN

Direct binding of estrogen to ERs acts on joint tissues, protecting their biomechanical structure and function and maintaining overall joint health, but the exact effect of estrogen on osteoarthritis remains controversial.[130-132]

Preclinical studies and clinical trials of ET have reported inconsistent results of the effects of estrogen on osteoarthritis and arthralgia, with suggestive evidence that estrogen and SERMs may have benefits.[133]

In the WHI, women on combined CEE + MPA had less joint pain or stiffness compared with those on placebo (47.1% vs 38.4%; OR, 1.43; 95% CI, 1.24-1.64) and more discomfort when stopping.[134] In the CEE-alone arm, women randomized to CEE had a statistically significant reduction in joint pain frequency after 1 year compared with the placebo group (76.3% vs 79.2%; $P = 0.001$).[135]

**Key point**

- Women in the WHI and other studies have shown less joint pain or stiffness compared with those on placebo.

## SARCOPENIA

Frailty is associated with AEs such as falls, hospitalization, disability, and death.[136] Skeletal muscle has been shown to have ERs, but there is a paucity of studies evaluating the interplay between estrogen and muscle. The regulation of energy intake and expenditure by estrogens in women has not been well studied, with limited basic and preclinical evidence supporting the concept that the loss of estrogen because of menopause or oophorectomy disrupts energy balance through decreases in resting energy expenditure and physical activity.[137]

Reviews of preclinical studies and limited clinical studies of HT in postmenopausal women suggest a benefit on maintaining or increasing muscle mass and related connective tissue, improving strength and improving posttraumatic or postatrophy muscle recovery when combined with exercise.[138-140]

**Key points**

- Development of frailty with aging is a health risk.
- Sarcopenia and osteoporosis are related to aging, estrogen depletion, and the menopause transition. Intervention to improve bioenergetics and prevent loss of muscle mass, strength, and performance is needed.
- Preclinical studies suggest a possible benefit of ET when combined with exercise to prevent the loss of muscle mass, strength, and performance.

## GALLBLADDER AND LIVER

Cholelithiasis, cholecystitis, and cholecystectomy occur more frequently in women who take oral estrogen, presumably because of the first-pass hepatic effect after oral ingestion. Estrogens increase biliary cholesterol secretion and saturation, promote precipitation of cholesterol in the bile, and reduce gallbladder motility, with increased bile crystallization.[141,142]

The transdermal route of administration bypasses involvement of the liver, with less risk of gallbladder disease seen in observational studies.[143] The attributable risk for gallbladder disease as self-reported in the WHI was an additional 47 cases per 10,000 women per year for CEE + MPA and 58 cases per 10,000 women per year for CEE alone, both statistically significant ($P < 0.001$).[14]

Preclinical and observational studies suggest possible benefits of HT on liver fibrosis and fatty liver,[144] but research is needed before definitive recommendations can be made.

**Key points**

- Risk of gallstones, cholecystitis, and cholecystectomy is increased with oral estrogen-alone and combination HT.

- Observational studies report lower risk with transdermal HT than with oral and with oral estradiol compared with CEE, but neither observation is confirmed in RCTs.
- An association of HT with slower fibrosis progression in hepatitis C and with fatty liver has been observed, but randomized trials are needed to establish any potential benefits and risks of HT in postmenopausal women with liver disease.

## DIABETES MELLITUS, METABOLIC SYNDROME, AND BODY COMPOSITION

In the WHI, women receiving continuous-combined CEE + MPA had a statistically significant 19% reduction (HR, 0.81; 95% CI, 0.70-0.94; $P = 0.005$) in the incidence of type 2 diabetes mellitus (DM), translating to 16 fewer cases per 10,000 person-years of therapy.[14] In the CEE-alone cohort, there was a reduction of 14% in new diagnoses of type 2 DM (HR, 0.86; 95% CI, 0.76-0.98), translating to 21 fewer cases per 10,000 person-years. Meta-analyses of published studies found that combined HT (EPT) reduced type 2 DM incidence almost 40%, with lower fasting glucose levels and levels of hemoglobin $A_{1c}$.[145,146] The benefit reverses when HT is discontinued.

### Metabolic syndrome and weight

In general, ERα protects against fat accumulation, whereas ERβ promotes fat gain. There is evidence from basic and preclinical work that disruption of estradiol signaling, either with ER deletion (genetic manipulation) or surgical oophorectomy, may accelerate fat accumulation, which appears to accumulate disproportionately in the abdominal area, with increased insulin resistance and dyslipidemia.[137]

Estrogen-progestogen therapy either has no effect on weight or is associated with less weight gain in women who are using it than in women who are not.[147-151] In the WHI, women on combined CEE + MPA showed small but significant decreases in body mass index and waist circumference during the first year.[152]

### Key points

- Hormone therapy significantly reduces the diagnosis of new-onset type 2 DM, but it is not US-government approved for this purpose.
- Hormone therapy may help attenuate abdominal adipose accumulation and the weight gains that are often associated with the menopause transition.

## MOOD, DEPRESSION, AND COGNITION

For postmenopausal women without clinical depression, evidence is mixed concerning the effects of HT on mood, with small, short-term trials suggesting that HT improves mood, whereas others showed no change.[153] Postmenopausal women with a history of perimenopause-related depression responsive to HT may experience a recurrence of depressive symptoms after estradiol withdrawal.[154]

Small clinical trials support the use of ET for cognitive benefits when initiated immediately after surgical menopause.[155,156] Three large RCTs demonstrate neutral effects of HT on cognitive function when used early in the postmenopause period versus initiating treatment in women aged older than 65 years.[7,157,158]

Two hypotheses—the *critical window* hypothesis[159,160] and the *healthy cell bias* hypothesis[161]—provide a framework for understanding the scientific literature on HT and cognition, but neither has been definitively supported in RCTs of postmenopausal women.

