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# Management of Menopause and the Role For Hormone Therapy

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JOANN V. PINKERTON, MD, FACOG, NCMP,\*  
EDWARD A. CONNER, MD,\*  
and ANDREW M. KAUNITZ, MD, FACOG, NCMP†

\*Department of Obstetrics and Gynecology, Division of Midlife Health, University of Virginia Health System, Charlottesville, Virginia; and †University of Florida College of Medicine-Jacksonville, Jacksonville, Florida

**Abstract:** Hormone therapy remains the most effective treatment for menopausal symptoms but decisions are complex, requiring an assessment of benefits and risks and determination of best treatment type, dose, and duration. Benefits exceed risks for most women with bothersome menopausal symptoms or high risk for fracture if initiated under age 60 years or within 10 years since menopause. Long-term mortality and safety data from the Women's Health Initiative is reassuring, with no increase in deaths from cardiovascular disease or cancer compared with placebo after 18 years of follow-up and a trend towards less mortality in those who initiate hormone therapy ages 50 to 59 years.

**Key words:** menopausal hormone therapy, menopause, hormone therapy, hot flashes, Women's Health Initiative, vaginal estrogen

*Correspondence:* JoAnn V. Pinkerton, MD, FACOG, NCMP, Department of Obstetrics and Gynecology, Division Director Midlife Health, University of Virginia Health System, PO Box 801104, Charlottesville, VA. E-mail: jvp9u@virginia.edu

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## Key Points

- (1) Hormone therapy (HT) at menopause remains the most effective treatment for menopausal symptoms, but the decision to use HT is complex and requires balancing of the benefits and risks for the individual woman and determination of best type, route, dose, and duration.
- (2) HT benefits exceed risks for symptomatic women who are generally healthy and free of contraindications to HT if initiated under age 60 years or within 10 years since menopause.
- (3) Long-term mortality and safety data from the large, randomized Women's Health Initiative (WHI) is reassuring with no increase in deaths from cardiovascular disease (CVD) or cancer compared with placebo after 18 years of follow-up and a trend towards less

mortality in those who initiate HT aged 50 to 59 years.

*Controversy—what have we learned about the benefits and risks of hormone therapy since the early results of the large, randomized Women’s Health Initiative Trial? Is estrogen safe, and if so, for whom and for how long?*

### **Clinical Vignette**

A 53-year-old menopausal female presents to your office with bothersome menopausal hot flashes, intermittent night sweats, and sleep disruption. Her family history is significant for a mother with a hip fracture at age 80 and a maternal aunt with breast cancer. She is interested in starting HT but remembers hearing concerns about HT causing heart disease, breast cancer, and memory loss.

### **Introduction**

In 2002, the initial published findings from the WHI suggested that HT was associated with more harm than benefit with increased risk of CVD, dementia, breast cancer, stroke, and venous thromboembolic (VTE) disease.<sup>1</sup> In 2004, findings from the estrogen-alone arm of the WHI showed fewer breast cancer cases than placebo.<sup>2</sup> In 2007, results were stratified by age and time from menopause showing that risks and mortality were less for women under age 60 and within 10 years from menopause.<sup>3</sup> In 2017, The North American Menopause Society Hormone Therapy Position Statement was published to increase evidence-based decision making about HT for symptomatic menopausal women and those at elevated risk of fracture (Table 1). In 2017, 18-year follow-up data showed no increased mortality and a trend towards fewer heart events and fewer deaths in women in the WHI who initiated HT aged 50 to 59 and within 10 years of menopause.<sup>5</sup>

### **WHI Findings Regarding Mortality With Long-Term Follow-Up**

Mortality represents an important measure of the safety of menopausal HT. In 2017, Manson et al<sup>5</sup> published an important report describing overall and cause-specific mortality with 18-year follow-up. Overall mortality was almost identical among women randomized to estrogen-progestin therapy (EPT) or estrogen therapy (ET) HT (27.1%) and those randomized to placebo (27.6%). Among the youngest WHI participants (those aged 50 to 59 y at baseline), overall mortality was lower compared with the oldest participants (aged 70 to 79 y). With respect to cardiovascular mortality, cumulative mortality was essentially identical in the HT and the placebo group ( $P=0.98$ ). With respect to overall cumulative cancer mortality, deaths occurred in similar proportions of the HT and placebo groups. These landmark findings provide reassurance regarding the overall safety of menopausal HT, particularly when initiated by younger menopausal women.

