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MIDLIFE MENOPAUSE MANAGEMENT:

ASSESSING RISKS AND BENEFITS, INDIVIDUALIZING STRATEGIES

SUPPLEMENT EDITOR:

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Content/Overview

The management of vasomotor symptoms and other menopause-related health issues should be tailored to the individual woman, based on her assessment of her most bothersome symptom(s) and her personal priorities regarding risks, benefits, and quality of life. For most symptomatic menopausal women, hormone therapy remains the best treatment, although it does not treat all symptoms and has some well-defined risks in addition to health benefits. For women who cannot or will not use hormone therapy, an increasing number of nonhormonal therapies are available for relief of vasomotor symptoms, bone health, and treatment of urogenital atrophy.

Statement of Need

In recent years physicians and women have faced a confusing mix of information about the benefits and risks of hormone therapy for peri- and postmenopausal women. Recent data refinements and age-stratified findings from the Women's Health Initiative trial help to clarify the role of postmenopausal hormone therapy and its risk-benefit balance, especially with regard to cardiovascular disease. At the same time, emerging nonhormonal therapies for vasomotor symptoms and other menopause-related health issues are broadening the spectrum of treatments for menopausal conditions. Practicing physicians need to be familiar with these recent data on hormone therapy and newer nonhormonal therapies in order to best counsel and manage their women patients at midlife and beyond.

Learning Objectives

Upon completing this activity, participants will be able to:

- Compare and contrast new information on the cardiovascular effects of postmenopausal hormone therapy in younger, recently menopausal women as opposed to older, late-postmenopausal women
- Better understand menopausal risk assessment and explain the need to individualize therapy for symptomatic women
- Describe the controversies surrounding menopausal hormone therapy and avoid misapplying data derived from older women to younger women
- Recognize the problem of vasomotor instability in symptomatic peri- and postmenopausal women and the availability of new therapeutic options—both hormonal and nonhormonal—to deal with common menopausal symptoms.

Intended Audience

This activity is intended for internists, cardiologists, and other physicians who care for menopausal and postmenopausal women.

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From the editor

Recent years have brought forth data refinements and age-stratified information from the Women's Health Initiative (WHI). These data have enabled a better understanding of the role of postmenopausal hormone therapy (HT) and its benefit/risk equation, especially with respect to cardiovascular disease. New information on HT, together with the emergence of nonhormonal options for vasomotor symptoms and other menopause-related health issues, makes it imperative for clinicians to understand the new paradigm in evaluating and treating women at midlife.

This supplement was conceived to make internists, cardiologists, and other physicians caring for midlife women aware of this newer research, which indicates compellingly that the benefit/risk equation for HT use in younger symptomatic menopausal women is quite favorable. Since these data suggest that there may be actual cardiovascular benefit and mortality reduction with HT use in younger women, it is critical that physicians be familiar with this newer evidence in order to help their women patients make informed and individualized choices with respect to both long-term health and quality of life.

We begin with noted women's health cardiologist and researcher, Dr. Howard N. Hodis, who elucidates the latest cardiovascular data with respect to HT and provides a fascinating comparison of risks between HT and other drugs commonly used in midlife women. Then Dr. Margery Gass, a WHI investigator and North American Menopause Society (NAMS) leader, interprets WHI research and highlights key recommendations from a recent NAMS position statement on HT use in peri- and postmenopausal women. Next, women's health specialists Drs. Marjorie R. Jenkins and Andrea L. Sikon review nonhormonal therapies for menopausal problems. We conclude with an interactive discussion of actual case studies presented by obstetrician-gynecologist Dr. Margaret McKenzie.

Our approach is interdisciplinary, focusing on choice and individual options. Our aim is to update physicians who are not women's health specialists on the latest benefit/risk balance associated with HT and nonhormonal therapies.

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Assessing benefits and risks of hormone therapy in 2008: New evidence, especially with regard to the heart

ABSTRACT

Observational studies, including the observational component of the Women's Health Initiative, consistently found that women who chose to use menopausal hormone therapy (HT) had a reduction in mortality and cardiovascular disease incidence relative to women who did not use HT. Randomized controlled trials have taught us that initiation of HT in older women (> 60 years old) remote from menopause (> 10 years since menopause) potentially has more risk than benefit. Additionally, randomized controlled trials have confirmed observational studies indicating the safety and benefit of HT in young (< 60 years old) recently menopausal women (< 10 years since menopause). In other words, we have come full circle in our understanding of HT, with a caveat concerning initiation in older women. Importantly, the magnitude and types of risk associated with HT are similar to those of other commonly used therapies. These data have led to recommendations that the benefits of HT exceed the risks when initiated in menopausal women younger than 60 years.

Physicians and their women patients have faced a continuous, confusing mix of information about the risks and benefits of hormone therapy (HT) for perimenopausal and postmenopausal women, most of it without respect to age or the timing of HT relative to menopause. Initial data from the Women's Health Initiative (WHI) estrogen + progestin (E+P) trial, a prevention study conducted predominantly in older postmenopausal women without menopausal symptoms,[1] resulted in questioning of the role of HT (unfortunately and inappropriately in younger symptomatic women). Cumulative trial data and further analyses of the WHI have refined and added to our understanding of the effects of HT, particularly with regard to cardiovascular health. This review will update physicians on the latest data on the risks and benefits of HT, with a particular focus on the heart, and will put the risks of HT into appropriate clinical context.