### Later initiation of hormone therapy

Several large clinical trials indicate that HT does not improve memory or other cognitive abilities and that CEE + MPA may be harmful for memory when initiated in women aged older than 65 years.[162-164]

### Alzheimer disease

Four observational studies provide support for the view that timing of HT initiation is a significant determinant of Alzheimer disease risk, with early initiation lowering risk and later initiation associated with increased risk.[165-168]

### Dementia

In the WHI Memory Study, CEE + MPA doubled the risk of all-cause dementia (23 cases per 10,000 women) when initiated in women aged older than 65 years,[164] whereas CEE alone did not significantly increase the risk of dementia.[169] The effect of HT may be modified by baseline cognitive function, with more favorable effects in women with normal cognitive function before HT initiation.[170,171]

### Key points

- In the absence of more definitive findings, HT cannot be recommended at any age to prevent or treat a decline in cognitive function or dementia.
- On the basis of the WHI Memory Study, caution should be taken in initiating continuous-combined daily CEE + MPA in women aged older than 65 years, given the relatively small or infrequent increase in risk for dementia of an extra 23 cases per 10,000 person-years seen in the WHI.
- Estrogen therapy may have positive cognitive benefits when initiated immediately after early surgical menopause, but HT in the early natural postmenopause period has neutral effects on current cognitive function.
- Only limited support (observational studies) is available for a critical window hypothesis of HT in Alzheimer disease prevention.
- The effect of HT may be modified by baseline cognitive function, with more favorable effects in women with normal cognitive function before HT initiation.
- Evidence is insufficient to support HT use in the treatment of clinical depression. In small RCTs, ET was effective in improving clinical depression in perimenopausal but not postmenopausal women.
- Progestins may contribute to mood disturbance.
- Women whose depression improves with HT are likely to experience a worsening of mood after estrogen withdrawal.

## CARDIOVASCULAR DISEASE AND ALL-CAUSE MORTALITY

Newer observational data and reanalysis of older studies by age or time since menopause, including the WHI, suggest that for healthy, recently menopausal women, the benefits of HT (estrogen alone or with a progestogen) outweigh its risks, with fewer CVD events in younger versus older women.[14,172-182]

### Initiation fewer than 10 years after menopause onset

#### *Surrogate markers*

Some earlier studies suggested benefit on coronary artery calcification,[183-185] whereas more recent RCTs in younger, recently postmenopausal women have not.[106,186] In the Early versus Late Intervention Trial With Estradiol, HT (oral 17β-estradiol 1 mg/d plus progesterone vaginal gel 45 mg administered sequentially for women with a uterus) reduced carotid artery intima-media thickness (CIMT) progression after a median of 5 years when initiated within 6 years of menopause onset but not when initiated 10 or more years after menopause onset.[106] The Kronos Early Estrogen Prevention Study in healthy postmenopausal women aged 42 to 58 years who received HT (oral CEE 0.45 mg/d; transdermal estradiol patch 50 μg/wk, each with cyclic oral MP 200 mg for 12 d/mo) found no effect on CIMT progression.[186]

#### *Meta-analysis of clinical outcomes*

A 2015 Cochrane review of RCT data found that HT initiated fewer than 10 years after menopause onset lowered CHD in postmenopausal women (RR, 0.52; 95% CI, 0.29-0.96).[177] It also found a reduction in all-cause mortality (RR, 0.70; 95% CI, 0.52-0.95) and no increased risk of stroke but an increased risk of VTE (RR, 1.74; 95% CI, 1.11-2.73), similar to the findings of a prior meta-analysis of studies in women who initiated HT within 10 years of menopause onset and/or in women aged younger than 60 years.[180]

#### *Women's Health Initiative*

For CEE alone, CHD, total MI, and coronary artery bypass grafting or percutaneous coronary intervention showed a lowered HR in women aged younger than 60 years and fewer than 10 years since menopause onset, even in intention-to-treat analyses.[14] Age-group analysis in the WHI CEE + MPA trial was an outlier. In the 50- to 59-year-old age group, the HR for CHD was elevated but not statistically significant at 1.34 (95% CI, 0.82-2.19) for CEE + MPA.

### Initiation more than 10 years from menopause onset or in women aged older than 60 years

For women who initiated HT more than 10 years from menopause onset or when aged older than 60 years, a meta-analysis of studies found no evidence that HT reduced or had an effect on CHD (RR, 1.07; 95% CI, 0.96-1.20) or all-cause mortality (RR, 1.06; 95% CI, 0.95-1.18).[177] Risks included an increased risk of stroke (RR, 1.21; 95% CI, 1.06-1.38) and VTE (RR, 1.96; 95% CI, 1.37-2.80).

### Initiation across all ages

When HT is initiated across all ages, there is no evidence for primary or secondary prevention of all-cause mortality, CV death, nonfatal MI, angina, or revascularization.[177] Compared with placebo, HT use was associated with an extra 6 strokes per 10,000 women (RR, 1.24; 95% CI, 1.10-1.41), 8 cases of VTE per 10,000 women (RR, 1.92; 95% CI, 1.36-2.69), and 4 cases of pulmonary embolism (PE) per 10,000 women (RR, 1.81; 95% CI, 1.32-2.48).

### Attributable risk of stroke in women aged younger than 60 years or who were within 10 years of menopause onset

A meta-analysis of studies found no increased risk of stroke in women aged younger than 60 years or who were fewer than 10 years from menopause onset.[177] In subgroup analysis, the attributable risk of stroke in the WHI for women who initiated HT when aged younger than 60 years and/or who were within 10 years of menopause onset was rare (< 1/1,000 person-years) and statistically nonsignificant for CEE + MPA, with an absolute risk of 5 per 10,000 person-years in women aged younger than 60 years or within 10 years of initiation,[181] similar to other studies.[172,181]

For CEE alone in the WHI, findings were inconsistent. For women aged 50 to 59 years at randomization, a decrease of 1 per 10,000 person-years was seen for stroke, whereas for women fewer than 10 years from menopause onset, an increase in 13 strokes per 10,000 person-years was seen (Figure 1).[14]

Based only on observational studies, lower doses of either oral[187] or transdermal[188] estrogen may have less risk of stroke; no clear association with age has been found. No head-to-head data comparing oral to transdermal are available.