### **Cardiovascular Disease (CVD) [Coronary Heart Disease (CHD) and Stroke]**

Observational studies suggested that HT was beneficial for both primary and secondary prevention of CHD, but this was not seen in the larger randomized controlled trial (RCT) such as The Heart and Estrogen/Progestin Replacement Study (HERS) trial, parts I and II, and the WHI Trial.<sup>4</sup> This discordance between observational studies and RCTs findings is now felt related to age and timing of initiation of HT relative to the onset of menopause. There was a suggestion of a protective effect in the women aged 50 to 59 years or within 10 years of menopause.

Two smaller studies evaluated the timing hypothesis. No significant association between HT (oral or transdermal) and the

**TABLE 1. Key Points 2017 Hormone Therapy Position Statement of The North American Menopause Society**


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<p>Hormone therapy at menopause remains the most effective treatment for bothersome VMS and has been shown to prevent bone loss and reduce fractures</p> <p>Benefits are most likely to outweigh risks for the treatment of VMS for menopausal women without contraindications and for the prevention of bone loss and fractures in women at higher risk who are under age 60 or within 10 y of menopause when they initiate hormone therapy</p> <p>Significant reduction in all-cause mortality was seen for women who initiated hormone therapy when younger than 60 y and/or within 10 y from menopause onset. However, no protective effect was found in women with initiation &gt; 10 y from menopause onset</p> <p>Risks of hormone therapy vary depending on the formulation, dose, duration of use, route of administration, age and time from menopause at initiation, and whether a progestogen is needed</p> <p>Treatment should be individualized based on women's health risks and treatment goals using the best available evidence with periodic reevaluation as women age</p> <p>Compounded non-FDA approved hormone therapies are lacking adequate safety and efficacy data. Concerns include minimal government monitoring or regulation and unique risks associated with compounding of sterility; impurities; overdosing or underdosing, the potential of increased breast or uterine cancer risk, and lack of a label providing warnings about potential risks of hormone therapy</p> <p>For women who initiate hormone therapy at older ages (&gt; 60 or 70 y) or &gt; 10 or 20 y from menopause, the benefit-risk ratio is less favorable as these women have higher absolute risks of heart disease, stroke, VTE, and dementia in women and risk of CHD appears increased</p> <p>Hormone therapy does not need to be routinely discontinued as women age or if they are older than 65 y. If continuation is considered for longer durations or beyond 60 or 65 y for persistent VMS, quality of life or prevention of osteoporosis, women need appropriate evaluation and counseling of benefits and risks, with periodic reevaluation as new health risks arise or new information becomes available</p> <p>For genitourinary syndrome of menopause not relieved with over the counter lubricants or vaginal moisturizers or other therapies, low-dose vaginal hormone therapy (estrogen or intravaginal DHEA) or other nonestrogen therapies are recommended</p>	<p>Hormone therapy at menopause remains the most effective treatment for bothersome VMS and has been shown to prevent bone loss and reduce fractures</p> <p>Benefits are most likely to outweigh risks for the treatment of VMS for menopausal women without contraindications and for the prevention of bone loss and fractures in women at higher risk who are under age 60 or within 10 y of menopause when they initiate hormone therapy</p> <p>Significant reduction in all-cause mortality was seen for women who initiated hormone therapy when younger than 60 y and/or within 10 y from menopause onset. However, no protective effect was found in women with initiation &gt; 10 y from menopause onset</p> <p>Risks of hormone therapy vary depending on the formulation, dose, duration of use, route of administration, age and time from menopause at initiation, and whether a progestogen is needed</p> <p>Treatment should be individualized based on women's health risks and treatment goals using the best available evidence with periodic reevaluation as women age</p> <p>Compounded non-FDA approved hormone therapies are lacking adequate safety and efficacy data. Concerns include minimal government monitoring or regulation and unique risks associated with compounding of sterility; impurities; overdosing or underdosing, the potential of increased breast or uterine cancer risk, and lack of a label providing warnings about potential risks of hormone therapy</p> <p>For women who initiate hormone therapy at older ages (&gt; 60 or 70 y) or &gt; 10 or 20 y from menopause, the benefit-risk ratio is less favorable as these women have higher absolute risks of heart disease, stroke, VTE, and dementia in women and risk of CHD appears increased</p> <p>Hormone therapy does not need to be routinely discontinued as women age or if they are older than 65 y. If continuation is considered for longer durations or beyond 60 or 65 y for persistent VMS, quality of life or prevention of osteoporosis, women need appropriate evaluation and counseling of benefits and risks, with periodic reevaluation as new health risks arise or new information becomes available</p> <p>For genitourinary syndrome of menopause not relieved with over the counter lubricants or vaginal moisturizers or other therapies, low-dose vaginal hormone therapy (estrogen or intravaginal DHEA) or other nonestrogen therapies are recommended</p>
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Data from the NAMS 2017 Hormone Therapy Position Statement.<sup>4</sup>

