**Position Statement**

# AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY POSITION STATEMENT ON MENOPAUSE–2017 UPDATE

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## EXECUTIVE SUMMARY

This American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) Position Statement is designed to update the previous menopause clinical practice guidelines published in 2011 but does not replace them. The current document reviews new clinical trials published since then as well as new information regarding possible risks and benefits of therapies available for the treatment of menopausal symptoms. AACE reinforces the recommendations made in its previous guidelines and provides additional recommendations on the basis of new data. A summary regarding this position statement is listed below:

- New information available from randomized clinical trials and epidemiologic studies reported after 2011 was critically reviewed.
- No previous recommendations from the 2011 menopause clinical practice guidelines have been reversed or changed.
- Newer information enhances AACE's guidance for the use of hormone therapy in different subsets of women.
- Newer information helps to support the use of various types of estrogens, selective estrogen-receptor modulators (SERMs), and progesterone, as well as the route of delivery.

- Newer information supports the previous recommendation against the use of bioidentical hormones.
- The use of nonhormonal therapies for the symptomatic relief of menopausal symptoms is supported.
- Newer information enhances AACE's guidance for the use of hormone therapy in different subsets of women.
- Newer information helps to support the use of various types of estrogens, SERMs, and progesterone, as well as the route of delivery.
- Newer information supports the previous recommendation against the use of bioidentical hormones.
- The use of nonhormonal therapies for the symptomatic relief of menopausal symptoms is supported.

**New recommendations in this position statement include:**

1. **Recommendation:** the use of menopausal hormone therapy in symptomatic postmenopausal women should be based on consideration of all risk factors for cardiovascular disease, age, and time from menopause.
2. **Recommendation:** the use of transdermal as compared with oral estrogen preparations may be considered less likely to produce thrombotic risk and perhaps the risk of stroke and coronary artery disease.
3. **Recommendation:** when the use of progesterone is necessary, micronized progesterone is considered the safer alternative.
4. **Recommendation:** in symptomatic menopausal women who are at significant risk from the use of hormone replacement therapy, the use of selective serotonin re-uptake inhibitors and possibly other nonhormonal agents may offer significant symptom relief.
5. **Recommendation:** AACE does not recommend use of bioidentical hormone therapy.
6. **Recommendation:** AACE fully supports the recommendations of the Comité de l'Évolution des Pratiques

en Oncologie regarding the management of menopause in women with breast cancer.

7. **Recommendation:** HRT is not recommended for the prevention of diabetes.

8. **Recommendation:** In women with previously diagnosed diabetes, the use of HRT should be individualized, taking in to account age, metabolic, and cardiovascular risk factors.

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**Abbreviations:**

**AACE** = American Association of Clinical Endocrinologists; **ACE** = American College of Endocrinology; **BMI** = body mass index; **CAC** = coronary artery calcification; **CEE** = conjugated equine estrogen; **CEPO** = Comité de l'Évolution des Pratiques en Oncologie; **CAD** = coronary artery disease; **CIMT** = carotid intima media thickness; **CVD** = cardiovascular disease; **FDA** = Food and Drug Administration; **HDL** = high-density lipoprotein; **HRT** = hormone replacement therapy; **HT** = hypertension; **KEEPS** = Kronos Early Estrogen Prevention Study; **LDL** = low-density lipoprotein; **MBS** = metabolic syndrome; **MPA** = medroxyprogesterone acetate; **RR** = relative risk; **SERM** = selective estrogen-receptor modulator; **SSRI** = selective serotonin re-uptake inhibitor; **VTE** = venous thrombo-embolism; **WHI** = Women's Health Initiative

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## INTRODUCTION

The most recent American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) clinical practice guidelines for the treatment of menopause was published in 2011 (1). This AACE/ACE Position Statement was produced in accordance with the "American Association of Clinical Endocrinologists and American College of Endocrinology Protocol for Standardized Production of Clinical Practice Guidelines, Algorithms, and Checklists – 2014 Update." Each recommendation was graded and based on evidence, which was evaluated and rated by a panel of experts. The position statement does not replace the previous guideline. Unless otherwise noted, recommendations have not changed. This statement will focus on new information from evidence published since the last guidelines, "AACE Medical Guidelines for Clinical Practice for Diagnosis and Treatment of Menopause."

The publication of the Women's Health Initiative (WHI) in 2002 represented the first large, randomized controlled clinical trial of hormone replacement therapy (HRT). In contrast to previous epidemiologic studies, observational studies, or smaller trials, the WHI found a negative impact of HRT on cardiovascular risk in postmenopausal women, while finding a small increase in relative risk of breast cancer in women treated with estrogen/

progesterone combination, but not with estrogen alone. The previous AACE/ACE menopause clinical practice guidelines reviewed these and other outcomes from the WHI. The WHI, however, was confined to older women with a mean age of 63 years, many years after menopause, and to those without vasomotor symptoms.

Since the publication of the AACE/ACE menopause guidelines, a number of post hoc analyses of WHI have been published. The Kronos Early Estrogen Prevention Study (KEEPS) trial evaluated the impact of HRT on younger postmenopausal women. A number of additional studies of breast cancer in hormone-treated women have also been completed. Additional studies comparing various hormone types and routes of administration have been published. The use of bioidentical hormone treatment was discussed in the last edition of the guidelines, but since then, the U.S. Food and Drug Administration (FDA) has issued further warnings regarding this form of therapy, re-enforcing AACE's previous recommendation. Finally, the use of nonhormonal remedies in the management of menopausal symptoms has been expanded.

