Clinical Expert Series

CME

A Contemporary View of Menopausal Hormone Therapy

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Enthusiasm for the use of hormones to ameliorate symptoms of perimenopause and menopause has waxed and waned over the years. Both treatment for symptoms and training of women's health care practitioners in the management of menopause have sharply declined since publication of the Women's Health Initiative initial results in 2002. Findings from that trial, which treated a population of older, asymptomatic patients, have been extrapolated over the past 21 years to all estrogen products, all menopausal women, and all delivery mechanisms. Our patients deserve a more nuanced, individualized approach. Conjugated equine estrogens and medroxyprogesterone acetate are no longer the predominant medications or medications of choice available for management of menopausal symptoms. All hormones are not equivalent any more than all antiseizure medications or all antihypertensives are equivalent; they have different pharmacodynamics, duration of action, and affinity for receptors, among other things, all of which translate to different risks and benefits. Consideration of treatment with the right formulation, at the right dose and time, and for the right patient will allow us to recommend safe, effective, and appropriate treatment for people with menopausal symptoms.

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A thorough literature review affirms that, in postmenopausal women, estradiol (E2) effectively relieves vasomotor symptoms and symptoms associated with the *genitourinary syndrome of menopause*, that is, vulvovaginal atrophy symptoms, while maintaining bone mineral density. The evidence also supports that estrogen–E2 is associated with decreased breast cancer and cardiovascular mortality.

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WHY ARE PHYSICIANS HESITANT TO PRESCRIBE MENOPAUSAL HORMONE THERAPY?

The past year has seen a significant increase in public interest in menopause in the press, in social media, among employers, and within the investment community. Although this highlights a condition that will affect every person born female, it has also led to much misinformation and "snake oil," in addition to direct-to-consumer marketing of supplements, devices, and products purporting to safely treat menopausal symptoms, often without scientific support or touting purposefully misleading evidence. In this Clinical Expert Series, we briefly discuss the history of menopausal hormone therapy (HT); the evolution of scientific thinking about the benefits and risks of hormones; the variations in hormone formulations, routes of administration, and doses; and current scientific literature supporting the safety and effectiveness of isomolecular (identical to human) forms of estradiol and progesterone.

THE HISTORY OF MENOPAUSAL HORMONE THERAPY

The pioneering work of Allen and Doisy first identified estrogen as the female hormone in the early

1900s.[1] Not too long thereafter, the pharmaceutical industry found an abundant source for estrogen in the urine of pregnant mares. Premarin (pregnant mares' urine) was approved by the U.S. Food and Drug Administration (FDA) for the treatment of menopausal symptoms in 1942, and sales increased until the association was made between unopposed estrogen use and endometrial hyperplasia or carcinoma in 1975. By the early 1980s, it became evident that the addition of a progestin–a synthetic, well-absorbed progesterone derivative–to continuous estrogen would prevent overgrowth and cancer of the endometrium. Sales again surged as millions of women were enthusiastic about relieving their hot flushes, night sweats, and vaginal symptoms. In the early 1980s, there were reports of preservation of bone mineral density and prevention of osteoporosis[2] and epidemiologic studies suggesting a reduction in cardiovascular morbidity and mortality.[3] Although the Framingham Heart Study[4] suggested harm with respect to cardiovascular disease (CVD) in women taking conjugated equine estrogen and medroxyprogesterone acetate, several subsequent cohort studies published in the late 1980s, including the Nurses' Health Study, the Leisure World Study, and a Kaiser Permanente study, all with long-term follow-up, pointed to a substantial reduction in cardiovascular risk for the cohorts using menopausal HT.[5–7] On the basis of these inconsistent findings, the argument that cohort studies were biased by a "healthy user" effect, and the overwhelming effect of CVD in the United States and other developed countries, the NIH was granted funding for a large, randomized, prospective clinical trial to study the effects of menopausal HT on cardiovascular risk (among other health and aging strategies): the WHI (Women's Health Initiative).

The WHI was a randomized controlled trial (RCT) designed to determine whether postmenopausal HT should be offered to all women to reduce the incidence of CVD. Given the relatively low incidence of cardiovascular events in younger women, an older cohort was purposefully recruited to adequately power the study. It was a massive, expensive undertaking, enrolling 160,000 women at a budget of more than $600 million. In July 2002, an NIH press conference announced the preliminary findings of the WHI hormone study, focusing on the harms identified with conjugated equine estrogen plus medroxyprogesterone acetate. The significant benefits in reduction of osteoporosis, osteoporotic fractures, and colon cancer were not mentioned. As a result of the publicity around the risks of menopausal HT, prescriptions plummeted by 79%.[8] Symptomatic patients in their early menopausal years were taken off hormones as a result of widespread confusion and fear among both health care professionals and the public. The WHI's preliminary data release changed physician practice patterns and professionals' menopause education for the ensuing decades.

Since the 2002 WHI publication,[9] the risks and benefits for both symptom relief and preservation of function associated with menopausal HT, especially with E2 and micronized progesterone, have been hotly debated. Should menopausal HT be considered for symptoms only–lowest dose for the shortest time–or, for example, for preservation of function, preserving bone mineral density, blood vessel elasticity, vulvovaginal epithelium, which would require long-term, even lifelong therapy? Preservation of function is not totally equivalent to prevention of disease, a distinction that is not explored here but requires further elucidation.