CHD indicates coronary heart disease; DHEA, dehydroepiandrosterone; FDA, Food and Drug Administration; VMS, vasomotor symptoms; VTE, venous thromboembolism.

cardiovascular benefit was seen for women within 3 years of menopause, whereas for women who initiated at age 60 years or older or > 10 years from menopause, both ET and EPT increased CHD risk.<sup>6</sup> Oral estradiol therapy was associated with less progression of subclinical atherosclerosis (carotid intima-media thickness) if therapy was initiated within 6 years after menopause but not when initiated  $\geq 10$  years from menopause.<sup>7</sup> Thus age and time from menopause at the initiation of HT matter as excess CHD risk appears to be confined to postmenopausal women older than age 60 or those who are > 10 years postmenopause leading to the development of a “timing hypothesis” with less risk at menopause.<sup>3,5</sup>

## STROKE

Data on stroke have been conflicting. In the combined analysis of the 2 WHI trials,

EPT and estrogen alone (ET), an increased risk of stroke was found but did not vary by age or time since menopause.<sup>4</sup> For women aged 50 to 59, however, there was no absolute increase in stroke due to low baseline risk. The absolute risks of stroke are lower in women under age 60 and appear lower with low-dose transdermal products, but RCT data are lacking.<sup>4</sup>

## VTE Risk Including Pulmonary Embolism

VTE is a rare but serious risk associated with HT which appears to depend on the route of administration. Oral estrogens increase the risk of VTE especially during the first year of treatment and past users revert to risk similar to that of nonusers.<sup>8</sup> The increased thrombosis risk seen with

oral estrogen alone or combined with progestin may be due to oral estrogen's first-pass liver metabolism, with the creation of a procoagulant state. Transdermal estradiol bypasses the first-pass effect and, at least in observational data, has shown less risk of VTE.<sup>4</sup> A recent large observational United Kingdom<sup>9</sup> also found an increased risk for VTE with oral estrogen alone [higher risk with conjugated equine estrogen (CEE) than estradiol], and with combined oral HT [highest risk for combined CEE with medroxyprogesterone acetate (MPA)] with higher doses of oral estrogen associated with higher VTE risks. However, transdermal HT was not associated with an increased risk for VTE. For women at risk of VTE such as those with increasing age, obesity, cancer, or recent surgery, a safer HT regimen appears to be avoiding oral estrogen combined with synthetic progestins and instead of using transdermal estradiol combined with oral micronized progesterone.<sup>8</sup>

#### **PULMONARY EMBOLISM**

An increased risk of pulmonary embolism was seen in both arms of the WHI (oral CEE with or without MPA progestin). Although rare, pulmonary embolism accounts for one third of the excess potentially fatal events associated with HT use.<sup>10</sup>

#### ***Diabetes Mellitus***

Large, RCTs suggest that HT reduces the incidence and delays the onset of type 2 diabetes in postmenopausal women, but mechanisms remain unclear. At the time of menopause, 17 $\beta$ -estradiol deficiency appears to increase the risk of type 2 diabetes. Most long-term studies suggest that HT at menopause increases lean body mass and reduces abdominal fat deposition. There appears to be a beneficial effect of HT on pancreatic cells, skeletal muscle, liver and adipose tissue associated with decreases in abdominal fat, fasting glucose and insulin levels,

improved islet b cell function and insulin secretion, with improved glucose control and insulin sensitivity, all leading to a reduced incidence of diabetes.<sup>11</sup> Despite the potential benefits of HT, the effect of HT on diabetes prevention has not been a primary outcome in large randomized trials and thus HT is neither recommended nor approved for the prevention of type 2 diabetes.<sup>4,11</sup>