The current review will provide an update on these issues.

## EFFECT OF AGE ON OUTCOMES

### KEEPS Trial

This randomized controlled clinical trial was based on the hypothesis that a critical window of time exists when cardiovascular risk may not be increased, and perhaps may actually be decreased, by the administration of HRT, particularly estrogen-only replacement. The study randomized 728 women at 9 sites, age 42 to 58 years, 6 to 36 months postmenopausal and in good health, with extensive exclusion criteria:

- prior or current cardiovascular disease (CVD), including myocardial infarction, angina, congestive heart failure, thromboembolic disease;
- smoking more than 10 cigarettes per day;
- body mass index (BMI) >35 kg/m$^2$;
- dyslipidemia (low-density lipoprotein [LDL] cholesterol >90 mg/dL, triglycerides >400 mg/dL);
- uncontrolled hypertension (HT) (systolic blood pressure >150 mm Hg and/or diastolic blood pressure >95 mm Hg);
- glucose >126 mg/dL.

Subjects were treated with either oral conjugated estrogens (Premarin, 0.45 mg), transdermal estradiol (Climara, 50 μg) or placebo, with micronized progesterone (Prometrium, 200 mg) for 12 days per month or placebo for women with intact uterus. Primary end points were progression in coronary artery calcification (CAC) score (as measured by computed tomography) and carotid intima media thickness (CIMT), with secondary studies includ-

ing inflammatory and coagulation markers in each group. Results were reported at the end of 4 years.

Preliminary results have shown no difference in the rate of progression in CIMT in the three groups. Given only very small changes during the study period and small numbers of subjects, no statistically significant difference could be seen. Initial reports, however, indicate less progression in CAC in the estrogen-treated groups (in women with baseline CAC equal to 0); new development of CAC (defined as 5 units or more) occurred in 10.5% of those on oral conjugated equine estrogen (CEE), 12.8% on transdermal estrogen, and 14.3% on placebo. For women with baseline CAC >0, corresponding values were 63, 64, and 73%.

Neither estrogen formulation increased blood pressure. Oral CEE improved high-density lipoprotein (HDL), decreased LDL, raised triglycerides and C-reactive protein, while transdermal estradiol improved glucose levels and insulin sensitivity and had no effect on other biomarkers. It was noted that even when changes were seen, they were quite small and levels remained in the normal range, even when "statistically significant."

As expected in such a short study of relatively young women who were preselected as healthy at baseline, there were no statistically significant differences in rates of any clinical events including breast cancer, endometrial cancer, myocardial infarction, transient ischemic attack, or stroke between the three groups. Importantly, there was no difference in the treated group versus placebo in the incidence of venous thrombo-embolism (VTE) (2).

In hormone-treated women as compared with controls, hot flashes and night sweats were reduced, bone density was improved, and sexual function improved, as reflected in better lubrication and less dyspareunia in the estrogen-treated groups compared with controls (3).

### ELITE Trial

The more recently published ELITE (Early versus Late Intervention Trial with Estradiol) study (4) was performed to test the hypothesis that cardiovascular outcome after estrogen therapy is related to the time after menopause when treatment is started (<6 or >10 years). In this 5-year randomized, double-blind study of 643 healthy postmenopausal women the primary outcome was the rate of change of CIMT, measured every 6 months, with a secondary outcome of CAC at the end of the study. Therapy consisted of estradiol 1 mg daily plus progesterone vaginal gel 45 mg for 10 days of each 30-day cycle in women with a uterus, versus placebo for each. The median age in the early postmenopausal group was 55.4 years, with a mean duration of menopause of 3.5 years, while in the later group, the median age was 63.6 years and 14.5 years since menopause.

The baseline CIMT was higher in the older treated women and their controls than in the younger women, but baseline CIMT within age groups was the same. The older

women had a greater use of antihypertensive and lipid-lowering drugs than did the younger women. Estradiol-treated women in both age/timing groups had lower LDL and higher HDL and triglyceride levels compared with untreated women in both groups. BMI was the same in both groups. Cigarette use was greater in the older women in both groups. Nonetheless, when results were analyzed, the CIMT progression rate was lower in the estrogen-treated early postmenopausal group than in its placebo group or the group treated with estrogen later in menopause. The group treated later in menopause did not differ from its placebo-matched cohort.

Other confounding variables mentioned above did not affect the outcomes. There were no differences in CAC. Clinical events during the study included breast cancer, myocardial infarction, VTE, pancreatic cancer, and glioblastoma multiforme. There was no difference in adverse outcomes among the groups. The authors postulate a dose-response effect at the level of the arterial wall to explain the difference between the benefit shown in younger women in the current study versus the lack of effect (positive or negative) in CIMT effect in the KEEPS trial.

*In the opinion of this AACE/ACE Scientific Committee, while these studies are suggestive of an effect of the timing of estrogen use, they certainly do not alter previous findings enough to suggest a clinical benefit strong enough to change previous guidelines regarding the use of HRT for CVD protection, but is reassuring enough that if estrogen therapy is used for previous recommendations, it is less likely to be harmful early in menopause than later, in concordance with the findings of the post hoc analysis of the WHI.*

### DANISH OSTEOPOROSIS STUDY

Additional reassuring data comes from the Danish Osteoporosis Prevention Study. A total of 502 young (age 45 to 58 years) recently menopausal women were randomized to treatment with triphasic estradiol and norethisterone acetate or with 2 mg estradiol only, if prior hysterectomy, and matched to 504 untreated women. An intervention phase lasted 11 years, and further observation continued up to 16 years. The primary endpoint was a composite of death, admission to hospital for heart failure, and myocardial infarction.