### Venous thromboembolism

In a meta-analysis of trials of women who began HT treatment fewer than 10 years after menopause onset or who were aged younger than 60 years, strong evidence of increased risk of VTE was found in the HT group compared with placebo (RR 1.74; 95% CI, 1.11-2.73).[177] Lower doses of oral ET may confer less VTE risk than higher doses,[189] but comparative RCT data are lacking. Micronized progesterone may be less thrombogenic than other progestins.[190] Limited observational data suggest less risk with transdermal HT than oral.[188,190,191] No excess risk has been seen with vaginal estrogen.

### Area of scientific uncertainty and need for randomized, controlled trial data

Although newer observational data are consistent with older observational data, caution is recommended when considering the data that suggest reduced CHD and all-cause mortality when HT is initiated in women aged younger than

60 years and/or who are within 10 years of menopause onset. Clinical decisions need to be individualized by reviewing the data and taking all specific circumstances into account on a case-by-case basis.

### Key points

#### *Coronary heart disease*

- Hormone therapy represents a safe and effective option for the treatment of menopause symptoms when initiated in healthy postmenopausal women aged younger than 60 years or are within 10 years of menopause onset; however, the effects of HT on CHD may vary depending on when HT is initiated in relation to a woman's age and/or time since menopause onset.
- There are older and newer observational data; the Early versus Late Intervention Trial With Estradiol surrogate markers; the Danish Osteoporosis Prevention Study data; and meta-analyses that suggest reduced risk of CHD in women who initiate HT when aged younger than 60 years and/or who are within 10 years of menopause onset.
- In women who initiate HT more than 10 years from menopause onset, and clearly by 20 years, there is potential for increased risk of CHD. The WHI found that both CEE alone and CEE + MPA increased risk of CHD, with potentially greater risk with CEE + MPA, which was significant when initiated in women who were more than 20 years from menopause onset.

#### *Mortality*

- Meta-analyses of RCTs report a significant reduction in all-cause mortality in women who initiate HT when aged younger than 60 years and/or who are within 10 years from menopause onset. However, no protective effect was found in women with initiation more than 10 years from menopause onset.

#### *Stroke*

- A meta-analysis of RCTs of women who initiate HT found no increased risk of stroke in women aged younger than 60 years or who were within 10 years of menopause onset, whereas observational study findings are mixed.
- In subgroup analysis, both the WHI CEE + MPA and CEE-alone studies found a rare, absolute risk of stroke (< 1/1,000 woman-years) in women who initiated HT when aged younger than 60 years, with an increase in women on CEE alone who were within 10 years of menopause onset.
- A meta-analysis of RCTs found an increased risk of stroke in women who initiate HT when aged older than 60 years and/or who are more than 10 years from menopause onset.
- Observational studies across all ages, including meta-analyses, suggest that compared with standard-dose oral HT, lower-dose oral as well as lower-dose transdermal therapy has less effect on risk of stroke, although RCT data are lacking.

#### *Venous thromboembolism*

- Data from the WHI across all ages show increased risk of VTE with oral CEE-alone and CEE + MPA therapy, with higher risk seen in the first 1 to 2 years. For women who initiated HT when aged younger than 60 years, the absolute risk of VTE was rare but significantly increased, as shown in a meta-analysis of studies.
- A meta-analysis of RCTs found higher absolute risks of VTE (with risk of PE) in women initiating HT more than 10 years from menopause onset.
- A meta-analysis of observational studies across all ages suggests that, compared with standard-dose oral HT, transdermal HT as well as lower doses of oral or transdermal HT have less effect on risk of VTE; however, RCT data are lacking.
- There is no evidence of increased risk of VTE with low-dose vaginal ET used for genitourinary symptoms.

#### *Conclusions*

- For healthy symptomatic women aged younger than 60 years or who are within 10 years of menopause onset, the more favorable effects of HT on CHD and all-cause mortality should be considered against potential rare increases in risks of breast cancer, VTE, and stroke. Hormone therapy is not FDA indicated for primary or secondary cardioprotection.
- Women who initiate HT when aged older than 60 years and/or who are more than 10 years, and clearly by 20 years, from menopause onset are at higher absolute risks of CHD, VTE (risk of PE), and stroke than women initiating HT in early menopause.
- Personal and familial risk of CVD, stroke, and VTE should be considered when initiating HT.

## BREAST CANCER

Potential differences may exist in breast cancer risk with ET, EPT, and CEE combined with bazedoxifene therapies. Different types of estrogen or progestogen, as well as different formulations, doses, timing of initiation, durations of therapy, and patient characteristics, may play a role in HT's effect on the breast.

### Estrogen-alone therapy

Compared with women who received placebo, women who received CEE alone in the WHI showed a nonsignificant reduction in breast cancer risk after an average of 7.2 years of randomization, with 7 fewer cases of invasive breast cancer per 10,000 person-years of CEE (HR, 0.79; 95% CI, 0.61-1.02; Figure 1).[14] The nonsignificant pattern of reduction in breast cancer remained evident for up to a median 13 years' cumulative follow-up (HR, 0.80; 95% CI, 0.58-1.11). A statistically significant reduction of breast cancer risk resulting from CEE in the WHI was observed overall in women who were at least 80% compliant with therapy (HR, 0.67; 95% CI, 0.47-0.97) and in women with no prior HT use (HR, 0.65; 95% CI, 0.46-0.92; $P_{\text{for interaction}}$, 0.09) versus prior use of HT.[192] Smaller trials have shown similar nonsignificant reductions in breast cancer with ET[182,193]; however, many but not all observational studies have shown an increased risk.[194]

#### *Longer duration of estrogen-alone therapy use*

There are no RCTs designed or powered for breast cancer to inform our understanding of long durations of ET and the risk of breast cancer. One small, randomized, nonblinded trial found no increased risk of breast cancer for up to 10 years' HT use and

16 years' follow-up, but this was not a primary outcome.[182] Observational studies on long duration are mixed, with some observational studies and meta-analyses reporting an elevated risk of breast cancer with estrogen-alone use for more than 5 years,[195,196] whereas others have not.[197-204]

### Estrogen-progestogen therapy

In the WHI, daily continuous-combined CEE + MPA resulted in increased risk of breast cancer (a rare absolute risk of breast cancer), with 9 additional breast cancer cases per 10,000 person-years of therapy (Figure 1).[14] The increase in breast cancer risk in the WHI for CEE + MPA was found after 5.6 years, significant in nominal statistics (HR, 1.24; 95% CI, 1.01-1.53) but not significant in multiadjusted statistics[14,205] or when adjustments were made for multiple risk factors.[206] The increase appears to begin at 3 years,[207] and the HR remained elevated at 13 years in the postintervention, unblinded follow-up (HR, 1.32; nominal 95% CI, 1.08-1.61).[14] In post hoc subgroup analysis, the increased incidence of breast cancer was limited to women who had prior exposure to HT (HR, 1.85; 95% CI, 1.25-2.80), whereas in women without prior exposure to HT, breast cancer incidence was not significantly affected by CEE + MPA (HR, 1.16; 95% CI, 0.98-1.37) over 11 years' follow-up (including mean intervention time of 5.6 y; $P_{\text{for interaction}}$, 0.03).[205,206] These results should be treated with caution until confirmed elsewhere.