Dr. Hodis reported that he has no financial relationships with commercial interests that pose a potential conflict of interest with this article.

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HORMONE THERAPY AND CARDIOVASCULAR DISEASE: A HISTORICAL PERSPECTIVE

Observational studies conducted prior to the WHI found consistently that women who self-selected to use HT had a reduction in mortality and in the incidence of cardiovascular disease relative to women who did not choose to use HT.[2–8] This reduction in risk was apparent whether the HT users had taken ET (estrogen therapy) or EPT (estrogen-progestogen therapy). In contrast, randomized controlled trials failed to confirm these findings from observational studies. However, the findings from randomized controlled trials were derived from older postmenopausal women who were many years past menopause. Often overlooked is the WHI observational study of ET and EPT,[9,10] in which women who chose to use HT had a reduction in the risk of coronary heart disease (CHD) similar to that observed among the HT users in other observational studies.

RECENT REPORTS FROM THE WHI

Since the original publication of the WHI E+P trial in 2002,[1] an extensive collection of data have been published in piecemeal fashion, contributing to the confusion and misperception of the effects of HT on risks and benefits. It is important to note that the WHI consists of both randomized and observational components, as detailed below, and that data have come from both. Together, these data help clarify the misperceptions generated from the first WHI report of 2002,[1] particularly misperceptions regarding the timing of

TABLE 1
Relative and absolute risks and benefits of clinical events with estrogen-progestin therapy compared with placebo in the Women's Health Initiative randomized trial (WHI E+P), 2007 update*

Health event	Overall hazard ratio	95% CI, nominal	95% CI, adjusted	Absolute risk per 10,000 women/yr	Absolute benefit per 10,000 women/yr
Coronary heart disease[12]	1.23	0.99–1.53	NR	8	—
Stroke[12]	1.31	1.03–1.68	0.93–1.84[13]	8	—
Breast cancer[14]	1.20†	‡	0.94–1.53†	8	—
Venous thromboembolism[15]	2.06	1.57–2.70	NR	18	—
Colorectal cancer[16]	0.56	0.38–0.81	0.33–0.94	—	7
Hip fracture[17]	0.67	0.47–0.96	0.41–1.10	—	5
Any fracture[17]	0.76	0.69–0.83	NR	—	47
New-onset diabetes[18]	0.79	0.67–0.93	NR	—	15

*See text for recent 2008 data analysis.
†Adjusted for age, race/ethnicity, body mass index, physical activity level, smoking, alcohol use, parity, oral contraceptive use, family history of breast cancer and fractures, frequency of screening mammography, and vasomotor symptoms.
‡Without adjustment for the covariates in the preceding footnote, the hazard ratio was 1.24 (95% CI, 1.02–1.50).
NR = not reported

HT initiation relative to menopause and the effect of HT duration on cardiovascular disease outcomes. In most instances, the conclusions drawn from this recent research run counter to the inaccurate but prevalent perception that HT use at any time and at any age is associated with cardiovascular harm, a perception that has unfortunately prevailed since the initial publication of the WHI E+P trial findings in 2002.

The WHI randomized trials and combined analysis

The WHI trials enrolled 27,347 postmenopausal women aged 50 to 79 years at baseline; almost two-thirds of the women enrolled were 60 years of age or older, and the majority of women were more than 10 years past menopause. WHI actually comprised two parallel randomized trials:

- One among 16,608 women who had not undergone hysterectomy (ie, with uterus intact), who were randomized to EPT or placebo (ie, WHI E+P trial) [1]
- One among 10,739 women who had undergone hysterectomy, who were randomized to ET or placebo.[11]

Recent analyses from the WHI, published in 2007, assessed the cardiovascular effects of ET and EPT independently and combined, both overall and according to subject age and years since menopause when randomized.[12] Other analyses following the initial WHI E+P trial publication have analyzed the effects of HT according to duration of HT use and according to secondary end points. Many of these analyses have presented risks and benefits in terms of both nominal and adjusted confidence intervals (CIs). Nominal 95% CIs describe the variability in risk estimates that would arise from a simple trial for a single end point. Although nominal CIs are traditionally used, they do not take into account the multiple statistical testing issues (across time and across outcome categories) that occur in a trial. In contrast, adjusted 95% CIs correct for these stastical testing issues. From a clinical perspective, it is most appropriate to look at the adjusted CIs.

WHI: EPT vs placebo

Table 1 enumerates current relative and absolute risks and benefits, including nominal and adjusted CIs (where available), of various end points in the placebo-controlled WHI E+P trial.[12–18]

CHD. Although the point estimate for CHD is increased, the 95% CI indicates that EPT has a nonsignificant effect on CHD outcome relative to placebo among all women randomized in the WHI E+P trial (mean age, 63 years).[12] This is a very important point for cardiologists and primary care physicians to note.