After 10 years of intervention, 16 women in the treatment group experienced the primary composite endpoint, compared with 33 in the control group (hazard ratio [HR], 0.48; 95% confidence interval [CI], 0.26 to 0.87; *P* = .015), and 15 died, compared with 26 (HR, 0.57; 95% CI, 0.30 to 1.08; *P* = .084). Cancer of any type occurred in 36 in the treated group versus 39 in the control group (HR, 0.92; 95% CI, 0.58 to 1.45; *P* = .71), and breast cancer occurred in 10 patients in the treated group versus 17 in the control group (HR, 0.58; 95% CI, 0.27 to 1.27; *P* = .17). The HR

for deep vein thrombosis (2 in treated group vs. 1 in control group) was 2.01 (95% CI, 0.18 to 22.16) and for stroke (11 in treated group vs. 14 in control group) was 0.77 (95% CI, 0.35 to 1.70). After 16 years, the reduction in the primary composite outcome was still present and was not associated with an increase in any cancer (5).

Although the composite end point was not prespecified and the study lacked power to investigate safety, the observations are of clinical importance (6).

## POST HOC ANALYSIS OF THE WHI: CVD OUTCOMES

Recognizing the difference in clinical outcomes following HRT reported by the WHI when women were stratified by age and time from menopause, the WHI committee has created a risk stratification model for HRT, suggesting that there is a group of women for whom HRT offers less risk of CVD (7) (Table 1).

Several characteristics that modify risk for CVD events in women while on HRT have been identified. As reviewed below, optimal candidates for HRT use include women of younger age (<60 years), recent onset of menopause (within 10 years), favorable lipid profile (LDL cholesterol <130 mg/dL or LDL/HDL cholesterol ratio <2.5), absence of metabolic syndrome (MBS), and absence of factor V Leiden genotype (8). In addition, recent evidence suggests that women at high risk for VTE should either avoid systemic HRT or choose a transdermal rather than oral delivery route.

Additional adjustment for the presence or absence of MBS in the WHI population results in the finding of an odds ratio for coronary artery disease (CAD) of 0.98 (95% CI, 0.66 to 1.48) in women without the MBS treated with either estrogen alone or in combination with progesterone as compared with the placebo group, whereas women with the MBS had an odds ratio of 1.72 (95% CI, 1.2 to 2.47) (Table 2). This analysis offers further

| Table 1 Effects of Postmenopausal Hormone Therapy on Cardiovascular Outcomes in the WHI Estrogen-Progestin and Estrogen-Alone Trials, According to Age at Study Entry | | | | |
|---|---|---|---|---|
| | **Intervention phase** | | | |
| | **Estrogen-progestin** | | **Estrogen alone** | |
| **Outcome** | **RR (95% CI)** | ***P*** | **RR (95% CI)** | ***P*** |
| CAD | | | | |
| 50-59 years | 1.34 (0.82-2.19) | .81 | 0.60 (0.35-1.04) | .08 |
| 60-69 years | 1.01 (0.73-1.39) | | 0.95 (0.72-1.24) | |
| 70-79 years | 1.31 (0.93-1.84) | | 1.09 (0.80-1.49) | |
| MI | | | | |
| 50-59 years | 1.32 (0.77-2.25) | .55 | 0.55 (0.31-1.00) | .02 |
| 60-69 years | 1.05 (0.74-1.47) | | 0.95 (0.69-1.30) | |
| 70-79 years | 1.46 (1.00-2.15) | | 1.24 (0.88-1.75) | |
| Stroke | | | | |
| 50-59 years | 1.51 (0.81-2.82) | .50 | 0.99 (0.53-1.85) | .77 |
| 60-69 years | 1.45 (1.00-2.11) | | 1.55 (1.10-2.16) | |
| 70-79 years | 1.22 (0.84-1.79) | | 1.29 (0.90-1.86) | |
| Pulmonary embolism | | | | |
| 50-59 years | 2.05 (0.89-4.71) | .61 | 1.53 (0.63-3.75) | .28 |
| 60-69 years | 1.69 (1.01-2.85) | | 1.72 (0.94-3.14) | |
| 70-79 years | 2.54 (1.27-5.09) | | 0.85 (0.39-1.84) | |
| Deep vein thrombosis | | | | |
| 50-59 years | 3.01 (1.36-6.66) | .58 | 1.66 (0.75-3.67) | .93 |
| 60-69 years | 1.52 (0.97-2.40) | | 1.41 (0.87-2.27) | |
| 70-79 years | 1.96 (1.19-3.24) | | 1.53 (0.87-2.69) | |

Abbreviations: CAD = coronary artery disease; CI = confidence interval; MI = myocardial infarction; RR = relative risk.
Data from (7), **Manson JE, Chlebowski RT, Stefanick ML, Aragaki AK, Rossouw JE, Prentice RL, et al.** Menopausal hormone therapy and health outcomes during the intervention and extended posts stopping phases of the Women's Health Initiative randomized trials. *JAMA.* 2013;310:1353-1368. Copyright © 2013. American Medical Association. All rights reserved.