### Attributable risk of breast cancer

The attributable risk of breast cancer in women (mean age, 63 y) randomized to CEE + MPA in the WHI is less than 1 additional case of breast cancer diagnosed per 1,000 users annually,[14] a risk slightly greater than that observed with one daily glass of wine, less than with two daily glasses, and similar to the risk reported with obesity, low physical activity, and other medications.[202,208]

### Early hormone therapy in women at genetic risk for breast cancer

One study provides some reassurance about estrogen given to younger women at higher risk.[209] The Two Sister Study of 1,419 sister-matched cases of breast cancer in women aged younger than 50 years and 1,665 controls showed no increased risk of young-onset breast cancer with use of EPT (OR, 0.80; 95% CI, 0.41-1.59), whereas unopposed estrogen use was associated with a reduced diagnosis of young-onset breast cancer (OR, 0.58; 95% CI, 0.34-0.99)

### Role of progestogens

Some but not all observational data suggest that MP may have less effect on breast cancer risk, whereas more potent progestogens such as MPA may have a more adverse effect,[15,204] but randomized trials are needed.

### Mammographic breast density and estrogen

Different HT regimens may be associated with increased breast density, which may obscure mammographic interpretation.[210] More mammograms and breast biopsies were required in women receiving CEE + MPA in the WHI.[211] In trials up to 2-years' duration, breast tenderness, breast density, and breast cancers were not increased with oral CEE plus bazedoxifene compared with placebo.[212-214]

### Use of hormone therapy in women with genetic risk factors for breast cancer

Limited observational evidence suggests that HT use does not further increase risk of breast cancer in women with a family history of breast cancer or in women after oophorectomy for *BRCA 1* or *2* gene mutation.[215-220]

### Hormone therapy after breast cancer

The use of systemic HT in survivors of breast cancer is generally not advised. Observational studies and randomized trials report both neutral effects[221-230] and increased risk of breast cancer recurrence.[221,228,231] However, low-dose vaginal ET remains an effective treatment option for GSM, with minimal systemic absorption, and treatment may be considered after an initial trial of nonhormone therapies and in consultation with an oncologist, with more concern for women on AIs.[69]

### Area of scientific uncertainty

Breast tissue recently exposed to endogenous estrogen and progesterone may react differently to exogenous hormones than if more distantly exposed, but this theory of estrogen-induced apoptosis of occult tumors remains unproven.[232,233] Different types of estrogen may have different effects on the breast, thus limiting the generalizability of the findings of reduced breast cancer cases with CEE in the WHI.

### Key points

- The effect of HT on breast cancer risk may depend on the type of HT, dose, duration of use, regimen, route of administration, prior exposure, and individual characteristics.
  - Women's Health Initiative results suggest a nonsignificant reduced risk of breast cancer with CEE alone in women with a hysterectomy. Similar nonsignificant reductions for estradiol were observed in two smaller randomized trials (approximately 1,000 perimenopausal and postmenopausal participants), although not in all large observational studies.
  - A rare absolute risk of breast cancer (< 1 additional case/1,000 person-years of use) was seen with daily continuous-combined CEE + MPA in the WHI but not seen in all trials or all subanalyses of the WHI, such as in women without prior HT exposure, but it is consistent with many observational trial results.
  - The potential risk of breast cancer should be included in discussions about benefits and risks of HT.
- Duration of HT use may be an important factor in breast cancer risk, because in some studies, risk increased with longer durations of use.
- Different HT regimens may be associated with increased breast density, which may obscure mammographic

interpretation, leading to more mammograms or more breast biopsies.
- In trials up to 2-years' duration, breast tenderness, breast density, and breast cancers were not increased with oral CEE plus bazedoxifene compared with placebo.
- Limited observational evidence suggests that HT use does not further increase risk of breast cancer in women with a family history of breast cancer or in women after oophorectomy for *BRCA 1* or *2* gene mutation.
- Systemic HT is not recommended for survivors of breast cancer, although selected cases with compelling reasons may be discussed in conjunction with an oncologist after nonhormone options have been unsuccessful.
- For survivors of breast cancer with bothersome GSM symptoms, low-dose vaginal ET, with minimal systemic absorption, may be considered after a failed trial of nonhormone therapies and in consultation with an oncologist. There is a concern even with low-dose vaginal ET for women on AIs because of suppressed estradiol levels.

## ENDOMETRIAL CANCER

Unopposed systemic ET in postmenopausal women with an intact uterus increases the risk of endometrial cancer, which is dose and duration related. More risk is seen earlier with higher doses and persisting for several years after discontinuation.[8] Adequate concomitant progestogen is recommended for women with an intact uterus when using systemic ET.

### After endometrial cancer

Current data, including a meta-analysis based largely on retrospective studies with one RCT, suggest that recurrence and death rates are similar for women who have been treated for early stage, low-risk endometrial cancers (grade 1 and grade 2 endometrioid subtypes with negative estrogen and progesterone receptors) if HT is used.[234-239] However, ET is not recommended for those with more advanced stages or higher risk endometrial cancer.[234,240-244]

### Key points

- Use of HT may be considered in symptomatic women with surgically treated, early stage endometrial cancer (low risk) if other options are not effective, particularly in women with early surgical menopause who are at higher risk of health consequences related to estrogen loss.
- Nonhormone therapies are recommended for women with more advanced cancer or higher-risk endometrial cancer.