There are several issues with centering the WHI data as the basis for most, if not all, professional society and government agency (ie, FDA, U.S. Preventive Services Task Force [USPSTF]) guidelines and recommendations regarding current postmenopausal HT. The patient population was almost a decade older on average than women undergoing the menopausal transition and were generally asymptomatic. In addition, the hormonal formulations studied, although the most commonly prescribed drugs at the time, were not the most commonly recommended hormones in 2023.

CONJUGATED EQUINE ESTROGEN COMPARED WITH ESTRADIOL-17β

In the past 2 decades, we have learned a great deal more about the differences between estrogens as a general class, including conjugated equine estrogen and isomolecular estradiol (same chemical structure as endogenously produced estradiol in humans). Conjugated equine estrogen differs from estradiol-17β in structure, receptor binding, and cardiovascular effect. At least 10 of the many estrogens in conjugated equine estrogen are structurally like human estrogens, and there are additional estrogens found in horses but not humans.

We now know that there are two unique estrogen receptors, α and β, which were cloned in 1996.[10] Although estradiol binds equally to the α and β estrogen receptors, conjugated equine estrogen binds predominantly to the β receptors, leading to overall more potent clinical effects.[11] Conjugated equine estrogen is far more active in increasing inflammatory markers, that is, C-reactive protein, and inducing matrix

metalloproteinase 9, a potent enzyme that breaks down collagen, among other actions. In fact, the early increases seen in the WHI's cardiovascular events are now attributed to plaque destabilization and rupture potentially involving these mechanisms. It is interesting that after the first year of the WHI, cardiovascular events dropped, and by the time the study was discontinued, the relative risk for cardiovascular events was less than 1.[12] Whether this rapid falloff in events was attributable to attrition of people susceptible to plaque rupture or the existing plaque in older patients being stabilized after initial exposure to conjugated equine estrogen is not known.

Estradiol tablets, transdermal patches, and gels have been studied extensively and documented to improve clinical outcomes, including vasomotor symptoms, vulvovaginal symptoms, and preservation of bone mineral density (gels are not FDA approved for osteoporosis prevention). A significant number of head-to-head comparative trials document differences between the biological activities of conjugated equine estrogen and estradiol-17β [13] but are beyond the scope of this commentary.

MEDROXYPROGESTERONE ACETATE COMPARED WITH MICRONIZED PROGESTERONE

We have also learned that synthetic progestins have distinctive receptor binding, which, for the progestin used in the WHI, medroxyprogesterone acetate (Provera and generics), may have contributed to an increased risk for breast cancer and other potentially adverse metabolic effects. Medroxyprogesterone acetate binds to progesterone receptors and to androgen and glucocorticoid receptors. It increases insulin-like growth factor 1, resulting in increased insulin resistance, and medroxyprogesterone acetate enhances thrombotic risk when added to estrogen therapy.[14,15] Micronized progesterone has not been associated with an increase in thrombogenic risk or with an increase in breast cancer incidence.[16,17]

RISKS OF BREAST CANCER RELATED TO MENOPAUSAL HORMONE THERAPY

Conjugated Equine Estrogen Plus Medroxyprogesterone Acetate

The WHI Estrogen Plus Progestin Trial randomized 16,608 postmenopausal women with a uterus to a combination of daily oral conjugated equine estrogen 0.625 mg/d and medroxyprogesterone acetate 2.5 mg/d or placebo.[18] The CEE+MPA (Conjugated Equine Estrogen+Medroxyprogesterone Acetate) trial was stopped early because of "an increased breast cancer incidence." The trial was not a breast cancer trial, and it is important to note that the randomization was for baseline cardiovascular risk, not for baseline breast cancer risk.

Hodis and Sarrel,[19] in a 2018 review, critically evaluated breast cancer risk through the lens of the WHI studies. They found that conjugated equine estrogen (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) in the typical postmenopausal population (women who have never used menopausal HT) had a null effect on breast cancer risk. In other words, breast cancer incidence was not affected by conjugated equine estrogen plus medroxyprogesterone acetate relative to placebo for up to 11 years (Fig. 1).

It was the unusually low breast cancer incidence in the placebo group, specifically participants who were previously on menopausal HT (25% of the study population) and washed out before WHI study initiation, that created the controversial breast cancer data. Instead of asking why the placebo group's annualized breast cancer incidence was so low compared with all the other placebo groups in the WHI studies, the WHI authors focused on the treatment arm. The treatment group's annualized breast cancer incidence was no different from the incidence in the cohort of never users of hormones randomized to placebo (Fig. 1). Participants who had used menopausal HT before randomization to this placebo group had an unusually low breast cancer incidence. In other words, conjugated equine estrogen plus medroxyprogesterone acetate had a null effect on both breast cancer incidence and breast cancer mortality. Hodis and Sarrel also concluded that, in this population, breast cancer risk associated with combined conjugated equine estrogen plus medroxyprogesterone acetate was similar in magnitude to or lower than the breast cancer risk associated with a host of other factors, including obesity, low physical activity, and drinking two glasses of wine daily.