In a 2008 analysis of the WHI E+P trial that included a 2.4-year open-label follow-up subsequent to the randomized trial,[19] the randomized trial data reported were again different than in previous reports, but remained nonsignificant. The hazard ratio (HR) reported for CHD in the 2008 analysis for the randomized portion of the trial was 1.22 (95% CI, 0.99 to 1.51), as compared with 1.23 (95% CI, 0.99 to 1.53) reported

in 2007[12] **(Table 1)**, 1.24 (95% CI, 1.00 to 1.54) reported in 2003,[20] and 1.29 (95% CI, 1.02 to 1.63) reported in 2002.[1] In the 2.4-year open-label follow-up period in which women were no longer on their randomized regimens (EPT or placebo), the HR for CHD between the original randomized treatment groups was nonsignificant at 0.95 (95% CI, 0.73 to 1.26) and the change in the HR over time from the randomized phase to the open-label phase was not significant.[19]

Stroke. The risk of stroke was increased significantly (by an additional 8 events per 10,000 women treated per year) in the EPT arm versus the placebo arm in the nominal analysis,[12] but this difference was nonsignificant after adjustment.[13]

In the 2008 WHI E+P analysis, the HR reported for stroke during the randomized trial phase was different than in previous reports—1.34 (95% CI, 1.05 to 1.71)[19] versus 1.31 (95% CI, 1.03 to 1.68) reported in 2007[12] **(Table 1)**—and the adjusted analysis was not reported. In the 2.4-year open-label follow-up period in which women were no longer on their randomized regimens, the HR for stroke between the original randomized treatment groups was nonsignificant at 1.16 (95% CI, 0.83 to 1.61) and the change in the HR over time from the randomized phase to the open-label phase was not significant.[19]

Breast cancer. Breast cancer risk was originally reported to be increased significantly (by an additional 8 cases per 10,000 women per year) in the EPT arm versus the placebo arm with the nominal statistic, but this increase was nonsignificant after adjustment.[1] This risk estimate was revised in a follow-up publication 1 year after the original data were reported, and the increase in risk in the EPT arm was still no longer significant in the adjusted analysis.[21] Importantly, another subsequent analysis that adjusted for baseline risk factors for breast cancer resulted in a further revision of the risk estimate, which again showed a nonsignificant increase in the EPT arm relative to the placebo arm.[14] This is very important since it is commonly accepted that EPT increases the risk of breast cancer when this has not been definitively proven in any randomized controlled trial.

Unfortunately, the most recent breast cancer data[14] **(Table 1)** were not used in the 2008 WHI E+P analysis.[19] However, even using the unadjusted data in the 2.4-year open-label follow-up in which women were no longer on their randomized regimens, the HR for breast cancer between the original randomized treatment groups was nonsignificant and the change in the HR over time from the randomized phase to the open-label phase was not significant.[19]

Venous thromboembolism (VTE). EPT was associated with a doubling of the risk of VTE (ie, deep vein thrombosis and pulmonary embolism) compared with placebo, resulting in an excess of 18 VTE events per 10,000 women per year of therapy.[15] The risk of VTE was significant across the entire cohort of women (mean age, 63 years).

In the 2008 WHI E+P analysis, the HR reported for VTE during the randomized phase was different than in previous reports—1.98 (95% CI, 1.52 to 2.59)[19] versus 2.06 (95% CI, 1.57 to 2.70) reported in 2004[15] **(Table 1)**—and the HR during the 2.4-year open-label follow-up, in which women were no longer on their randomized regimens, was no longer significant (HR = 0.95; 95% CI, 0.63 to 1.44). This change in the HR over time from the randomized phase to the open-label phase was statistically significant.[19]

Fracture. The risk of hip fracture was reduced by 33% with EPT relative to placebo, which was statistically significant in the nominal analysis but not in the adjusted analysis.[17] The risk of any fracture was reduced by 24% in women randomized to EPT compared with placebo, which was statistically significant and translated to 47 fewer fractures per 10,000 women per year of therapy.[17] Clinically, these results are most impressive given that women randomized in the WHI were not selected on the basis of risk for osteoporosis or fracture. This claim cannot be made for any other therapy.

In the 2008 WHI E+P analysis of the 2.4-year open-label follow-up in which women were no longer on their randomized regimens, the HR between the original randomized treatment groups was nonsignificant for hip fracture and any fracture—0.92 (95% CI, 0.64 to 1.34) and 0.91 (95% CI, 0.78 to 1.06), respectively—and the change in the HR over time from the randomized phase to the open-label phase was not significant for either fracture outcome.[19]

Diabetes. The risk of new-onset diabetes was reduced by a statistically significant 21% in women randomized to EPT compared with placebo.[18]

WHI: ET vs placebo

Table 2 presents the most current relative and absolute risks, including adjusted risks (where available), of various end points in the WHI trial comparing ET with placebo in women who had undergone hysterectomy.[11,12,22–24]

CHD. Importantly, no significant difference was found between the ET and placebo arms with respect to CHD events in the overall cohort of women, whose average age was 64 years.[12]