## OVARIAN CANCER

There are no convincing data that estrogen initiates or promotes the development of epithelial ovarian cancer. In the WHI, CEE + MPA after a mean of 5.6 years was not associated with an increased risk of ovarian cancer (HR, 1.41; 95% CI, 0.75-2.66), with an absolute risk of 4 cases with CEE alone versus 3 cases with placebo per 10,000 person-years, which remained nonsignificant after a median 13 years' cumulative follow-up (HR, 1.24; 95% CI, 0.83-1.87).[14] Observational data has suggested a possible increased risk of ovarian cancer with long-term HT use in some, but not all, studies, with inconsistent risk across studies.[245-249]

In the UK Million Women Study, attributable risk was calculated at 0.8 additional ovarian cancer cases per 10,000 women per year of HT and 0.6 additional ovarian cancer deaths per 10,000 women per year of HT (defined as very rare risks).[250]

In a 26-year follow-up of the Nurses' Health Study, a significantly increased risk of ovarian cancer was seen with more than 5 years' estrogen use, regardless of current or past use status (RR, 1.41; 95% CI, 1.07-1.86, and RR, 1.52; 95% CI, 1.01-2.27, respectively).[251] Similarly, increased risks were seen in the NIH-AARP Diet and Health Study, with long duration ($\geq$ 10 y) with unopposed estrogen (RR, 2.15; 95% CI, 1.30-3.57) and with combined estrogen plus progestin (RR, 1.68; 95% CI, 1.13-2.49).[252] Neither RCT (WHI) nor observational data show consistent findings of risk with duration of use.

Limited observational data have not found an increased risk of ovarian cancer in women with a family history or a *BRCA* mutation who use EPT.[219]

### After ovarian cancer

A meta-analysis (largely cohort studies) found no increased risk of recurrence or death in women receiving HT after treatment for ovarian cancer.[253] Concern has been raised regarding HT in tumors that are likely to contain ERs, such as low-grade serous carcinomas, and sex cord stromal malignancies, such as ovarian granulosa cell and Sertoli-Leydig ovarian tumors, but data are very limited.

### Key points

- If an association between HT and ovarian cancer exists, the absolute risk is likely to be rare ($<$ 1/1,000) or very rare ($<$ 0.01/1,000) and more likely with longer durations of use.
- Limited observational data have not found an increased risk of ovarian cancer in women with a family history or a *BRCA* mutation who use EPT.
- Concern has been raised regarding HT in tumors that are likely to contain ERs, but data are limited.
- In the WHI, the only randomized trial to date to study ovarian cancer, CEE + MPA had no significant effect on the incidence of ovarian cancer relative to placebo after 5.6 years' active therapy and 13 years' follow-up.
- Observational data are inconsistent, with some but not all studies showing an increased risk after 5 or 10 years.

## COLORECTAL CANCER

Observational studies suggest a reduced risk of colorectal cancer in HT users, particularly if initiated early in menopause.[254] In the WHI across all ages, women on CEE + MPA therapy had a one-third (38%) lower risk of colorectal cancer than those on placebo, 10 cases per 10,000 person-years compared with 16 cases per 10,000 person-years, respectively (HR, 0.62; 95% CI, 0.43-0.89; Figure 1).[14] However, statistical significance was lost when included with the

postintervention period. Further analysis of the WHI data, including postintervention data for women not taking the randomized treatment, found no strong evidence of a protective effect of either CEE + MPA or CEE-alone on risk of colorectal cancer.[14,143,255]

**Key points**

- Observational studies suggest a reduced incidence of colorectal cancer with HT, particularly if initiated early in menopause.
- The use of CEE + MPA across all ages reduced colorectal cancer incidence during treatment.
- Further analysis of the WHI data and postintervention data found no strong evidence of a protective effect of CEE-alone or CEE + MPA on risk of colorectal cancer.

## LUNG CANCER

In the WHI, after a median 13 years' cumulative follow-up across intervention and posttrial follow-up, the incidence of lung cancer did not differ significantly between placebo and treatment with either CEE alone or CEE + MPA.[14,256] Post hoc analysis of the WHI intervention phase showed that women randomized to CEE + MPA had more deaths from non-small cell lung cancer compared with placebo, limited to past and current smokers in women aged older than 60 years.[256,257] Five meta-analyses showed consistency of either no association or a significant reduction in the association of lung cancer with HT.[258-262]

**Key points**

- There appears to be an overall neutral effect of HT on lung cancer incidence.
- Smoking cessation should be encouraged, with increased surveillance for older smokers, including current or past users of HT.

## THERAPEUTIC ISSUES: EXTENDED USE AND RISKS OF DISCONTINUATION

Extended use of HT may benefit women for relief of persistent VMS, prevention of bone loss and fracture, or prevention or treatment of GSM. Vasomotor symptoms have an approximately 50% chance of recurring when HT is discontinued, independent of age and duration of use.[57,58] Bone loss and fracture risk continue to progress throughout aging, as does untreated GSM. With discontinuation of HT, virtually all women will lose BMD, with increased risk of bone fractures[128,263] and excess mortality from hip fracture,[264] although no rebound in fractures was seen in WHI off-treatment,[129] and GSM will recur.

Concern regarding HT use centers around potential risk on the breast or CV system with initiation of HT at an age older than 60 years or more than 10 or 20 years from menopause onset and with increased duration of therapy.