Conjugated Equine Estrogen Alone

Surprisingly little attention was given to the WHI conjugated equine estrogen–alone trial, which randomized 10,739 postmenopausal women with a prior hysterectomy to either daily conjugated equine estrogen 0.625 mg/d or placebo. There was a documented trend toward decreased breast cancer risk when conjugated equine estrogen alone was compared with placebo. In 2020, Chlebowski et al[20] published WHI 20-year follow-up data. The most significant and overlooked conjugated equine estrogen–alone finding was the 45% statistically significant reduction in breast

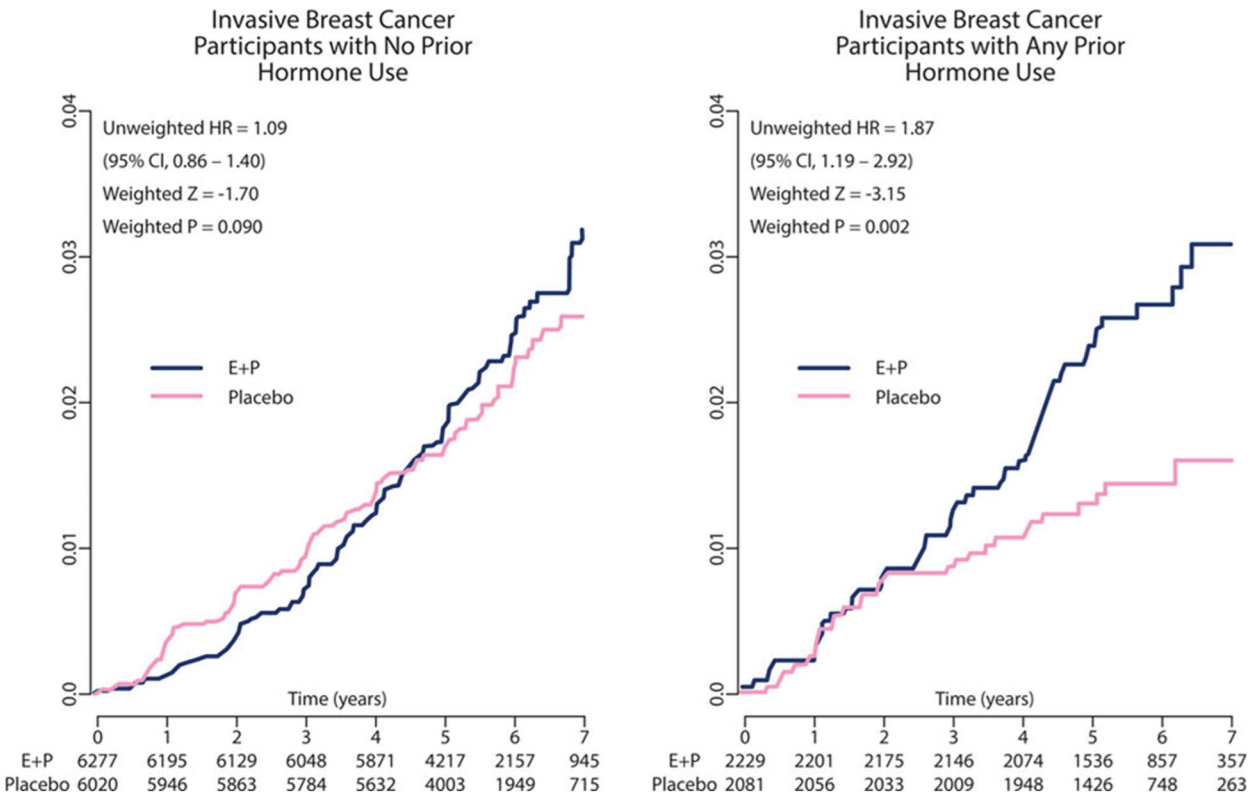

Fig. 1. Breast cancer incidence in the Women's Health Initiative trial of conjugated equine estrogen plus medroxyprogesterone acetate (E+P in figure) compared with placebo, stratified by prior use of hormone therapy, showing similar trends for all the subgroups except for women with prior hormone therapy use randomized to placebo where breast cancer incidence unexpectedly sharply diverges without explanation. It is the divergence in the trend line for women with prior hormone therapy use randomized to placebo that accounts for the elevated hazard ratio for breast cancer, falsely giving the impression that breast cancer incidence was increased in the trial due to conjugated equine estrogen plus medroxyprogesterone acetate, where in fact, the elevated hazard ratio was due to a decreased breast cancer incidence in the placebo-treated group. Reprinted with permission from Hodis HN, Sarrel PM. Menopausal hormone therapy and breast cancer: what is the evidence from randomized trials? Climacteric 2018;21:521–8. doi: 10.1080/13697137.2018.1514008

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cancer mortality in the conjugated equine estrogen alone group after 18 years of cumulative follow-up compared with placebo. The data confirm that estrogen alone (specifically conjugated equine estrogen alone) significantly decreases breast cancer incidence and breast cancer mortality. Unfortunately, Chlebowski et al did not address or correct the previously noted analytical flaws in the WHI's CEE+MPA study. It is important to note, however, that the authors did document that after long-term follow-up, there was no increase in breast cancer mortality in the group randomized to combined conjugated equine estrogen plus medroxyprogesterone acetate.