Stroke. The risk of stroke was greater with ET than

TABLE 2
Most current relative and absolute risks and benefits of clinical events with estrogen therapy compared with placebo in the Women's Health Initiative randomized trial

Health event	Overall hazard ratio	95% CI, nominal	95% CI, adjusted	Absolute risk per 10,000 women/yr	Absolute benefit per 10,000 women/yr
Coronary heart disease[12]	0.95	0.78–1.16	NR	—	3
Stroke[12]	1.33	1.05–1.68	0.97–1.99[11]	11	—
Breast cancer[22]	0.82	0.65–1.04	NR	—	8
Venous thromboembolism[23]	1.32	0.99–1.75	NR	8	—
Colorectal cancer[11]	1.08	0.75–1.55	0.63–1.86	1	—
Hip fracture[11]	0.61	0.41–0.91	0.33–1.11	—	6
Any fracture[11]	0.70	0.63–0.79	0.59–0.83	—	56
New-onset diabetes[24]	0.88	0.77–1.01	NR	—	14

NR = not reported

with placebo in the nominal analysis, but importantly, the difference in event rates (11 per 10,000 women per year of therapy) failed to reach significance in the adjusted analysis.[11,12]

Breast cancer. A strong but nonsignificant trend toward a reduction in breast cancer risk was apparent in the ET arm (8 fewer breast cancer cases per 10,000 women per year of therapy). Among women who actually were adherent to their study regimen (ie, consuming ≥ 80% of their study medication), there was a statistically significant 33% reduction in breast cancer risk with ET relative to placebo.[22] Importantly, the reduction in breast cancer risk relative to placebo was found across all the age ranges studied.[11]

VTE. The excess risk of VTE with ET versus placebo (32%) was less than the excess risk of VTE associated with EPT **(Table 1)**. Importantly, the risk of VTE associated with ET was not statistically significant.[11,23]

Fracture. The risk of any fracture (hip or vertebral) was reduced significantly in the ET arm compared with the placebo arm.[11]

Diabetes. In a nominal analysis, there was a trend toward a reduction in the risk of new-onset diabetes in women randomized to ET relative to placebo, which nearly achieved statistical significance.[24]

WHAT EXPLAINS THE DISCORDANCE BETWEEN OBSERVATIONAL AND RANDOMIZED TRIALS OF HT?

How can the perceived discordance between the results from observational studies and those from randomized controlled trials be explained? There are currently three hypotheses:

- The populations differ in the two types of study designs (observational studies and randomized controlled trials)
- The duration of HT use differs
- The timing of HT initiation differs in relation to age, time since menopause, and stage of atherosclerosis.

Population characteristics

One obvious difference between randomized trials and observational studies of HT is the presence of menopausal symptoms. To maintain blinding, women with hot flashes were predominantly excluded from randomized trials of HT, whereas the presence of hot flashes is the predominant menopausal symptom of women included in observational studies and the main reason women seek HT from their providers.

Other consistent and possibly explanatory differences between clinical trials and observational studies of HT are patient age at enrollment, years since menopause, and body mass index (BMI). Comparing randomized controlled trials with observational studies, age at enrollment was much higher in the clinical trials (mean age ≥ 63 years) than in the observational studies (range of 30 to 55 years). Similarly, women enrolled in randomized trials were more than 10 years beyond menopause, whereas those in observational studies were less than 5 years beyond menopause. In fact, more than 80% of HT users in observational studies initiated HT within 1 or 2 years of menopause.

Additionally, women in randomized trials of HT tend to have higher BMIs than their counterparts in observational studies. For example, mean BMI was considerably higher in the WHI randomized trials

(28.5 kg/m^2 and 30.1 kg/m^2)[1,11] than in the observational Nurses' Health Study (25.8 kg/m^2),[25] and a full third (34%) of women in the WHI randomized trials were severely obese (BMI ≥ 30 kg/m^2).

This point about BMI is noteworthy in light of findings on the effect of BMI on breast cancer risk from an analysis of the WHI observational study among 85,917 women aged 50 to 79 years old at enrollment.[26] This analysis found that BMI was unrelated to breast cancer risk among women who had used HT; however, among nonusers of HT, a baseline BMI greater than 31.1 kg/m^2 was associated with a 2.52 relative risk of breast cancer compared with a baseline BMI less than 22.6 kg/m^2. The risk of breast cancer with increasing BMI was most pronounced in younger postmenopausal women. One interpretation is that high endogenous estrogen levels in postmenopausal women with an elevated BMI serve to increase breast cancer risk to a level beyond which HT adds no further risk. Alternatively, conjugated equine estrogens may act through a selective estrogen receptor modulator mechanism to block any potential adverse breast tissue effects of elevated endogenous estrone and estradiol levels.

Duration of HT

Another hypothesis for the discordant findings between observational and randomized studies of HT focuses on differences in duration of HT use between the two types of studies. Duration of HT use has been substantially longer in observational studies, ranging from 10 years to 40 years, compared with no more than 7 or 8 years in randomized trials to date. Moreover, the results from observational studies have suggested that the longer the duration of HT use, the greater the benefit in terms of CHD risk.