#### ***Mood and Cognition***

Menopause symptoms often overlap with depression. First-line treatments for mood disorders at menopause include antidepressants and psychotherapy. Estrogen has been shown to improve mood during perimenopause, particularly in women with vasomotor symptoms (VMS), but not during menopause. Synthetic progestins may worsen mood, whereas less effect is seen with progesterone.<sup>12</sup>

The research on HT and cognition is complex and somewhat contradictory. The Women's Health Initiative Memory Study (WHIMS) found that CEE plus the synthetic progestin did not improve cognitive function; instead, HT was associated with increased dementia for women over the age of 65.<sup>13</sup> Neither CEE nor transdermal estradiol improved cognitive function.<sup>14</sup> For women with the APOE4 gene, estradiol was associated with lower levels of  $\beta$ -amyloid plaques seen in Alzheimer disease compared with CEE or placebo.<sup>15</sup> A protective benefit was seen in women aged 47 to 56 years who used HT over 10 years with a decreased risk of Alzheimer disease compared with those who used it just at menopause.<sup>16</sup>

In terms of cognition, current recommendations<sup>4</sup> are that there is no clear benefit or risk to initiating HT within a few years of menopause. It is possible that HT may have a benefit if initiated during the critical window around menopause and continued for over 10 years,<sup>16</sup> but this has not been confirmed in RCTs.

## ***Nonprogestogen Option For Women With a Uterus: Tissue-Selective Estrogen Complex (Conjugated Estrogens/Bazedoxifene)***

Bazedoxifene has a highly antiproliferative impact on the endometrium and can be safely combined with CEE to protect the endometrium without the need for a progestogen. The combination of CEE with bazedoxifene demonstrated a reduction in hot flush frequency and severity, prevention of bone loss with a reduction in bone turnover markers (no fracture data available), and improvement in vaginal maturation index, sleep and menopause-specific quality of life.<sup>4</sup> Rates of vaginal bleeding, breast density, and breast pain and tenderness were similar to placebo and favorable compared with an active comparator CEE 0.45/MPA 1.5 mg. There was a minimal increase in endometrial thickness, (<1 mm), no increase in endometrial hyperplasia (<1%), endometrial polyps or endometrial cancer compared with placebo with a bleeding pattern similar to placebo. In phase 3 RCTs, rates of cardiovascular events, cerebrovascular events, cancers (breast, endometrial, ovarian) and mortality rates were similar to placebo.<sup>17</sup> Appropriate candidates for this formulation include women with bleeding (after appropriate evaluation), breast tenderness, or unpleasant mood changes associated with conventional EPT.

## ***Concerns About Compounded Bioidentical Hormone Therapies***

Despite media and celebrity hype about safety and effectiveness of custom-compounded HT, including use of high dose estrogen and testosterone pellets, compounded hormone therapies are neither Food and Drug Administration approved nor Food and Drug Administration

monitored. They lack adequate safety and efficacy data. Concerns regarding compounded HT include risks associated with lack of sterility, impurities; and accuracy of dosing including potential for overdosing or underdosing. Overdosing of estrogen or underdosing of progesterone leads to increased potential cancer risk with reports of increased endometrial cancer.<sup>4</sup> The lack of a label providing warnings about potential risks of HT and lack of a boxed warning does not mean that these therapies are safer than government-approved therapies.<sup>4</sup>

## ***Special Populations***

### **EARLY MENOPAUSE INCREASES HEALTH RISKS**

Observational studies have found that women with early menopause without the use of HT until the usual age at menopause have an increased risk of atherosclerosis and CVD, mood and cognition changes, loss of sexuality, and Parkinson disease.<sup>4</sup> For women with hypoestrogenism, primary ovarian insufficiency, or early menopause (natural, surgical, or induced) without contraindications, HT is recommended at least until the median age of menopause (52 y).<sup>4</sup> Early initiation of HT reduces the risk for osteoporosis and related fractures, genitourinary syndrome of menopause (GSM), and dyspareunia. For women under age 40, higher doses may be needed to provide symptom relief or protection against bone loss.<sup>4</sup>