ESTRADIOL-17β AND BREAST CANCER RISK

The Nationwide Finnish Comparative Study,[21] a large observational trial, found a statistically significant breast cancer mortality reduction in women using isomolecular E2 alone (oral E2, transdermal E2 patches, or transdermal E2 gels) compared with a group not using hormones or those using combined menopausal HT (isomolecular estradiol plus a progestin). This Finnish study did not differentiate between E2 delivery systems (oral, transdermal patches, or gels) and doses (1 or 2, 0.025–0.1, and 0.5–1.5 mg, respectively) when analyzing the data. Thus, delivery system and dose effect could not be analyzed. The authors' reasoning was that their previous data analysis failed to show any marked difference between these factors and breast cancer risk. This study noted that E2, when used for more than 10 years, was safe for the breast. Any history of E2-based menopausal HT, including combined with a progestin, was associated with an up to 50% breast cancer mortality risk reduction. This remained true for more than 10 years of use and across all age groups.

ESTRADIOL-17β AND CARDIOVASCULAR DISEASE

DOPS (Danish Osteoporosis Prevention Study) randomized 1,006 patients to 2 mg oral E2 plus progestin when indicated or no HT.[22] This study enrolled patients at the onset of menopause and followed them for up to 16 years. During the 10 years of treatment, compared with placebo, those randomized to menopausal HT experienced significantly lower rates of myocardial infarction, heart failure, or death with no increase in thromboembolism, cancer, or stroke. These findings are markedly different from the WHI outcomes. Estradiol, as opposed to conjugated equine estrogen, appears to be safe for the cardiovascular system and may be protective against CVD and all-cause mortality, especially when initiated in women younger than age 60 years or less than 10 years since menopause onset (Fig. 2). DOPS was terminated early because of the WHI published findings. Although most women in DOPS stopped menopausal HT with the 2002 publication of the WHI, at 16 years, there remained a significant improvement in rates of myocardial infarction, heart failure, and mortality 6 years after exposure in the group randomized to menopausal HT. It is unfortunate that the DOPS randomized trial was terminated early despite positive findings. Long-term treatment and follow-up could have answered existing questions, including whether we continue treatment indefinitely.

Endogenous estradiol-17β plays an important role in maintaining vascular health. There are numerous proposed mechanisms by which endogenous E2 may protect against CVD. A short list of such mechanisms includes the positive effect of estradiol-17β on lipids, its antiplatelet effects, and its anti-inflammatory and antioxidant effects. Studies have shown that postmenopausal women have greater arterial stiffening than premenopausal women, that estrogen improves endothelium-dependent vasodilatation, and that estrogen inhibits monocyte adhesion to vascular endothelium, which is an important step in atheroma development.[7]

Strengthening the case for the cardiovascular protective properties of E2 is the known increased cardiovascular risk and event rate documented with E2 deprivation, as is seen with primary ovarian insufficiency, either natural or surgical.[23] The American College of Obstetricians and Gynecologists (ACOG) recommends treating patients at least until the age of natural menopause to reduce the deleterious health consequences of early E2 deprivation found in women with primary ovarian insufficiency and in naturally or surgically menopausal women.

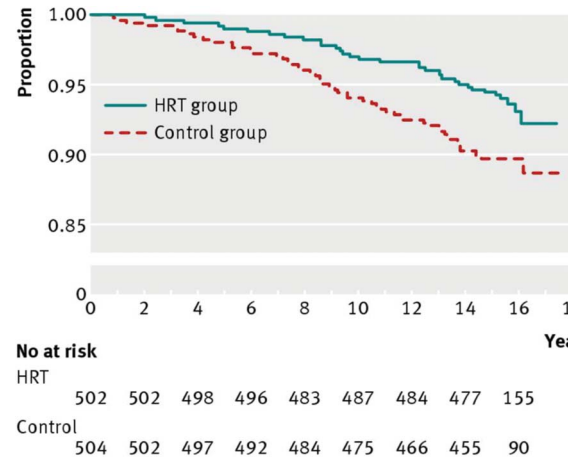

Fig. 2. Survival curve from the Danish Osteoporosis Study showing a statistically significant reduction of cardiovascular disease by 52% (HR, 0.48; 95% CI, 0.27–0.89) after 10 years of randomized hormone therapy (estrogen with or without progestogen) relative to no hormone therapy and reduction by 39% (HR, 0.61; 95% CI, 0.39–0.94) after 16 years of total follow-up (10 years of randomized treatment and 6 years of postintervention follow-up). Risk of death or admission to hospital due to heart failure or myocardial infarction (primary end point) over 16 years of follow-up, including 11 years of randomized treatment. Reprinted from Schierbeck LL, Rejnmark L, Tofteng CL, Stilgren L, Eiken P, Mosekilde L, et al. Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial. BMJ 2012; 345:e6409. doi: 10.1136/bmj.e6409. This article is available under the Creative Commons CC-BY-NC 4.0 license and permits non-commercial use, distribution and reproduction in any medium, provided the original work is properly cited.