For example, a case-control study by Chilvers et al showed that HT protected against nonfatal myocardial infarction only when used for more than 60 months.[27] Analysis of data on EPT use from the Heart and Estrogen/progestin Replacement Study (HERS),[28] the randomized WHI E+P trial,[20] and the WHI observational study[9] reveals an interesting and consistent trend: rates of CHD events increased during the first year of EPT therapy (compared with placebo or nonuse) but then declined over time, ending up below the rates of CHD events in placebo recipients or nonusers of HT after approximately 5 years of therapy. This trend was not as pronounced with ET use in either the WHI randomized trial[29] or the WHI observational study,[10] but the incidence of CHD events did decline over time with ET use in both studies, and in the WHI observational study, greater than 5 years of ET use was associated with a significant 27% reduction (HR, 0.73; 95% CI, 0.61 to 0.84) in CHD events compared with nonuse.[10]

TABLE 3
Odds ratios for CHD events according to age and time since menopause in 23 randomized trials of HT[30]

Population	Odds ratio (95% CI), HT vs placebo
All ages	0.99 (0.88–1.11)
Women < 10 yr since menopause and < 60 yr old	0.68 (0.48–0.96)
Women > 10 yr since menopause and > 60 yr old	1.03 (0.91–1.16)
Younger (< 60 yr) vs older (> 60 yr) women	0.66 (0.46–0.95)

CHD = coronary heart disease; HT = hormone therapy

Timing of HT initiation

A third hypothesis for the discordance between randomized and observational studies of HT concerns the timing of HT initiation relative to patient age, time since menopause, and stage of atherosclerosis. As noted above, women enrolled in randomized trials have tended to be considerably older and further from menopause compared with their counterparts in observational studies. The effects of differences in timing of HT initiation on specific clinical end points, particularly in relation to cardiovascular health, are reviewed below.

CHD. Stanford University researchers performed a meta-analysis of 23 randomized trials in 39,049 postmenopausal women (representing 191,340 patient-years) in which HT use was compared with placebo.[30] The analysis revealed no difference in CHD rates between those assigned to HT and those assigned to placebo in the overall cohorts, but among women who were younger than 60 years of age and within 10 years of menopause, there was a significant 32% reduction in CHD events in HT users compared with controls **(Table 3)**. HT was also associated with a significant 34% reduction in CHD events in younger (< 60 years) versus older (> 60 years) women.

Similarly, recent analyses from the WHI randomized trials show that women who were enrolled less than 10 years from the onset of menopause had a trend toward a reduction in CHD risk with HT use.[12] The relative risk of CHD events increased progres-

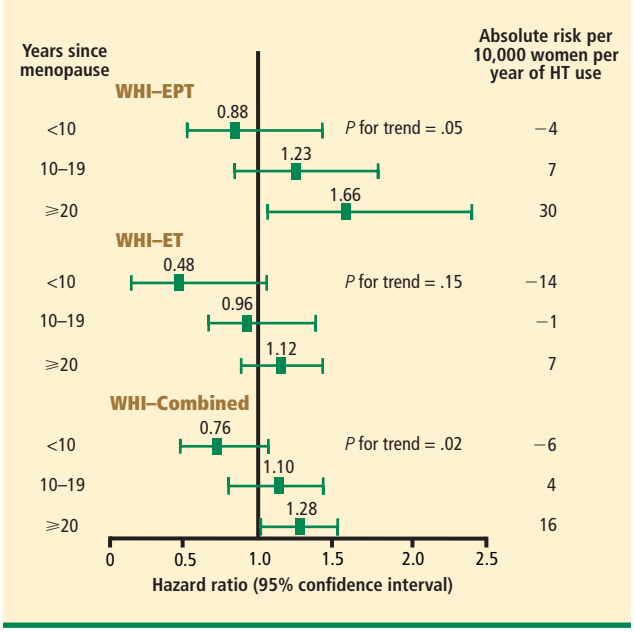

FIGURE 1. Effect of timing of hormone therapy (HT) initiation on risk for coronary heart disease events.[12] WHI = Women's Health Initiative (randomized trial); EPT = estrogen-progestin therapy; ET = estrogen therapy.

sively the further from menopause that women initiated HT. These trends held true in both the ET and EPT portions of the trial **(Figure 1)**. This same analysis showed that among WHI enrollees younger than age 60, the risk of CHD was lower in HT recipients than in placebo recipients.[12] The risk of CHD increased progressively with HT relative to placebo in women older than 60 years of age.[12]

Early and continued HT use may interrupt the pathogenic sequence of vascular aging, potentially preventing progression of atherosclerosis to the late stage at which plaque rupture and clinical events occur. In contrast, late intervention with HT may have little effect on established plaque and, in the case of EPT, may actually predispose to plaque rupture. This concept has been demonstrated in a pair of sister studies, the Women's Estrogen-Progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial (WELL-HART)[31] and the Estrogen Prevention Atherosclerosis Trial (EPAT).[32]

Mortality. The same Stanford University researchers who performed the above meta-analysis of CHD events also assessed odd ratios for overall mortality in a meta-analysis of 30 randomized trials of HT versus placebo that included a total of 26,708 postmenopausal women (representing 119,118 patient-years).[33] They found the timing of HT initiation to have an effect on mortality similar to its effect on CHD events. In the overall cohort of women, the odds of death were not different between the HT and placebo groups, but among women younger than 60 years (mean, 54 years), those randomized to HT had a significant 39% reduction in the risk of death (HR = 0.61; 95% CI, 0.39 to 0.95) compared with those randomized to placebo. HT had no effect on mortality among women older than 60 years (mean, 66 years) in this analysis.