### **HIGH RISK OF BREAST CANCER—FAMILY HISTORY BREAST CANCER OR BRCA-POSITIVE WITHOUT CANCER**

Family history of breast cancer should be taken into account when deciding and counseling about use, type, and duration of HT.<sup>4</sup> Observational studies suggest that HT does not further increase the risk for breast cancer in women with a family history of breast cancer. For *BRCA*-positive women

with intact breasts without a history of cancer and who have undergone risk-reducing bilateral salpingo-oophorectomy, observational data<sup>18</sup> suggest that systemic HT taken to the average age of menopause does not further increase breast cancer risk. However, in this high-risk group, use, type, and duration of HT should be considered on an individual basis and reevaluated periodically.<sup>4</sup>

#### **PRIOR HISTORY OF ENDOMETRIAL AND BREAST CANCER WITH BOTHERSOME VMS**

HT is not generally recommended for women who have had prior estrogen-sensitive cancers, including breast and endometrial cancer. For these women, non-HT options include low-dose antidepressants (serotonin reuptake inhibitors and norepinephrine reuptake inhibitors, or clonidine or gabapentanoids) or complementary therapies (cognitive behavioral therapy or hypnosis). For selected well-counseled women with early treated estrogen-sensitive cancers and persistent severe VMS, off-label use of HT may be considered but should include input from the woman's oncologist, recognizing the potential risk of stimulating estrogen-sensitive cancer cells.<sup>4</sup>

### ***Longer Duration Use of Systemic Menopausal Hormone Therapy***

Obstetrician-gynecologists frequently see women interested in long-term use of HT. Because VMS may persist for many years, short term (eg, up to 5 y of use) may not be long enough to address bothersome VMS in some women. Despite the inclusion of oral and transdermal HT in the American Geriatric Society's Beer's Criteria list of potentially inappropriate medications for the elderly, the evidence is lacking to support routine discontinuation of HT after age 60 or 65.<sup>4,19</sup>

Available data to inform decisions are limited as clinical trials have not assessed the use of HT for > 10 years. Decisions regarding long-term use of HT should be individualized for indications such as persistent VMS, bone loss in women at elevated risk of fracture, or quality of life reasons, with shared decision making, documentation, and periodic reevaluation, including assessment for the development of comorbidities.

Standard dose (eg, micronized estradiol 1.0 mg, CEE 0.625 mg, or transdermal estradiol 0.05 mg) HT prevents osteoporosis and fractures.<sup>4</sup> When prevention of osteoporosis represents the only indication for use of HT in aging menopausal women, lower than standard HT doses (eg, micronized estradiol 0.5 mg, CEE 0.3 or 0.45 mg, transdermal estradiol 0.025 or 0.0375 mg, and CEE 0.45 mg combined with bazedoxifene 20 mg) are effective at preventing bone mineral density loss, with less risk.<sup>19</sup> An even lower dose tested in women over the age of 60, weekly estradiol 0.14 mg patch, also prevented bone loss despite serum estradiol levels remaining in the menopausal range. Unlike with bisphosphonates, the decline in bone mineral density occurs rapidly after discontinuation of HT.

Although RCTs are not available, observational studies<sup>9</sup> suggest less risk of VTE with transdermal compared with oral ET. Accordingly, the transdermal route thus may have safety advantages for women requesting longer durations of estrogen therapy or EPT.

Whether HT is stopped abruptly, or tapered gradually, VMS often recur in women stopping HT. Slowly lowering the dose over months or years may facilitate dose reduction while minimizing recurrent bothersome VMS. Long-term users who note a loss of well-being after discontinuing HT may benefit from resuming use of low-dose systemic HT, whereas those who note symptoms of GSM are candidates low-dose vaginal ET or other therapies for GSM.<sup>4</sup>

## **Extended Duration Use of Systemic HT and Dementia**

Two large observational studies found that, among women who initiated HT soon after menopause and continued it for > 10 years, risk of being diagnosed with dementia was lower compared with women who had never use of HT.<sup>16,20</sup> The North American Menopause Society<sup>4</sup> advises that prevention of dementia should not be considered an indication for use of HT, however, the position statement recognizes that there is some tentative support from observational studies that initiation of HT soon after the onset of menopause might reduce future risk for dementia.<sup>4</sup> For recently menopausal women without contraindications, who request to take HT specifically to prevent loss of cognitive ability, counseling should include health risks of HT use and that, due to conflicting data, prevention of dementia is not an established indication for using systemic HT.