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The WHI subgroup analysis confirmed that CVD risk was influenced by age and time since menopause. In the conjugated equine estrogen–alone group, the extended 13-year follow-up documented that the group initiating menopausal HT between the ages of 50 and 59 had a 40% lower myocardial infarction risk and lower all-cause mortality than the placebo group. These significant event reductions seen in younger women did not extend to older women.[24]

Thus, the timing hypothesis, also known as the gap hypothesis, began receiving attention. The hypothesis posits that age and time since menopause influence the menopausal HT and CVD relationship such that the benefits are greater and the risks are lower in women treated with menopausal HT closer to menopause onset than in those distant from their last menstrual period when menopausal HT carries fewer benefits and greater risks. As a result, several clinical trials set out to confirm and clarify the timing hypothesis.

KEEPS (Kronos Early Estrogen Prevention Study)[25] was a 4-year RCT that aimed to evaluate the effects of menopausal HT on atherosclerosis progression as measured by carotid intima–media thickness and coronary artery calcification. From nine U.S. clinical centers, 727 healthy, naturally menopausal women aged 42–58 years (mean age 52 years) who were within 3 years of menopause were recruited. They were randomized into three arms, two of which included cyclical oral micronized progesterone (200 mg for 12 d/mo). The arms were oral low-dose Premarin (0.45 mg/d), a standard-dose weekly Climara (estradiol-17β 0.05 mg/d) patch, or placebo. After 4 years, neither Premarin nor the Climara (estradiol-17β) patch affected the rate of carotid intima–media thickness progression. There was a trend for reduced coronary artery calcification accumulation with Premarin. There were no severe adverse effects, including venous thrombosis. The investigators suggested that the study may have been underpowered to find a difference because of either the small sample size or the inadequate duration.

In contrast to the KEEPS trial, the ELITE (Early Versus Late Postmenopausal Treatment With Estradiol)[26] study did find significant benefit for oral estradiol-17β therapy on carotid intima–media thickness accumulation of plaque. The ELITE trial was a randomized, double-blind, placebo-controlled trial that evaluated the effects of oral estradiol-17β on subclinical atherosclerosis by measuring carotid intima–media thickness every 6 months and using cardiac computed tomography for coronary artery calcification score at study completion. A total of 643 postmenopausal women, stratified according to time since menopause (less than 6 years vs 10 years or more, early vs late), were randomly assigned to receive either oral estradiol-17β (1 mg/d) plus sequential micronized vaginal progesterone gel (45 mg/d, days 1–10) or placebo over a median of 5 years. The median age at enrollment was 55.4 years in the early-postmenopausal arm and 63.6 years in the late-postmenopausal arm. The median time since menopause was 3.5 years in the early-menopausal treatment arm and 14.3 years in the late-menopausal arm.

Compared with placebo, 1 mg estradiol-17β treatment resulted in significantly slower carotid intima–media thickness progression (plaque accumulation), but only among women who initiated estradiol-17β therapy less than 6 years after menopause and only at the 5-year follow-up. This finding was thought to be estradiol-17β–specific and not affected by the use of progesterone. The authors suggested that estradiol-17β therapy suppresses atherosclerosis development when initiated early after menopause. There were no significant differences in adverse events between the active treatment arms and placebo arm.

In a posttrial analysis, the ELITE study group evaluated the association between serum estradiol-17β levels and carotid intima–media thickness.[27] They found that higher estradiol-17β levels were associated with decreased carotid intima–media thickness progression rate in the early-postmenopausal group (less than 6 years after menopause) and increased carotid intima–media thickness progression rate in the late-postmenopausal group (more than 10 years postmenopausal). It is surprising that the ELITE authors did not find significant adverse cardiovascular events or other adverse events compared with placebo in the older women (median age 63.6 years) who initiated HT 10 years or more after menopause (median 14.3 years), a group with demographics similar to the those of the WHI study population. This suggests that the perceived cardiovascular safety concerns identified in the WHI with conjugated equine estrogen may not be relevant for treatment with estradiol-17β even in those women who do not initiate menopausal HT early. Potential mechanisms to explain this difference are reviewed elsewhere.[13]

How do we reconcile the different beneficial results of estradiol-17β therapy found in KEEPS and ELITE? One possibility is study duration. KEEPS was continued for only 4 years, whereas ELITE was continued for 5 years, which was when the first statistically significant difference in slowing carotid intima–media thickness progression was documented. The shorter study duration of KEEPS made it less likely that differences would be seen in 4 years because atherosclerosis is a slow, chronic progressive disease and may take longer to manifest or measure.

MENOPAUSAL HORMONE THERAPY AND VENOUS THROMBOEMBOLISM

Conjugated equine estrogen when combined with medroxyprogesterone acetate, as studied in the WHI, significantly increases the risk for venous thromboembolism (VTE), stroke, and pulmonary embolism. A population case–control study[28] from a large health maintenance organization in the Pacific Northwest published in 2014 compared the thrombosis risk in patients aged 30–79 years from 2003 to 2009. The mean age was 68.5 years. Those authors found a statistically significant increased risk of VTE with conjugated equine estrogen compared with E2 (odds ratio [OR] 1.78, 95% CI, 1.11–2.84). There was also a trend toward an increase in myocardial

infarction. In analyses of biomarkers of thrombosis, a higher level of activated protein C was found in conjugated equine estrogen users, possibly explaining the higher clotting propensity. Of note, these results were adjusted for the use of progestins. Because VTE increases with age, it is likely that age was a factor in risk as well, similar to WHI.