| | Controls | CAD | OR (95% CI) | P value for interaction |
|---|---|---|---|---|
| **Table 2**<br>**Pooled Results of the Two Hormone Trials (E+P and E Alone) in the WHI** | | | | |
| **MBS absent** | | | | .04 |
| Placebo | 217 | 67 | 1.0 referent | |
| HT | 243 | 70 | 0.98 (0.66-1.48) | |
| **MBS present** | | | | |
| Placebo | 185 | 87 | 1.0 referent | |
| HT | 172 | 135 | **1.72 (1.20-2.47)** | |

Abbreviations: CAD = coronary artery disease; CI = confidence interval; E = estrogen; HT = hypertension; MBS = metabolic syndrome; OR = odds ratio; P = progesterone; WHI = Women's Health Initiative.
Adjusted for baseline history of myocardial infarction, smoking, age, education, and lipid-lowering medication using logistic analysis (**Wild RA, et al.** CHD events in the WHI Hormone Therapy Trials: does presence or absence of metabolic syndrome at baseline modify the risk? Abstract S-3; 21st Annual Meeting of NAMS. *Menopause*. 2010;17:1216.)

guidance regarding women who may be at greater risk of cardiovascular adverse events when treated with HRT, while offering reassurance to those women who do not have MBS (9).

**CLINICAL IMPACT OF KEEPS, WHI, AND ELITE: These studies are reassuring to clinicians and their patients who require hormone replacement for the treatment of menopausal symptoms at a young age.**

**RECOMMENDATION: The use of menopausal hormone therapy in symptomatic young postmenopausal women should be based on consideration of all risk factors for CVD, age, and time from menopause.**

## THE EFFECT OF VASOMOTOR SYMPTOMS ON OUTCOMES

Although it had been postulated in the past that the presence of vasomotor symptoms might reflect better vascular integrity, and therefore the exclusion of these women in the WHI might have biased results toward the development of CVD, this theory has not been supported by data. In fact, in the population of relatively young, early menopausal women screened for participation in the KEEPS study, neither estrogen levels nor vasomotor symptoms predicted baseline CAC or CIMT (10). Vasomotor symptoms did not predict an adverse coronary outcome on HT in younger or recently menopausal women. In comparison, in the Heart and Estrogen/Progestin Replacement Study (HERS) trial, with an older study population, the adverse coronary impact of HT was more pronounced in those with vasomotor symptoms (11).

More frequent hot flashes were correlated with a higher CIMT and plaque level by carotid ultrasound, independent of other CVD risk factors and endogenous estradiol level among nonsmoking menopausal women (12).

In a genome-wide association study evaluation of data collected from 17,695 participants, ages 50 to 79 years of European, Hispanic, and African ancestry in the WHI and some of its substudies, a link between 14 single nucleotide polymorphisms (SNPs) in the tachykinin receptor 3 locus of chromosome 4 and the predisposition to vasomotor symptoms in menopausal women was recently noted. This finding has yet to be confirmed at the time of this writing. Until further information regarding the functional role of these SNPs and physiologic differences between women with and without this difference, it is impossible to link this genetic alteration with possible differences in cardiovascular health and hot flashes (13).

## MENOPAUSAL ESTROGEN REPLACEMENT: EFFECT OF DELIVERY ROUTE: VTE/ CEREBROVASCULAR ACCIDENT (CVA)

Since the publication of the last AACE/ACE menopause guidelines, further evidence has accumulated which tends to support the use of transdermal over oral estrogen replacement.

### Effects on Coagulation
Because oral estrogen is metabolized in the liver, its concentration there is higher, causing greater stimulation of hepatic procoagulant production. Procoagulant levels, therefore, would be expected to be greater with oral compared with transdermal estrogen. In vitro coagulation studies using plasma from oral versus transdermal estrogen recipients confirm higher thrombin activity, lower plasmin activity, and higher thrombin-activatable fibrino-

lysis inhibitor in the orally treated group compared with the transdermal group (14).

The use of oral estrogens results in a nonphysiologic estrone/estradiol ratio of 5:1 to 7:1, compared with a 1:1 ratio with transdermal estrogen, which is similar to the normal premenopausal ratio. There is also less stimulation of hepatic sex hormone-binding globulin production, resulting in higher free estradiol levels with transdermal delivery of estrogen (15). It has therefore been suggested that the transdermal route may be advantageous for women with diabetes, HT, and other cardiovascular risk factors, and also for women of advancing age (16).

### VTE

Meta-analyses of observational studies revealed a higher risk of clinical thromboembolic events with the use of oral as compared with transdermal estrogen. Compared with nonusers of estrogen, the odds ratio of first time VTE in current users of oral estrogen was 2.5 (95% CI, 1.9 to 3.4) and in current users of transdermal estrogen was 1.2 (95% CI, 0.9 to 1.7), with the risk being greatest in the first year of use compared with more than 1 year of use. Past use of oral estrogen did not confer current higher risk. In this study, there was no difference in the risk of VTE with oral estrogen if it was used with or without progesterone. Results from nine randomized controlled trials confirmed the increased risk of VTE among women using oral estrogen (relative risk [RR], 2.1; 95% CI, 1.4 to 3.1). The combination of oral estrogen and thrombogenic mutations or obesity further enhanced the risk of VTE, whereas transdermal estrogen did not confer additional risk, even in women at high risk of VTE (17).