These mortality data are consistent with those from the WHI randomized trials, in which both EPT and ET were associated with a 30% reduction in overall mortality relative to placebo among women 50 to 59 years old.[12] When both the EPT and ET portions of the WHI were combined to increase the sample size, HT was associated with a significant 30% reduction in mortality (HR = 0.70; 95% CI, 0.51 to 0.96) compared with placebo among women 50 to 59 years old.[12]

Stroke. The most recent WHI data indicate that stroke is not increased with ET in women 50 to 59 years of age, as there were 2 fewer events per 10,000 women per year of ET relative to placebo.[12] In this same age group, the risk of stroke from EPT was increased by 5 events per 10,000 women per year of therapy relative to placebo.[12] Among women randomized within 5 years of menopause, stroke risk was increased by 3 events per 10,000 women per year of EPT relative to placebo.[13]

VTE. Although age was not a significant contributing factor to the risk of VTE from HT in the WHI, the absolute risk of VTE was lower in younger versus older women. The additional absolute risk for VTE events per 10,000 women per year of EPT use was 11 events for women 50 to 59 years old at randomization, 16 events for women 60 to 69 years old at randomization, and 35 events for women 70 to 79 years old at randomization.[15] The additional absolute risk for VTE events per 10,000 women per year of ET use was 4 events for women 50 to 59 years old at randomization, 7 events for women 60 to 69 years old at randomization, and 11 events for women 70 to 79 years old at randomization.[23] A history of a prior thromboembolic event increases the risk of VTE with postmenopausal HT use, which should be considered before HT is initiated.

HORMONE THERAPY IN CLINICAL PERSPECTIVE

Comparative effects of lipid-lowering therapy and HT

Examination of the evidence regarding lipid-lowering therapy for prevention of CHD, as well as its effects on breast cancer risk and coronary artery calcium scores in women, can add some much-needed per-

TABLE 4
Comparative risks of breast cancer in randomized trials of hormone therapy and statin therapy

Therapy/study	No. of breast cancers (annualized %) Placebo	Therapy	Relative risk	95% CI	Additional cases per 10,000 women per year of therapy
EPT					
WHI–EPT	150 (0.33)	199 (0.42)	1.20	0.94–1.53	8
HERS	25 (0.45)	32 (0.57)	1.30	0.77–2.19	12
Statin therapy					
PROSPER	11 (0.23)	18 (0.38)	1.65	0.78–3.49	15
AFCAPS/TexCAPS	9 (0.35)	13 (0.50)	1.44	0.62–3.36	15
4S (10-yr follow-up)	5 (0.11)	7 (0.17)	1.44	0.46–4.52	5
CARE	1 (0.07)	12 (0.82)	12.17	2.48–59.80	77
LIPID	10 (0.22)	10 (0.22)	1.00	0.42–2.42	0
ALLHAT–LLT	37 (0.30)	34 (0.28)	0.93	0.58–1.48	−2
HPS	51 (0.40)	38 (0.30)	0.75	0.49–1.13	−10
ET					
WHI–ET	161 (0.42)	129 (0.34)	0.82	0.65–1.04	−8
17β-estradiol					
WEST	5 (0.55)	5 (0.53)	1.00	0.30–3.50	−2

EPT = estrogen-progestogen therapy; **WHI–EPT** = Women's Health Initiative estrogen + progestin trial; **HERS** = Heart and Estrogen/progestin Replacement Study; **PROSPER** = Prospective Study of Pravastatin in the Elderly Risk; **AFCAPS/TexCAPS** = Air Force/Texas Coronary Atherosclerosis Prevention Study; **4S** = Scandinavian Simvastatin Survival Study; **CARE** = Cholesterol and Recurrent Events Trial; **LIPID** = Long-Term Intervention with Pravastatin in Ischemic Disease; **ALLHAT–LLT** = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; **HPS** = Heart Protection Study; **ET** = estrogen therapy; **WHI–ET** = Women's Health Initiative estrogen trial; **WEST** = Women's Estrogen for Stroke Trial

spective and context to the HT data reviewed above.