In the WHI, many but not all benefits and risks did not persist beyond 5 to 7 years after therapy was stopped.[265] An elevated risk (rare absolute risk) of breast cancer persisted (HR, 1.28; 95% CI, 1.11-1.48) with CEE + MPA during a median 13-year cumulative follow-up (5.6 y of treatment plus 8.2 y of postintervention observation), but most CVD risk became neutral (Figure 1).[14] During the cumulative follow-up overall, a significant reduction in hip fracture risk persisted (HR, 0.81; 95% CI, 0.68-0.97), and a reduction in endometrial cancer risk was found (HR, 0.67; 95% CI, 0.49-0.91). For women randomized to CEE alone, the reduction in breast cancer risk became significant (HR, 0.79; 95% CI, 0.65-0.97) during the median 13-year cumulative follow-up (7.2 y of treatment plus 6.6 y of postintervention observation).[14,265]

All-cause mortality was neutral after a median 13-year cumulative follow-up for CEE + MPA in the WHI (HR, 1.01; 95% CI, 0.91-1.11) and not significantly reduced in the 50- to 59-year age group when examined separately nor for CEE alone (Figure 1).[14] Similarly, CV mortality was neutral poststopping in all age groups. Finnish population observational studies, using an age-matched standardized Finnish population as controls, suggest that CV mortality, CHD, and stroke mortality may increase in the year after discontinuing HT, but reduced risk was seen during follow-up the next year.[266] Within the first posttreatment year, the risk of cardiac death was significantly elevated (standardized mortality ratio [SMR], 1.26; 95% CI; 1.16-1.37), whereas follow-up for longer than 1 year was accompanied with a reduction (SMR, 0.75; 95% CI, 0.72-0.78). The risk of stroke death in the first posttreatment year was increased (SMR, 1.63; 95% CI, 1.47-1.79), but follow-up for longer than 1 year was accompanied with a reduced risk (SMR, 0.89; 95% CI, 0.85-0.94). This data has not been seen in RCTs and needs validation.

**Key points**

- Decisions about duration of use remain challenging because long-term follow-up data are complicated, especially in regard to breast cancer.
  - Benefits include relief of persistent VMS, prevention of bone loss and fracture, and prevention or treatment of GSM.
  - Concerns include potential risk of breast cancer that may increase with longer duration of use.
  - Coronary heart disease and all-cause mortality may be decreased when HT is initiated closer to menopause onset, with fewer MIs with estrogen alone. However, women who initiate HT when aged older than 60 years or who are more than 10 years, or clearly by 20 years, from menopause onset are at higher absolute risks of CHD, VTE, and stroke than women initiating HT in early menopause.[177]
- Research is needed on benefits and risks of longer durations of use and potential benefits and risks with discontinuation.

## NO GENERAL RULE FOR STOPPING AT AGE 65

Initiation by postmenopausal women aged older than 60 years or who are more than 10 years from menopause onset has complex risks and requires careful consideration, recognizing that there may be well-counseled women aged

older than 60 years who choose to initiate or restart HT. There are only limited nonblinded RCT data that address extended use of ET in younger, recently postmenopausal and perimenopausal women with or without added progestogen.[182] The WHI, the longest adequately powered blinded RCT, was limited to 5 to 7 years of therapy. However, the Beers criteria recommendation to routinely discontinue systemic HT in women aged 65 years and older is not supported by data.

Vasomotor symptoms persist on average 7.4 years and for many for more than 10 years.[43,267] In a study of Swedish women aged older than 85 years, 16% reported hot flashes at least several times per week.[268] Hormone therapy can be considered for prevention of osteoporosis in women aged 65 years and older at elevated risk for fracture when bothersome VMS persist or when HT remains the best choice for QOL reasons or because of lack of efficacy or intolerance of other osteoporosis-prevention therapies. Lower doses of transdermal estrogen may represent a preferable route of ET administration for older or menopausal women who are obese or for those with elevated triglycerides or liver concerns.[269] Ongoing monitoring for new health concerns, periodic trials of lower doses, transdermal formulations, or attempts at discontinuation may help healthcare providers and individual women aged older than 65 years clarify their decisions about continuing HT.

**Key points**

- Considerations for long-term (or extended) use of HT include persistent VMS, QOL issues, or prevention of osteoporosis in women at elevated risk of fracture.
- The safety profile of HT is most favorable when it is initiated by women aged younger than 60 years or within 10 years of menopause onset. In general, initiation by older menopausal women aged older than 65 years requires careful consideration of all individual health benefits and risks.
- Ongoing use of systemic HT by healthy women who initiated therapy within 10 years of menopause onset and without new health risks likely has a safety profile more favorable than that for women initiating HT when aged older than 65 years, although limited long-duration data are available.
- Hormone therapy does not need to be routinely discontinued in women aged older than 60 or 65 years and can be considered for continuation beyond age 65 years for persistent VMS, QOL issues, or prevention of osteoporosis after appropriate evaluation and counseling of benefits and risks. Annual reevaluation, including reviewing comorbidities and periodic trials of lowering or discontinuing HT or changing to potentially safer low-dose transdermal routes, should be considered
- Vaginal estrogen (and systemic if required) or other nonestrogen therapies may be used at any age for prevention or treatment of GSM.

## ECONOMIC CONSIDERATIONS

Greater severity of VMS is associated with lower levels of health status and work productivity and greater use of health resources.[42,270,271] The greatest benefit-risk ratio from pharmacoeconomic analyses in younger women[272] and those from the WHI[273] has been found for the use of HT for menopause-associated VMS,[274] particularly in women who have had a hysterectomy who can use ET.[275]

**Key points**

- Potential reduced costs by treating VMS and related symptoms or preventing bone fractures should be evaluated in the context of evaluation and treatment of AEs and costs of HT medications.
- Initiation of HT closer to menopause onset increased quality-adjusted life-years and was highly cost-effective compared with initiating HT in women aged older than 65 years.
- Indirect economic costs for menopausal women include effects on QOL, work productivity, healthcare resource use, and the potential costs of women who have had a hysterectomy not receiving HT.

## SUMMARY

In the 15 years since the publication of the first results in 2002 from the large WHI HT trials and almost 10 years since the 2007 reanalysis of the results by age and years since menopause, much has been learned, yet much controversy remains.

Hormone therapy formulation, dosing, regimen, route of administration, and the timing of initiation of therapy likely produce different effects, although these have yet to be evaluated in head-to-head RCTs, and there is a significant difference in the benefits and risk of estrogen alone compared with estrogen combined with different progestogens, at least as studied in the WHI. The concept of ''lowest dose for the shortest period of time'' may be inadequate or even harmful for some women. A more fitting concept is ''appropriate dose, duration, regimen, and route of administration.'' Given the more favorable safety profile of estrogen alone, longer durations may be more appropriate. Risk stratification by age and time since menopause is recommended. Transdermal or lower doses of HT may decrease risk of VTE and stroke.