In an observational study of over 1 million postmenopausal United Kingdom women during 3.3 million years of follow-up, there were 2,200 women with VTE, with significant variation depending on the type of HRT. Compared with never users, users of oral estrogen/progesterone had a greater risk than oral estrogen alone RR = 2.07; [95% CI, 1.86 to 2.31] vs. 1.42 [95% CI, 1.21 to 1.66]). There was no increased risk with transdermal estrogen-only therapy (RR, 0.82; 95% CI, 0.64 to 1.06). Among users of oral estrogen-progestin, the risk from HRT varied by progestin type, with significantly greater risks for preparations containing medroxyprogesterone acetate (MPA) than other progestins. The risk of VTE was twice as great in the first 2 years of use than later. Similar risk ratios were noted for deep vein thrombosis without pulmonary embolism (18).

### CVA/CAD

In the WHI review, oral estradiol compared with CEE showed a significantly lower HR for stroke, with limited statistical power in the analysis.

Transdermal estradiol was associated with a moderate but insignificantly lower risk of CAD compared with oral CEE (HR, 0.63; 95% CI, 0.37 to 1.06). For other outcomes, comparisons revealed no appreciable differences by estrogen doses, formulations, or routes of delivery. Absolute risks of CVD events and all-cause mortality were markedly lower in younger women compared with older women (19).

In a population-based, nested case control study comparing 15,710 stroke patients to 59,958 controls, both the route and dose of estrogen affected stroke risk. The overall rate of stroke was 2.85/1,000 years. The adjusted rate ratio of stroke associated with current use of transdermal HRT was 0.95 (95% CI, 0.75 to 1.20) relative to no use. The risk of stroke was not increased with use of low-dose estrogen patches (RR, 0.81; 95% CI, 0.62 to 1.05) compared with no use, whereas the risk was increased with high-dose patches (RR, 1.89; 95% CI, 1.15 to 3.11). Current users of oral HRT had a higher rate of stroke than nonusers (rate ratio, 1.28; 95% CI, 1.15 to 1.42) with both low dose and high dose, with or without a progestogen (20).

In a recent analysis of data from the WHI, the risk of subarachnoid hemorrhage was higher among women reporting active use of HRT compared with nonusers (RR 1.5; 95% CI, 1.0 to 2.2) after adjusting for age, systolic blood pressure, cigarette smoking, alcohol consumption, BMI, race/ethnicity, diabetes, and CVD (21).

**RECOMMENDATION: The use of transdermal estrogen preparations should be considered as less likely to produce thrombotic risk and perhaps the risk of stroke and CAD.**

### BREAST STUDIES

The WHI follow-up study for cumulative events over 13 years (5.6 years of intervention, remainder observation only) confirmed the intervention phase data for breast cancer risk in HRT treated women (i.e., that there was a significant risk of combined conjugated estrogen/medroxyprogesterone acetate therapy compared with placebo, with HRs of 1.24 in the intervention phase and 1.28 for cumulative events). With conjugated estrogen alone, however, the HR for treated women compared with placebo was 0.79 in both the intervention and postintervention cumulative follow-up (7). It has been hypothesized, based on WHI results, therefore, that since breast cancer outcomes are worse in women taking combination estrogen/progesterone using synthetic MPA, micronized oral progesterone, identical to endogenous progesterone, might be a safer alternative. In an observational study, a decreased risk of histologic and hormone receptor–defined invasive breast cancer was noted with use of a combination of micronized progesterone and estrogen versus the use of synthetic progestogens.

However, a further study is needed to establish long-term safety (22). Likewise, the use of norethisterone acetate as the progestin in the Danish Osteoporosis Study (5) was not associated with an increase in the risk of breast cancer.

In the National Institutes of Health–American Association of Retired Persons (NIH-AARP) study of postmenopausal women, the development of breast cancer in women aged 60 to 69 years was slightly higher in those who had taken menopausal hormone replacement (presumably CEE, CEE/MPA) than those who had not (HR for >10 years menopausal hormone therapy, 1.57; 95% CI, 1.43 to 1.73) (23).

## THE ROLE OF PROGESTERONE IN RISK/BENEFIT OF HRT ENDOMETRIAL PROTECTION

Studies have shown that the best protection against endometrial hyperplasia and carcinoma is with continuous rather than cyclic progestogen, regardless of the chemical nature of the progestogen (24). There are, however, conflicting data regarding the relative endometrial safety of different types of progestogens.

In a large European multi-site epidemiologic survey, users of estrogen-only therapy, compared with never users, were at increased the risk of endometrial cancer (HR, 2.52; 95% CI, 1.77 to 3.57). Combination estrogen-plus-progestin therapy was associated with greater risk than never use but significantly less risk than estrogen alone (HR, 1.41; 95% CI, 1.08 to 1.83). Risks differed according to regimen, duration, and type of progestin constituent. The use of sequential combined hormone therapy was positively associated with risk (HR, 1.52; 95% CI, 1.00 to 2.29), while use of continuous combined treatment was inversely associated with risk (HR, 0.24; 95% CI, 0.08 to 0.77), although this finding was based on only three cases. The association also varied by type of progestin constituent: preparations that contained micronized progesterone were associated with a significantly increased risk, while those that contained progesterone or testosterone derivatives were not associated with risk (25). It is recognized that although cyclic progesterone may not be as protective of the endometrium as continuous progesterone, not all women tolerate continuous progestins. Careful monitoring of the endometrium can lead to early intervention for those few patients who might develop hyperplasia on cyclic progestins.

The use of progestin-eluting intra-uterine devices (IUDs) can also be used in the prevention of endometrial hyperplasia, with minimal systemic effects.