CHD prevention. Walsh and Pignone examined six randomized controlled trials (N = 11,435) of primary prevention with lipid-lowering medication in women and found no significant effect on CHD events, nonfatal myocardial infarction, CHD mortality, or total mortality.[34] In eight randomized controlled trials of secondary prevention (N = 8,272), lipid-lowering therapy in women resulted in significant reductions in CHD end points but had no effect on total mortality.[34]

Breast cancer risk. In the WHI and in HERS, randomization to EPT resulted in nonsignificant increases of 20%[14] and 30%,[28] respectively, in the risk of breast cancer compared with placebo, and randomization to ET in the WHI was associated with a nonsignificant 18% reduction in breast cancer risk[22] **(Table 4)**. In randomized controlled trials of statins published to date,[35] the risk of breast cancer in the women randomized to a statin relative to placebo ranged from a reduction of 25% (Heart Protection Study [HPS])[36] to a 12-fold increase (Cholesterol and Recurrent Events [CARE] trial)[37] **(Table 4)**. In three meta-analyses of statins and cancer risk,[38–40] statin therapy was associated with a nonsignificant increase in breast cancer risk relative to placebo (HRs ranging from 1.04 to 1.33), accounting for 2 to 7 additional breast cancer cases per 10,000 women per year of statin use. These data suggest similar magnitudes of risk for HT and statins in terms of breast cancer diagnosis.[35]

Atherosclerosis progression. In three randomized controlled trials, 1 to 4 years of statin therapy had no effect on the progression of coronary artery calcium compared with placebo.[41–43] Among 1,064 women 50 to 59 years old who participated in a WHI substudy called the WHI Coronary Artery Calcium Study (WHI-CACS), those who were randomized to ET had significantly less coronary artery calcium at year 7 compared with those assigned to placebo.[44] The mean Agatston coronary artery calcium scores were 83.1 with ET versus 123.1 with placebo (P = .02).

Comparing risk of HT with risk of other therapies

The magnitude and types of risk associated with HT are similar to those associated with other commonly

TABLE 5
Relative and absolute risks of commonly used therapies

Therapy	Event	Risk ratio (95% CI)	Additional cases per 10,000 persons/yr
Beta-carotene[45]	Lung cancer	1.28 (1.04–1.57)	13
Calcium supplements[46]	CHD (MI, stroke, sudden death)	1.43 (1.01–2.04)	7
Atorvastatin[47]	Hemorrhagic stroke	1.66 (1.08–2.55)	18
Aspirin[48]	GI bleeding requiring transfusion	1.40 (1.07–1.83)	2
Aspirin[49]	Sudden death	1.96 (0.91–4.23)	5
Fenofibrate[50]	Total mortality	1.11 (0.95–1.29)	13
Rosiglitazone[51]	MI	1.66 (0.73–3.80)	8
Raloxifene[52]	Fatal stroke	1.49 (1.00–2.24)	20

CHD = coronary heart disease; MI = myocardial infarction; GI = gastrointestinal

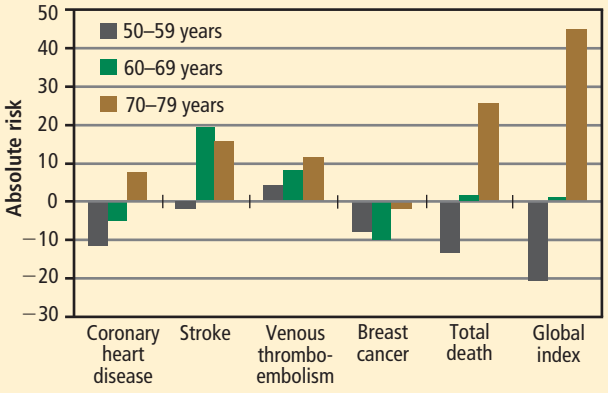

FIGURE 2. Absolute risk of clinical events associated with estrogen therapy (compared with placebo) in the Women's Health Initiative randomized trial, according to women's age at enrollment. Risk is presented as number of events (either excess or fewer) per 10,000 women per year of therapy.[11,12]

used therapies, such as vitamin supplements,[45] calcium supplements,[46] statins,[47] aspirin,[48,49] fibrates,[50] oral antidiabetic medications,[51] and selective estrogen receptor modulators[52] **(Table 5)**. For example, the risk of stroke associated with HT is less than that of fatal stroke with raloxifene[52] and the excess risk of hemorrhagic stroke with atorvastatin in secondary prevention of stroke.[47] Although comparing risks between therapies is imprecise because risk estimates are obtained from studies of different populations, it does serve to provide a perspective of the accepted magnitude of risks and reassurance concerning the safety of HT.

Other comparisons yield similar conclusions.[35] For instance, a comparison of the ET arm of the WHI randomized trial with raloxifene in the Raloxifene Use for the Heart (RUTH) trial[52] reveals similar effects on CHD, stroke, VTE, pulmonary embolism, deep vein thrombosis, and breast cancer, with the only large difference being a greater reduction in bone fracture risk with ET compared with raloxifene.[35] Finally, in putting the risk of VTE with HT into perspective, consider that the risk of thromboembolic events with selective estrogen receptor modulators[52] and with the fibric acid derivative fenofibrate in diabetics[50] is of similar magnitude as the risk with HT.