A more recent analysis of 51,571 veterans from 2003 to 2011 with a significantly lower mean age (54 years) demonstrated no increase in VTE risk for users of menopausal HT and no difference in risk for users of conjugated equine estrogen compared with either oral or transdermal E2.[29] The rate of VTE (1.9 per 1,000 person-years) did not differ from the baseline population risk (1–2 per 1,000 person-years).[30] VTE rates did increase with risk factors such as obesity (relative risk [RR] 1.62, 95% CI, 1.15–2.28) and age in years (RR 2.72, 95% CI, 1.78–4.15) for age older than 75 years compared with younger than 60 years.

The ESTHER (Estrogen and Thromboembolism Risk) trial[15] was a multicenter case–cohort study including women aged 45–70 years from 1999 to 2005 to assess the risk for VTE according to the route of estradiol administration and the formulation of progestogen. A total of 271 cases of first-time VTE were matched to 670 individuals in a control group and evaluated on the basis of route of estrogen administration and type of progestogen. After adjustment for potential confounding factors, the ORs for oral compared with transdermal estrogen were 4.2 (95% CI, 1.5–11.6) and 0.9 (95% CI, 0.4–2.1), respectively. Micronized progesterone and pregnane derivatives were not associated with VTE (OR 0.7, 95% CI, 0.3–1.9; and OR 0.9, 95% CI, 0.4–2.3, respectively). In contrast, norpregnane progestogens, including medroxyprogesterone acetate, were associated with a 4-fold increased VTE risk (OR 3.9, 95% CI, 1.5–10.0).

Clearly, VTE risk increases with age, and there may be an association among age, use of conjugated equine estrogen with or without medroxyprogesterone acetate, and VTE risk, whereas there appears to be no such association for estradiol-17β when administered transdermally or for micronized progesterone.[13,15]

Topical and Low-Dose Vaginal Estrogen Therapy

Despite the fear of both patients and oncologists, low-dose topical (vulvar and vaginal) estrogens appear to be safe even for people with hormone-sensitive cancers.[31] ACOG states in a consensus gynecology statement:

> If nonhormonal treatments have failed to adequately address symptoms, after discussion of risks and benefits, low-dose vaginal estrogen may be used in individuals with a history of breast cancer, including those taking tamoxifen. For individuals taking aromatase inhibitors (AIs), low-dose vaginal estrogen can be used after shared decision making between the patient, gynecologist, and oncologist.[32]

Breast cancer survivors deserve our clear communication that they will not compromise their survival by using topical therapies to improve their sexual function and their quality of life. Recently, several studies and reviews have suggested the safety of systemic HT in breast cancer survivors who have completed their tamoxifen or aromatase inhibitor course of treatment.[31,33]

WHAT ABOUT PREVENTION?

The error of extrapolating results from a beautifully designed randomized clinical trial to a population and hormonal formulations not studied in the trial has resulted in vast numbers of women having menopausal symptoms without relief and significant misunderstanding among health care professionals about the true risks and benefits of various hormone formulations for women within the menopausal transition and beyond. Currently, there is little recognition by health care professionals and very little training on the menopausal transition, a situation that has not improved in recent times.[34]

Disregarding evidence that HT can prevent osteoporosis and preserve cardiovascular function, in 2023, the USPSTF gave HT a grade of D for prevention of disease.[35] Despite 18 articles that showed marked reduction in osteoporotic fractures, any positive recommendation was negated because of the overwhelming preponderance of studies chosen from the WHI trials in older women using conjugated equine estrogen with its higher risk profile than E2. For this 2023 update, the USPSTF included only two additional RCTs compared with their 2017 analysis, both looking at the cognitive or structural brain effects of HT. Henderson et al[36] studied the effect of 1 mg oral E2 on verbal memory in women less than 6 years compared with more than 10 years after menopause in a proposal to assess the timing hypothesis. No significant differences in verbal memory as measured by the tests administered were found in either recent menopause or late treatment with 1 mg oral estradiol compared with placebo. Kantarci et al[37] compared brain magnetic resonance imaging of 95 women randomized to conjugated equine estrogen, transdermal E2, or placebo. They found a significant increase in ventricular volume with a loss of white matter in women taking oral conjugated equine estrogen but

not transdermal estradiol. No changes in cognitive function in any group could be appreciated. The remainder of the RCTs were extremely heavily weighted toward various WHI analyses, all assessing the effects of conjugated equine estrogen with or without medroxyprogesterone acetate. The USPSTF analysis included data from 39,145 individual patients, of whom fewer than 1,000 represented studies including E2. It is important to note that the authors declined to include the DOPS study. There are excellent studies showing that estradiol-17β is beneficial for the heart. A meta-analysis of randomized trials in young postmenopausal women (mean age 55 years) suggested a 27% reduction (RR 0.73, 95% CI, 0.52–0.96) in mortality with estradiol-17β–containing HT compared with no treatment.[38]