It has been suggested that vaginal progesterone administration might be valuable by reducing the systemic progesterone reaching the breast, while offering more endometrial protection. Given sequentially at 300 mg/day, vaginal micronized progesterone induced a full secretory endometrium in premenopausal women (26), while at a dose of 100 mg per day (along with 25 μg estradiol patches), there was no endometrial hyperplasia, and some patients developed vaginal atrophy (27). Progestin-eluting IUDs can also be used in the prevention of endometrial hyperplasia, with minimal systemic effects (28).

## CVD/VTE

Various progestins may have different impact on thromboembolic risk. For example, in the in the E3N cohort study of 80,308 postmenopausal women, with an average follow-up of 10.1 years (29), there was a significantly increased thrombotic risk with norpregnanes (HR, 1.8) compared with progesterone (HR, 0.9), pregnanes (HR, 1.3), and 19-nortestosterone derivatives (HR, 1.4). In general, MPA use seems to have greater risk with regard to multiple outcomes, including cardiovascular effects, blood pressure, VTE, probably stroke and breast cancer. Short-term use of less than 5 years, however, does not seem to be associated with significant increase in risk (30). Micronized progesterone as compared with MPA may have better outcomes with respect to cardiovascular effects, blood pressure, VTE, probably stroke and breast cancer.

## BREAST CANCER

Epidemiologic data on postmenopausal HT have consistently reported that the addition of any progestin to estrogen increases the risk of breast cancer diagnosis compared with estrogen alone. In a study by Kerlikowske et al (31), use of estrogen and progestin for greater than 5 years was associated with a greater risk of breast cancer diagnosis (RR, 1.49; 95% CI, 1.36 to 1.63), with no increased risk compared with nonusers and estrogen-only users. This relationship was confirmed by a meta-analysis (32) that reported an average RR of 0.79 (95% CI, 0.61 to 1.02) for invasive breast cancer diagnosis with estrogen use and of 1.24 (95% CI, 1.02 to 1.50) with estrogen-progestin use in four randomized trials.

The French E3N cohort study (33) assessed and compared the association between different HT regimens and breast cancer risk in 80,377 postmenopausal women, whose mean age was 53.1 years, followed up for an average of 8.1 postmenopausal years. Estrogen was combined with various progestogens, including progesterone, dydrogesterone, medrogestone, chlormadinone acetate, cyproterone acetate, promegestone, nomegestrol acetate, norethindrone acetate, and MPA.

Estrogen-progesterone and estrogen-dydrogesterone combinations were associated with no or slight and nonsignificant increases in risk, whereas all other estrogen/progestogen combinations showed substantially increased risks, most of which were statistically significant but did not differ significantly between preparations.

These studies and others support the concept that estrogen alone does not initiate or promote breast cancer. It is only when the progestogen is exposed to estrogen-stimulated breast tissue that there is an increase in the diagnosis of breast cancer. Given the above discussion regarding the addition of progestogens to estrogen therapy for the prevention of endometrial cancer, the use of micronized progesterone might be the best choice.

For a detailed review of progestin chemistry and pharmacology, the reader is referred to reference (34).

**RECOMMENDATION: When the use of progesterone is necessary, micronized progesterone is considered the safer alternative.**

## COGNITIVE FUNCTION

A study of 1,768 women revealed that the use of hormone therapy within 5 years of menopause was associated with a 30% reduction in the risk of developing Alzheimer disease later in life, especially if the duration of use was 10 years or longer. This is in contrast to the increase in the risk of Alzheimer disease in women who use hormone replacement later in life (35).

The ongoing KEEPS Cognitive and Affective study, with 700 women enrolled, is the first multi-site, randomized, placebo-controlled, double-blind, parallel-group design clinical study that will address major HRT-related issues raised by WHI and the Women's Health Initiative Memory Study (WHIMS). The study is designed to evaluate whether (*1*) there is cognitive benefit or harm associated with HRT administered during the 'critical period' (as opposed to late postmenopausal HRT investigated in WHIMS), (*2*) there are differential cognitive effects of various estrogen formulations (CEE vs. estradiol), (*3*) there is a preferred route of estrogen administration (oral vs. transdermal), (*4*) cyclic micronized progesterone is associated with cognitive benefit, and (*5*) to identify the most sensitive psychometric measures to characterize potential effects of estrogen on cognition and mood. Data from this study will help to determine the potential benefit of HRT soon after menopause on cognition, in parallel with other issues related to the timing, the type of preparation, and the route of administration of HRT and cardiovascular outcomes (2).

## DIABETES AND GLUCOSE TOLERANCE

While spontaneous menopause has not been associated with an increased risk of diabetes, MBS/insulin resistance is known to increase with age. Some studies have suggested that premature menopause or premenopausal oophorectomy increases the risk of type 2 diabetes.

In observational studies, treatment with HRT has resulted in either neutral or beneficial effects on glucose levels in patients with pre-existent type 2 diabetes. Both oral and transdermal estrogen conferred this effect, although in small studies, oral seemed better than transdermal estrogen.

In subjects without diabetes, the evidence from observational trials also suggested neutral or slightly beneficial effect of estrogen on glucose metabolism. In randomized controlled clinical trials, including HERS (women with known CVD), blood glucose levels did not rise over time in estrogen-treated women, and fewer women with impaired fasting glucose at study onset progressed to overt diabetes in the estrogen-treated group, both compared with controls. In the WHI, there was a 21% reduction in diabetes incidence over time in women treated with estrogen/ progesterone therapy. Age stratification revealed glucose benefit from combination therapy HRT was limited to women aged 50 to 69 years. Older HRT-treated women experienced slightly greater risk than age-matched placebo controls. In the estrogen-only arm of the WHI, the incidence of diabetes in treated women was 12% less than in controls at all age groups. As previously mentioned, in younger, nondiabetic women in the shorter KEEPS trial, no effect of conjugated estrogen was seen, while transdermal estrogen–treated subjects showed a modest reduction in blood sugar.