Individualization with shared decision making remains key, with periodic reevaluation to determine an individual woman's benefit-risk profile. Benefits may include relief of bothersome VMS, prevention of bone loss for women at high risk of fracture, treatment of GSM, and improved sleep, well-being, or QOL. Absolute attributable risks for women in the 50- to 59-year-old age group or within 10 years of menopause onset are low, whereas the risks of initiation of HT for women aged 60 years and older or who are further than 10 years from menopause onset appear greater, particularly for those aged 70 years and older or who are more than 20 years from menopause onset, with more research needed on potential risks of longer durations of use.

Women with POI or early surgical or natural menopause have higher risks of bone loss, heart disease, and cognitive or affective disorders associated with estrogen deficiency. In

 

observational studies, this risk appears to approach normal if ET is given until the median age of menopause, at which time treatment decisions should be reevaluated. In limited observational studies, women who are *BRCA*-positive appear to receive similar benefits from receiving HT until the average age of menopause, with minimal to no increased risks of breast cancer seen. There is a paucity of RCT data about the risks of extended duration of HT in women aged older than 60 or 65 years, although observational studies suggest an increased risk of breast cancer with increased duration of HT. Anticipated CHD benefit, based on long-term follow-up of the Nurses' Health Study, may decline with age. It remains an individual decision in select, well-counseled women aged older than 60 or 65 years to continue therapy. There are no data to support routine discontinuation in women aged 65 years.

For select survivors of breast and endometrial cancer, short-term observational data show that use of low-dose vaginal ET for those who fail nonhormone therapy appears safe and greatly improves QOL for many. The use of systemic HT needs careful consideration for survivors of estrogen-sensitive cancer and should only be used for compelling reasons in conjunction with a woman's cancer specialist after failure of nonhormone therapies.

Additional research is urgently needed on the thrombotic risk (VTE, PE, and stroke) of oral versus transdermal therapies. More clinical trial data are needed to confirm or refute the potential beneficial effects of HT on CHD and all-cause mortality when initiated in perimenopause or early postmenopause. Additional areas for research include the breast effects of different estrogen preparations, including the role for SERM therapies; the relationship between VMS and the risk for heart disease and cognitive changes; and the risks of POI and early surgical menopause. Studies are needed on the effects of longer use of low-dose vaginal ET after breast or endometrial cancer; extended use of HT in women who are early initiators; whether the theorized apoptotic effect of 5 years without estrogen provides additional safety with ET; improved tools to personalize or individualize benefits and risks of HT; the role of aging and genetics; and the long-term benefits and risks on women's health of lifestyle modification or complementary or nonhormone therapies if chosen over HT for VMS relief, bone health, and CVD reduction.

## CLINICAL GUIDELINES

Recommendations are provided and graded according to these categories:

- Level I: Based on good and consistent scientific evidence.
- Level II: Based on limited or inconsistent scientific evidence.
- Level III: Based primarily on consensus and expert opinion.

### I. General

- Hormone therapy is the most effective treatment for VMS and GSM and has been shown to prevent bone loss and fracture. (Level I)
- Benefits are most likely to outweigh risks for symptomatic women who initiate HT when aged younger than 60 years or who are within 10 years of menopause onset. (Level I)
- Hormone therapy should be individualized, taking into account the indication(s) or evidence-based treatment goals, consideration of the woman's age and/or time since menopause in relation to initiation or continuation, the woman's personal health risks and preferences, and the balance of potential benefits and risks of HT versus nonhormone therapies or options. (Level III)
- The risks of HT in the WHI and other studies differ overall for ET and EPT, with a more favorable safety profile for ET. (Level II)
- Practitioners should use an appropriate HT type, dose, formulation, route of administration, and duration of use to meet treatment objectives, with periodic reassessment of changes in a woman's health, and anticipated benefits, risks, and treatment goals over time. (Level III)
- Assessment of risk for estrogen-sensitive cancers, bone loss, heart disease, stroke, and VTE is appropriate when counseling menopausal women. (Level III)
- Decision making about HT should be incorporated into a broader discussion of lifestyle modification to manage symptoms and risks for chronic diseases of aging. (Level III)

### II. FDA-approved indications

- ***Vasomotor symptoms***: Hormone therapy is recommended as first-line therapy for bothersome VMS in women without contraindications. (Level I)
- ***Prevention of bone loss***: Hormone therapy may be considered as a primary therapy for prevention of bone loss and fracture in postmenopausal women at elevated risk of osteoporosis or fractures, primarily for women aged younger than 60 years or who are within 10 years of menopause onset. Bone-specific medications are also options; each has potential benefits and risks. (Level I)
- ***Hypoestrogenism:*** For women with hypoestrogenism caused by hypogonadism, POI, or premature surgical menopause without contraindications, HT is recommended until at least the median age of menopause (52 y). (Level II)
- ***The genitourinary syndrome of menopause/Vulvovaginal atrophy***: When isolated genitourinary symptoms caused by menopause are present, low-dose vaginal ET is recommended over systemic ET as first-line medical therapy. (Level I)

### III. Hormone therapy: type, dose, regimen, and duration of use

#### a. Type, dose, and regimen

- The type of HT, specific options, dose, and regimen should be individualized, using shared decision making and determined on the basis of known AE profiles and safety information, along with an individual woman's health risks and personal preferences. (Level III)

- Endometrial protection
  - For women with a uterus using systemic estrogen, endometrial protection requires an adequate dose and duration of a progestogen or use of the combination CEE with bazedoxifene. (Level I)
  - Progestogen therapy is not recommended with low-dose vaginal ET, but appropriate evaluation of the endometrium should be performed if vaginal bleeding occurs, given the limits of safety data. (Level I)
- Lowering doses and/or changing to transdermal HT may be appropriate as women age or in those with metabolic syndromes such as hypertriglyceridemia with risk of pancreatitis or fatty liver. (Level III)
- Compounded bioidentical HT should be avoided, given concerns about safety, including the possibility of overdosing or underdosing, lack of efficacy and safety studies, and lack of a label providing risks. (Level I) If compounded bioidentical HT is prescribed, concerns about safety should be discussed, and the indication for prescribing compounded rather than government-approved bioidentical HT should be documented (allergy, medical need for lower-than-available dose, different preparation). (Level III)