Similarly, meta-analyses limited to trial data stratified by either age or time since menopause showed that HT may decrease CVD and all-cause mortality by 30–48% when initiated in women younger than age 60 years or less than 10 years since menopause. In the most recent Cochrane systematic review evaluating RCTs of HT for preventing CHD in postmenopausal women, among women initiating HT before age 60 years or less than 10 years since menopause, CHD risk was reduced by roughly half and all-cause mortality by 30%[39] (Fig. 3). The USPSTF elected not to include the DOPS study in its updated analysis because of, "…its poor quality attributable to lack of blinding of outcomes assessors. In addition, its findings are limited by the small number of events and the imprecision of the estimates."[35] Mortality, cancer, and hospitalization for heart failure or myocardial infarction are not outcomes for which lack of blinding is likely to create bias, especially within the context of a national health care registry. The low number of events in this earlier-age population of patients in fact lends credence to the timing hypothesis and justifies the WHI choice to recruit older patients to power a study for CVD outcomes. The DOPS study did find a statistically significant reduction in the composite outcome of death or hospital admission for CVD (heart failure or myocardial infarction). The hazard ratio was 0.48 (95% CI, 0.28–0.87, P=.015), remarkably similar to the protection from CVD in the population studies that formed the impetus for the WHI. Langer et al,[40] in an editorial published in *Menopause*, discuss the public health implications associated with the USPSTF guidance against the use of menopausal HT for prevention They illustrate quite eloquently the risks associated with alternative preventive strategies such as statins for primary cardiovascular prevention (elevated risk of non–insulin-dependent diabetes mellitus) or low-dose aspirin (no cardiovascular benefit and risk of bleeding) and place the purported harms into appropriate context given current menopausal HT treatment options. Finally, even when we consider the results from the WHI CEE+MPA trial, the benefits are significant and meaningful with the potential for huge effect on public health.

ALTERNATIVE THERAPIES

Fear of breast cancer with HT has caused many people to search for alternatives. The use of "bioidentical" HT, a marketing term, as popularized by the late Suzanne Somers,[41] and the exploitation of menopausal women by industries promoting devices, supplements, and regular laboratory testing have risen exponentially. There is no evidence to support the value of any of these interventions. ACOG, the Menopause Society, and the National Academies of Sciences, Engineering, and Medicine advise against the use of compounded products when FDA-approved formulations are available. There are FDA-approved formulations of both oral and transdermal estradiol and oral micronized progesterone. In addition, ACOG does not recommend routine testing of hormones or follicle-stimulating hormone to determine menopausal status or to direct therapy.[42] Menstrual history, evaluation of symptoms, and examination are key in determining menopausal status. For women without menses related to a levonorgestrel intrauterine device, previous endometrial ablation, or hysterectomy with ovarian preservation, it may occasionally be helpful to assess hormone levels.

The FDA has recently approved a neurokinin 3 receptor antagonist for the treatment of vasomotor symptoms associated with menopause. Fezolinetant reduced vasomotor symptoms associated with menopause in about 60% of those randomized to treatment compared with a placebo response rate of 45%.[43]

Other nonhormonal interventions with evidence to support value in the treatment of menopause include the selective serotonin reuptake inhibitor paroxetine (7.5 mg), the serotonin–norepinephrine reuptake inhibitor venlafaxine, and gabapentin (off label). Paroxetine at any dose should not be given with tamoxifen because of its effect on tamoxifen metabolism. The Menopause Society also recommends cognitive–behavioral therapy, clinical hypnosis, oxybutynin, weight loss, and stellate ganglion block.[44] All of these alternatives carry their own not insignificant risks. In particular, oxybutynin is associated with a decrease in cognitive function and is contraindicated for long-term use in older patients.[45]