No study has addressed the issue of diabetic micro- or macrovascular complications. Furthermore, since patients with diabetes are known to have greater cardiovascular risk, the information regarding cardiovascular and stroke outcomes discussed earlier are of critical importance. Likewise, since CVD risk in HRT-treated women has been shown to be greater in women with MBS, caution should be exercised in treatment of this subgroup of women, with or without overt diabetes (36). For a detailed review of the literature, the reader is referred to reference (36).

- **RECOMMENDATION: HRT is not recommended for the prevention of diabetes.**
- **RECOMMENDATION: In women with previously diagnosed diabetes, the use of HRT should be individualized, taking in to account age, metabolic, and cardiovascular risk factors.**

## BIOIDENTICAL HORMONES

The most recent version of the AACE/ACE menopause guidelines cautioned against the use of bioidentical hormone replacement, noting that there is no evidence to support superior safety with these products and that there is often lack of consistency in the content of compounded products, leading to either less or greater amounts of biologically active hormone being received (Table 3). Authorities have noted that there are no controlled trials which support claims for better efficacy, and most importantly, safety concerns (37).

AACE believes that practitioners and their patients should be aware of the published testimony of the FDA

| Table 3 |
|---|
| **Common Compounded Bioidentical Hormone Preparations** |
| Tri-estrogen: Estriol, Estrone, Estradiol (8:1:1 ratio) 1.25 to 2.5 mg/day |
| Bi-estrogen: Estriol, Estradiol (4:1 or 9:1 ratio) 1.25 to 2.5 mg/day |
| Estriol/Progesterone (2 to 8 mg/day + 100 to 200 mg/day) |
| Testosterone |
| Dehydroepiandrosterone |
| Adapted from **Files JA, Ko MG, Pruthi S.** Bioidentical hormone therapy. *Mayo Clin Proc*. 2011;86:673-680, with permission from Elsevier. |

on the topic of bioidentical hormones. FDA officials testified before the Senate Special Committee on Aging on April 19, 2007. The FDA was most concerned that unsubstantiated claims have been made for both safety and efficacy of these products and that promotional materials contain inaccurate information and do not adequately warn consumers about the potential risks of hormone replacement.

*"The FDA is also not aware of sound evidence showing the superiority of compounded BHRT products over FDA-approved drugs. Likewise, FDA has no information indicating that the side effects and risks of compounded BHRT products are dissimilar to those of FDA-approved drugs. Thus, claims regarding the safety, efficacy, and superiority of compounded BHRT products have not been substantiated by FDA and may mislead patients and practitioners… The absence of warnings and risk information may be viewed by patients as implicit evidence that compounded BHRT products are safer than FDA-approved drugs, when there is no data to support this conclusion"* (38).

The FDA has provided information for consumers on its webpage, most recently updated (39).

## TREATMENT OF HOT FLASHES

### Combination Selective
### Estrogen-Receptor Modulator (SERM)/CEE

Bazedoxifene, a SERM with efficacy in preventing and treating postmenopausal osteoporosis, is available in combination with CEE. The SERM alone is similar to raloxifene in fracture prevention but is associated with a risk of hot flashes and deep vein thrombosis. There seems to be no effect on the endometrium, and animal data suggest no increase in breast cancer risk, but no robust human data are yet available. The combination of SERM/CEE decreased the incidence of hot flashes and improved vaginal dryness compared with SERM alone; the risk of deep vein thrombosis, however, remains. It is not clear whether the two agents are additive in this effect. The risk of stroke from estrogen remains. Clinical trials have demonstrated no increased risk of endometrial hyperplasia. Therefore, the use of a progestin with this combination is considered unnecessary (40-42).

### Phytoestrogens

Although supplemental phytoestrogens have been available and promoted to treat menopausal symptoms, their physiologic potency as estrogens or anti-estrogens is not required to be disclosed, as they are considered food supplements, adding to concern, especially for women who have contra-indications to the use of estrogen (e.g., breast cancer patients). Phytoestrogens are found naturally in foods, including isoflavones, prenylfavonoids, coumestnas, and lignans. For each of this multitude of compounds, one must consider its chemical structure compared with physiologic estradiol, whether the compound acts as an estrogen agonist or antagonist, and how this occurs with respect to the type of estrogen receptor present in various tissues, especially the breast and uterus. In the gut, genetic differences in biome composition may also affect the metabolism and action of dietary or supplemental phytoestrogens taken orally. Finally, the timing of exposure to these compounds in a woman's lifespan may affect their action, as it appears to do with physiologic estradiol (vide supra). Several in vitro and in vivo animal studies have explored the physiologic effects; there have been, however, few randomized controlled clinical trials of sufficient power and duration to make conclusions regarding the impact of phytoestrogens on hot flashes and other menopausal symptoms, as well as their long-term effects on breast, uterus, brain, CVD, and thyroid function. For an extensive review, of this topic, see reference (43).