## **Types of Progestogens**

MPA and levonorgestrel are more likely to attenuate estrogen's beneficial effect on glucose control, whereas norethindrone acetate and micronized progesterone are more likely to be neutral. Differences in lipid levels, coagulation factors, mood, bloating and effect on breast density are also seen. Norethindrone acetate appears to suppress the endometrium more than progesterone or MPA. Drospirenone possesses anti-aldosterone activity similar to that of spironolactone with less bloating and bleeding compared with other progestins. Because of its risk of hyperkalemia, drospirenone should not be used in patients with renal insufficiency, hepatic dysfunction, or adrenal insufficiency.

## **GSM**

Vulvovaginal (vaginal dryness, dyspareunia, vulvar pain) or urinary symptoms (urinary urgency, recurrent urinary tract

infections) may be relieved using over the counter vaginal moisturizers (used regularly) and lubricants (used with sexual activity). If these do not provide adequate symptomatic relief, and there is no indication for systemic HT, low-dose vaginal estrogen therapies, intravaginal dehydroepiandrosterone, or the third-generation selective estrogen receptor modulator (SERM), oral ospemifene which is approved for relief of postmenopausal dyspareunia, are recommended. Ospemifene is particularly helpful for women who want to avoid systemic estrogen but need oral therapy due to difficulty with vaginal administration. Hot flashes occur more frequently with ospemifene than placebo, but not severe enough to lead to discontinuation. A small increase in venous thrombosis was seen, with minimal impact on breast cancer or endometrial hyperplasia. Intravaginal dehydroepiandrosterone is a non-estrogen prohormone used daily for relief of dyspareunia. Its metabolites, testosterone, and estradiol, were slightly higher in treated women compared with those receiving placebo but within the normal postmenopausal range.

Minimal absorption has been found with low-dose vaginal estrogen.<sup>4</sup> The American College of Obstetricians and Gynecologists<sup>21</sup> and the North American Menopause Society<sup>4</sup> indicate that low-dose vaginal ET may be used as long as needed, including indefinitely, and do not recommend routine use of concomitant progestin therapy for endometrial protection during long-term use vaginal ET in women with an intact uterus. However, trials evaluating the endometrial safety of vaginal estrogen administration for > 1 year are not available. Endometrial evaluation is appropriate for women reporting vaginal spotting or bleeding during the use of low-dose vaginal estrogen. In women not reporting bleeding, routine endometrial surveillance is not recommended.<sup>4</sup> Despite different risks of low-dose local vaginal estrogen and systemic HT, the same warnings,

contraindications, and adverse events are found in the boxed warning. In contrast with package labeling, 2 large observational studies of postmenopausal women conducted in the United States, the WHI prospective observational cohort study (median duration of vaginal estrogen use 2 years) and the Nurse's Health prospective observational cohort study (mean duration of use, 3 years) found that use of vaginal estrogen was not associated with an elevated risk of endometrial, breast or colorectal cancer, CHD or VTE.<sup>22,23</sup>

#### **PRIOR EARLY-STAGE ENDOMETRIAL OR BREAST CANCER WITH BOTHERSOME GSM**

On the basis of limited observational data, minimal to no demonstrated risk for recurrence of early-stage endometrial or breast cancer has been found using low-dose vaginal estrogen, but decisions should be made in conjunction with an oncologist, after the failure of nonhormone options.<sup>24</sup>

### ***Potential Risks of Hormone Therapy***

Major concerns about HT include the potential risk of breast cancer seen with combination EPT (< 1/1000), endometrial hyperplasia or cancer if estrogen effect is inadequately opposed, VTE, and biliary issues with oral estrogen. Risks across ages include myocardial infarction, CVD, stroke, and dementia.

### ***Principles Guiding Prescribing of Hormone Therapies For Menopausal Women***

Systemic HT is available in various formulations and doses as oral pills, transdermal patches, gels, sprays, lotions, and a vaginal ring. Estrogen alone can be used in women who have had a hysterectomy. In women with an intact uterus who are taking estrogen, a progestogen (synthetic

progestins or micronized progesterone) is needed to reduce the risk of endometrial cancer from estrogen alone. Progestogens are used either cyclically for 10 to 14 days each month or used daily in a continuous combined regimen with estrogen.<sup>5</sup> Less well studies are off-label use of intermittent progestogen therapy or levonorgestrel intrauterine devices. The novel tissue-selective estrogen complex—consists of conjugated estrogen combined with the SERM bazedoxifene, a progestogen free HT for women with a uterus provides relief of hot flashes and prevention of bone loss while protecting against estrogen-stimulated endometrial hyperplasia. Transdermal estrogen therapies may be safer for women who are obese, have existing hypertension, hyperlipidemia, metabolic syndrome or diabetes. Low doses of oral and transdermal HT are effective against VMS with lower risks of VTE and stroke compared with conventional doses (Table 2).