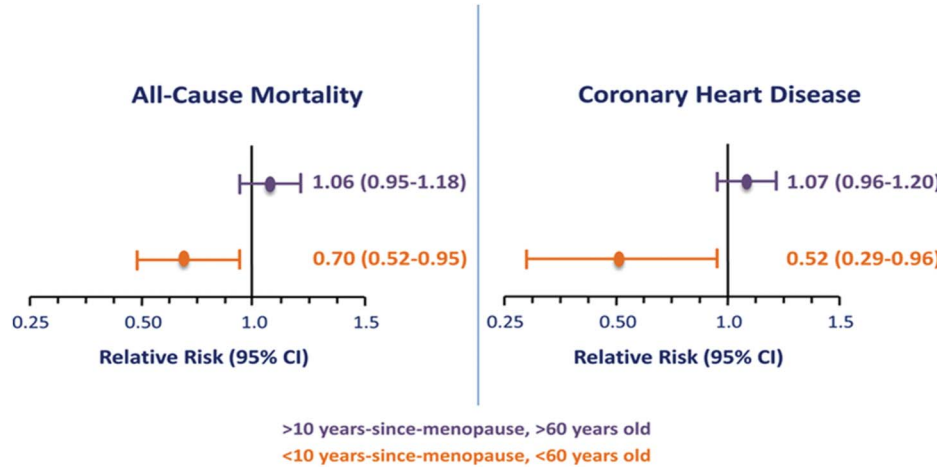

Fig. 3. Cochrane meta-analysis validates the Salpeter et al meta-analyses showing similar reductions in all-cause mortality and coronary heart disease in women initiating hormone therapy <60 year old and/or <10 years-since-menopause relative to placebo. Nineteen randomized controlled trials of 40,410 women comparing hormone therapy of estrogen with or without progestogen with placebo. Reprinted with permission from Hodis HN, Mack WJ. Menopausal hormone replacement therapy and reduction of all-cause mortality and cardiovascular disease: it is about time and timing. Cancer J 2022;28:208–23. doi: 10.1097/PPO.0000000000000591

Levy. Menopausal Hormone Therapy. Obstet Gynecol 2024.

Testosterone

ACOG suggests that a trial of transdermal testosterone therapy is appropriate for postmenopausal women with hypoactive sexual desire disorder when other causes have been addressed.[46] There is currently no testosterone product approved by the FDA for use in women despite dozens of FDA-approved options for men.[47] The typical starting dose of testosterone for women should be about 1/10th that for men. A step-by-step "how to do this" approach has recently been published by the International Society for the Study of Women's Sexual Health.[48] Given the difficulty in dividing the doses designed for men, compounding may be necessary to provide patients with a convenient mechanism for testosterone administration. The FDA and the Pharmacy Compounding Accreditation Board allow clinicians to research compounding pharmacies and find those that have not been sanctioned by the state or FDA and that voluntarily perform internal quality assurance activities.[49,50] ACOG recommends testing testosterone levels at baseline and at 3–6 weeks of therapy, not to diagnose hypoactive sexual desire disorder but to ensure that levels, with treatment, do not exceed premenopausal values.

It is estimated that 6,000 American women enter menopause every day. There is a compelling need to understand the risks and benefits of HT. To gain a clear understanding of the true risks and benefits of HT, it is time to stratify studies by age at initiation, HT formulation, and dose and route of administration. We should stop extrapolating the results of RCTs of women in their mid-60s taking conjugated equine estrogen with medroxyprogesterone acetate to recently menopausal women using isomolecular formulations, E2, and micronized progesterone. We should stop comparing oral conjugated equine estrogen with transdermal E2 and drawing conclusions about route when both formulation and route were variables. We know that there are differences in alcohols. Methanol does not behave the same way as ethanol in the body: One type of alcohol kills us, and the other has been used in social settings for millennia without fear of imminent death. The FDA clearly distinguished the outcomes with one cyclooxygenase 2 inhibitor, rofecoxib (Vioxx), withdrawn from the market by the manufacturer in 2004,[51] from studies of celecoxib (Celebrex), which remains approved. We do not consider all β-blockers or diuretics as a class when determining recommendations.

Our current system of grading the evidence in an evidence-based medicine hierarchy has neglected to consider the population studied and the true patient population in which the results and guidelines will be implemented. Many studies referenced in this article demonstrate clearly that the results from trials of significantly different hormonal formulations should not be extrapolated to inform the guidelines and labeling regarding the use of all hormones.

We know that women's increased risk for CVD, bone loss, and dementia starts with hormone loss at or near the time of menopause. Women who lose their hormones early have accelerated rates of osteoporosis, heart disease, and cognitive decline.

Newer studies using estradiol and progesterone are smaller and shorter in duration (except DOPS),

but their findings should not be discounted. It is evident that an RCT such as the WHI, powered to understand the risks and benefits of menopausal HT in an early menopausal population, is unlikely to be funded. Therefore, as we strive to develop robust and meaningful evidence about the effect of menopausal HT on the population of people who are most likely to benefit, those experiencing menopausal symptoms who are typically in their late 40s and early 50s, it will be important to combine the best data from RCTs with robust and ongoing real-world evidence to support guideline development and to develop clinical decision support. The pendulum has swung too far toward not treating menopausal women with HT. Evidence supports the use of estradiol for osteoporosis prevention, treatment of vasomotor symptoms, and prevention of CVD and premature death when started within 10 years of menopause.[21,22] The addition of micronized progesterone further enhances bone mineral density without any increase in breast cancer incidence or mortality.[52] It is time we listened to our patients and offered them the most effective therapy available for treatment of the whole person. Our patients deserve our best efforts to do this right.

CONCLUSIONS

Studies on menopausal HT should be stratified by age, formulation, and route of administration. Guidelines should be created on menopausal HT that are specific for age at onset of menopause, age at initiation of menopausal HT, and formulation and route. When appropriate, the evidence from RCTs should be combined with real-world evidence data sets to draw equitable, meaningful conclusions on outcomes that matter, including preservation of function, resolution of symptoms, and potentially prevention of long-term morbidity and mortality. To prevent harm to the public, the titles and conclusions of publications should be diligently scrutinized to ensure that they honestly and accurately represent the results of the research presented. Finally, physicians and the public should be educated on the importance of all these considerations when determining risks and benefits of menopausal HT and creating robust evidence-based guidelines.[34]

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