## NONHORMONAL TREATMENTS

### Selective Serotonin
### Re-Uptake Inhibitors (SSRIs)

SSRIs have been used with moderate success in the treatment of hot flashes in women who are unable or unwilling to use estrogen. Pooled individual-level data from three randomized clinical trials including 899 perimenopausal and postmenopausal women with at least 14 bothersome vasomotor symptoms per week compared 0.5 mg estradiol with venlafaxine 75 mg or 10 to 20 mg escitolapram and three nonpharmacologic interventions, with both SSRIs performing as well as estrogen. To reduce placebo effect, women whose vasomotor symptom frequency decreased more than 50% over the 3-week screening period were

excluded. The success of this approach is reflected in the fact that the vasomotor symptom frequency reductions from baseline in the placebo groups (14 to 34%) were at the low end of the range compared with other vasomotor symptom trials (44). In a double-blind, placebo-controlled trial, both agents outperformed placebo but were equal to one another. A pooled analysis of all three Menopause Strategies: Finding Lasting Answers for Symptoms and Health (i.e., MsFLASH) studies revealed a significant reduction in hot flashes of 54% for escitalopram, 48% for estradiol, and 49% for venlafaxine. Sexual desire was minimally better with estradiol than SSRI treatment, while venlafaxine was better than estradiol for therapy of anorgasmia, pain, and vaginal dryness. Improvement in sleep quality and duration was minimally and equally improved with both forms of therapy.

In a separate study, paroxetine 7.5 mg daily was shown to improve hot flashes without weight gain or sexual dysfunction (45).

**In breast cancer patients, fluoxetine and paroxetine should not be used, as they inhibit the effect of tamoxifen (46).**

### Gabapentin

In a randomized, placebo-controlled trial, 900 mg gabapentin offered better relief of hot flashes than placebo in a 3-month trial (47). An additional randomized, placebo-controlled trial evaluating gastro-retentive gabapentin (1,800 mg/day) in 600 women with 7 or more moderate to severe hot flashes per day over 6 months revealed efficacy over placebo for both reduction in hot flashes and improved sleep, although the drug-treated group had more dizziness (12.7% vs. 3.4%), headache (9.3% vs. 8.1%), and somnolence (6.0% vs. 2.7%), much of which improved after a few weeks (48).

The use of nonhormonal therapy for the treatment of hot flashes may be individualized, as patient preference dictates. In a relatively short-duration, 4-week study, venlafaxine (75 mg) and gabapentin (900 mg) were compared in 66 women, of whom 56 expressed a preference, 68% preferred venlafaxine, while 32% preferred gabapentin (49). As previous and subsequent studies without head-to-head comparisons have used larger doses of both agents for longer duration, it is likely that in clinical practice, patience and regular patient discussions may yield different results in individual women.

Of particular importance in the nonhormonal therapy of hot flashes, drug interactions must be considered. The Comité de l'Évolution des Pratiques en Oncologie (CEPO) recommended in a recent review that:

1. *for breast cancer patients being treated with tamoxifen: (a) the use of venlafaxine, citalopram, clonidine, gabapentin, and pregabalin be considered effective in*

*treating hot flashes, and (b) **the use of paroxetine and fluoxetine be avoided, given that they may reduce the efficacy of tamoxifen;***
2. *for breast cancer patients not being treated with tamoxifen: (a) the use of venlafaxine, paroxetine, citalopram, clonidine, gabapentin, and pregabalin be considered effective in treating hot flashes, and (b) fluoxetine not be used to treat hot flashes, given that there is insufficient evidence for its therapeutic efficacy;*
3. *for breast cancer survivors, sertraline, phytoestrogens, black cohosh, and St. John's wort should not be used to treat hot flashes* (50).

**RECOMMENDATION: In symptomatic menopausal women who are at significant risk from the use of HRT, the use of SSRIs and possibly other nonhormonal agents may offer significant symptom relief.**

**RECOMMENDATION: AACE fully supports the recommendations of CEPO as listed above.**

### Black Cohosh

Ongoing use of this botanical preparation as an unregulated herbal substance requires regular re-evaluation not only of its purported efficacy for the treatment of menopausal symptoms, but also its safety. Multiple studies have been published using a variety of different formulations in various test systems. Some extracts had estrogenic activity despite a lack of ability to bind the estrogen receptor, one extract exhibited SERM activity, and several extracts showed additive/synergistic activity (51).

Variable effects in breast cancer cell lines and in mice and rats may be different from those in the human estrogen receptor, leaving the true risk of this herbal substance in doubt (52,53). A recent review and meta-analysis of human studies included 14 randomized controlled trials, 7 uncontrolled trials, and 5 observational studies. Efficacy data were conflicting, but in general, black cohosh showed a response when compared with baseline but not with placebo. Two observational studies found no association between black cohosh and risk of breast cancer, whereas two studies reported significant reductions in risk of primary breast cancer among postmenopausal women (adjusted odds ratio, 0.47; 95% CI, 0.27 to 0.82) and risk of recurrence (adjusted hazard ratio, 0.75; 95% CI, 0.63 to 0.89). Seventeen trials showed no significant impact on circulating hormone levels or proliferation in estrogen-responsive tissues. This latter issue is significant, in that in vivo human studies have been short term, while in vitro assays vary considerably in methodology (54).

For women in whom estrogen exposure should be minimized (e.g., those who have had or are at high risk of having breast cancer), recommendations for or against the use of black cohosh are critical. The French oncology

committee advises against its use in breast cancer survivors (55). **AACE supports the CEPO recommendation until further more definitive data are reported.**

## DISCLOSURE

The authors have no multiplicity of interest to disclose.

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