**b. Duration of use**

- Decisions about duration of HT require individualization, including consideration of personal preferences, balancing potential ongoing benefits and risks, and decisions to continue HT for preventive and/or QOL purposes. (Level III)
- In women with POI or early natural or induced menopause or who have had surgical menopause before age 45, and particularly before age 40, and who are otherwise appropriate candidates for HT, early initiation of HT and continued use at least until the median age of menopause (52 y) is recommended. This is based on observational evidence of potential prevention of risks related to early estrogen loss on CHD, osteoporosis, affective disorders, sexual dysfunction, GSM, and lowered cognitive function. (Level II)
- Discussions of duration of therapy should account for the woman's health risks and the more favorable safety profile of CEE alone compared with the CEE + MPA seen in the WHI overall cohort.
  - Decision making about HT duration should take into account the woman's risk (personal or familial) of breast cancer, CHD, VTE, and stroke. (Level III)
  - There is more flexibility for duration of ET use because reduced incidence of breast cancer was found with CEE in the WHI and seen with estradiol in the less-powered, open-label Danish Osteoporosis Prevention Study. This reduced effect has not been shown in all other observational studies, and some show increased risk with long duration of use. (Level II)
  - For EPT, discussions of duration should include information about the potential of increased (rare) risk of breast cancer (absolute risk < 1 additional case/1,000 person-years of use) that began after 3 years of standard-dose CEE + MPA in the WHI. This increased risk was not seen in the subanalysis of the cohort without prior use of HT but was seen in past users. An increased risk of breast cancer over time has not been observed uniformly in other (less-powered) RCTs of HT using various EPT regimens. (Level II)
  - Discussion of benefits and risks of HT should include heart disease and all-cause mortality, particularly the reduced risk if started in women aged younger than 60 years or within 10 years of menopause onset and greater risks if initiated further from menopause onset or in women aged 60 years and older. (Level I)
  - Prevention of bone loss and fracture may be an indication for extended duration in select women after appropriate counseling about benefits and risks (Level III), recognizing that rapid bone loss is seen on discontinuation, but no rebound increase in fracture. (Level I)
  - Benefits and risks after withdrawing HT require consideration when deciding duration of therapy. (Level II)
  - The recommendation using the Beers criteria to routinely discontinue systemic HT in women aged 65 years and older is not supported by data. Decisions regarding whether to continue systemic HT in women aged older than 60 years should be made on an individual basis for quality of life, persistent VMS, or prevention of bone loss and fracture, after appropriate evaluation of medical risks and counseling about potential benefits and risks of HT and with ongoing surveillance. (Level III)

**IV. Special populations**

- ***Early menopause***: For women with POI or premature surgical menopause without contraindications, HT is recommended until at least the median age of menopause (52 y), because observational studies suggest that benefits outweigh the risks for effects on bone, heart, cognition, GSM, sexual function, and mood. (Level II)
- ***Family history of breast cancer***: Observational evidence suggests that use of HT does not further alter the risk for breast cancer in women with a family history of breast cancer, although family history is one risk, among many, that should be assessed when counseling women regarding HT. (Level II)
- ***Women who are* BRCA*-positive without breast cancer***
  - Women who are *BRCA*-positive without breast cancer are at higher genetic risk of breast cancer, primarily ER-negative. For those who have undergone surgical menopause (bilateral oophorectomy), benefits of estrogen to decrease health

risks caused by premature loss of estrogen need to be considered. (Level II)
  - On the basis of limited observational studies, consider offering systemic HT until the median age of menopause (52 y). Discussions about longer use should be individualized. (Level II)

**V. Breast and endometrial cancer survivors—systemic or vaginal hormone therapy**

- Bothersome VMS—consideration of systemic HT
  - Survivors of endometrial and breast cancer with bothersome VMS should be encouraged to consider nonhormone therapies that have been studied in RCTs in this population and found to be effective. (Level III)
  - For survivors of endometrial cancer with prior early endometrial cancer treated with hysterectomy and with bothersome VMS not well controlled with nonhormone therapies, decisions about use of systemic HT should be made in conjunction with an oncologist. (Level III)
  - For survivors of breast cancer, particularly estrogen-sensitive cancers, for which systemic HT is generally not offered, decisions about systemic HT should be made for compelling reasons after nonhormone or complementary options have been unsuccessful and after detailed counseling, with shared decision making and in conjunction with an oncologist. (Level III)
- Bothersome GSM symptoms—consideration of low-dose vaginal ET
  - Low-dose vaginal ET used for the GSM has minimal systemic absorption (blood levels in the postmenopause range) and, on the basis of limited observational data, appears to hold minimal to no demonstrated risk for recurrence of endometrial or breast cancer. (Level II)
  - For women with early endometrial cancer who have completed successful treatment, including hysterectomy, consideration may be given for low-dose vaginal ET for relief of GSM if nonhormone options are not successful, based on limited short-term safety trials. (Level II)
  - For women who are survivors of breast cancer, decisions about low-dose vaginal ET should involve the woman's oncologist, particularly for women using AIs who have lowered overall estradiol levels. (Level III)

**Conclusion—overall benefit-to-risk ratio**

- Hormone therapy is the most effective treatment for VMS and GSM and has been shown to prevent bone loss and fracture.
- Risks of HT differ for women, depending on type, dose, duration of use, route of administration, timing of initiation, and whether a progestogen is needed. Treatment should be individualized using the best available evidence to maximize benefits and minimize risks, with periodic reevaluation for the benefits and risks of continuing HT.
- For women aged younger than 60 years or who are within 10 years of menopause onset and have no contraindications, the benefit-risk ratio appears favorable for treatment of bothersome VMS and for those at elevated risk of bone loss or fracture. Longer duration may be more favorable for ET than for EPT, based on the WHI RCTs.
- For women who initiate HT more than 10 or 20 years from menopause onset or when aged 60 years or older, the benefit-risk ratio appears less favorable than for younger women because of greater absolute risks of CHD, stroke, VTE, and dementia.
- For GSM symptoms not relieved with over-the-counter or other therapies, low-dose vaginal ET is recommended.

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