#### **MINIMIZE RISKS OF HORMONE THERAPY**

The risks of HT can be minimized through the use of lower doses of HT as well as the use of micronized progesterone instead of synthetic progestins. Transdermal therapies (patches, gels, spray, lotions, and ring) avoid hepatic first-pass effect with the resultant increased hepatic production of clotting proteins. Accordingly, the transdermal route of administration for estradiol appears to avoid the elevated risk of venous thrombosis caused by oral estrogen. The use of the combination of CEE paired with the tissue SERM bazedoxifene provides endometrial protection without the need for a progestogen.

### ***Case Discussion***

Our 53-year-old symptomatic menopausal female meets the criteria for consideration of HT. She is under age 60 and within 10 years of menopause. Benefits

**TABLE 2. How to Decide on Formulation and Route of Therapy?**


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Women who may benefit from HT include women who are under age 60 y or within 10 y of menopause, with bothersome menopausal candidates or at elevated risk of bone loss and fractures. If the risk of CVD is low, either oral or transdermal therapy could be used

For women without a uterus, estrogen-alone may be beneficial for prevention of coronary heart disease and could reduce the incidence of diabetes. However, type 2 diabetes is considered a CVD risk factor in women

For women with a uterus, similar benefits may be obtained but consider the use of progestogens which minimize the impact on coagulation and insulin sensitivity (safer choices might include NETA, progesterone)

For women at higher risk of breast cancer, dense breasts, breast tenderness or history of bleeding, estrogen with a neutral progestogen or the combination of oral conjugated estrogen/bazedoxifene would be good choices

For women at higher risk of CVD, diabetes or who are obese, transdermal estradiol would be a better choice as there appears to be less VTE risk

For normal-weight women with diabetes, an oral route of estrogen delivery should be considered only if the 10-year CVD risk is low

Oral estrogens have beneficial effects on high-density and low-density lipoprotein cholesterol and may be prescribed in normal weight otherwise low-risk women with type 2 diabetes because they produce a stronger improvement in insulin sensitivity

For women with diabetes and a moderate 10-year risk of CVD, or/and in obese women with diabetes, transdermal E2 is preferred, along with progestogens which minimize the impact on coagulation and insulin sensitivity. In contrast with oral CEE, transdermal E2 does not elevate inflammatory markers or triglycerides and does not appear to increase the risk of VTE

In women 60 y of age or older or > 10 y past menopause onset, initiation of HT is associated with more adverse events and careful consideration should be given to risk factors

For women who are candidates for extended duration of use due to persistent VMS, elevated risk of osteoporosis or QOL concerns, consider lowering doses over time, use of transdermal or micronized progesterone or the use of nonapproved intermittent progestogen dosing with periodic reevaluation

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Data from the NAMS 2017 Hormone Therapy Position Statement.<sup>4</sup>

CEE indicates conjugated equine estrogen; CVD, cardiovascular disease; HT, hormone therapy; NETA, norethisterone acetate; QOL, quality of life; VMS, vasomotor symptoms; VTE, venous thromboembolism.

include a reduction in hot flashes and night sweats with improved sleep. Bone loss and fracture will be prevented while taking HT, although bone density loss will recur once she discontinues HT. She may have a benefit of reduced CVD or memory disorders, but neither is a primary indication for HT. She does not have a first degree relative with breast cancer nor a breast cancer genetic risk, allowing more choice for HT. With a uterus, she will need protection against estrogen-stimulated endometrial hyperplasia. She has no contraindications to oral HT and is interested in bioidentical HT and was offered an oral estradiol/progesterone combination. If she were more fearful of breast cancer, we could offer conjugated estrogen with bazedoxifene which has been shown to be neutral

on the breast in clinical studies up to 2 years. As she ages, we will encourage changing to transdermal and decreasing doses to minimize risks.

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