Risk must be viewed in light of age at HT initiation

Figure 2 presents the risks and benefits (in terms of CHD, stroke, VTE, breast cancer, and overall death) with ET (relative to placebo) in the WHI randomized trial according to age at enrollment.[11,12] Notably, ET recipients in the youngest age group (50 to 59 years) experienced a reduction in the risk of all outcomes except VTE. In contrast, ET recipients in the oldest age cohort (70 to 79 years) had an increase in the risk of all outcomes except, unexpectedly, breast cancer. The final column, which presents a "global index" for the cumulative events, shows that among women enrolled between ages 50 to 59, ET was associated with approximately 20 fewer events per 10,000 women per year of therapy compared with placebo. A null effect is observed among women enrolled at ages 60 to 69, and an excess of approximately 45 events is observed with ET among women enrolled at ages 70 to 79.

CONCLUSIONS FROM RANDOMIZED TRIALS

HT's effects on CHD and mortality: Timing is everything

Cumulative data from randomized trials indicate that in the overall population of women studied, HT, aspirin, and lipid-lowering therapy each have a null effect on the incidence of CHD and mortality. However, within this overall null effect, early initiation of HT (in terms of time from menopause [< 10 years] and age at initiation [< 60 years]) is associated

with reductions in total mortality and CHD incidence. Additionally, a duration of HT use beyond 5 years is associated with a reduction in the incidence of CHD.[9,10,20,28,29] These effects of the timing and duration of therapy are unique to HT. Unopposed ET may have an advantageous profile relative to EPT for reducing the incidence of CHD and mortality in postmenopausal women.

Gaining perspective on risks

The risks of stroke and VTE associated with HT are low for women overall and lower still for women who are within 10 years of menopause or younger than age 60 when they start HT. With respect to stroke, fewer cases of stroke developed in users of ET compared with placebo in women who started HT before age 60. The risks of EPT are comparable to those of other medications commonly used in this population of women. More broadly, the magnitude and types of risk associated with HT are similar to those associated with other commonly used therapies.

In addition, the underappreciated benefits of HT, such as potential prevention of diabetes mellitus (15 fewer cases of incident diabetes per 10,000 women per year with EPT and 14 fewer cases with ET), need to be recognized and discussed with our patients. These data are consistent in both observational studies and randomized trials.

The bottom line

As data from randomized trials of HT accumulate, the results are clearly similar to those from the more than 20 observational studies indicating that young, symptomatic postmenopausal women who use HT for long periods have lower rates of CHD and total mortality compared with postmenopausal women who do not use HT. Consistent with these data, the American Association of Clinical Endocrinologists issued a position statement in 2008 concluding that for symptomatic menopausal women under the age of 60, the benefits of HT exceed the risks.[53]

Nevertheless, the bottom line remains that the estrogen-cardioprotective hypothesis has yet to be studied, since randomized trials have not been conducted in the same population of women from which the hypothesis was generated. This hypothesis will be directly evaluated, however, in the ongoing Early versus Late Intervention Trial with Estradiol (ELITE). This randomized trial, funded by the National Institute on Aging, is designed to determine the effects of 17β-estradiol on the progression of atherosclerosis, cognition, and other postmenopausal health issues in recently menopausal (< 6 years) and remotely menopausal (≥ 10 years) women with no history of cardiovascular disease or diabetes. Until data from trials like ELITE emerge, guidelines such as those from the North American Menopause Society[54] (reviewed in the next article in this supplement) are reasonable for clinical practice.

REFERENCES

1. **Rossouw JE, Anderson GL, Prentice RL, et al.** Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002; 288:321–333.
2. **Rosenberg L, Palmer JR, Shapiro S.** A case-control study of myocardial infarction in relation to use of estrogen supplements. Am J Epidemiol 1993; 137:54–63.
3. **Mann RD, Lis Y, Chukwujindu J, Chanter DO.** A study of the association between hormone replacement therapy, smoking and the occurrence of myocardial infarction in women. J Clin Epidemiol 1994; 47:307–312.
4. **Psaty B, Heckbert SR, Atkins D, et al.** The risk of myocardial infarction associated with the combined use of estrogens and progestins in postmenopausal women. Arch Intern Med 1994; 154:1333–1339.
5. **Sidney S, Petitti DB, Quisenberry CP Jr.** Myocardial infarction and the use of estrogen and estrogen-progestogen in postmenopausal women. Ann Intern Med 1997; 127:501–508.
6. **Grodstein F, Stampfer MJ, Falkeborn M, Naessen T, Persson I.** Postmenopausal hormone therapy and risk of cardiovascular disease and hip fracture in a cohort of Swedish women. Epidemiology 1999; 10:476–480.
7. **Grodstein F, Manson JE, Colditz GA, Willett WC, Speizer FE, Stampfer MJ.** A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. Ann Intern Med 2000; 133:933–941.
8. **Varas-Lorenzo C, García-Rodríguez LA, Perez-Gutthann S, Duque-Oliart A.** Hormone replacement therapy and incidence of acute myocardial infarction. A population-based nested case-control study. Circulation 2000; 101:2572–2578.
9. **Prentice RL, Langer R, Stefanick ML, et al.** Combined postmenopausal hormone therapy and cardiovascular disease: toward resolving the discrepancy between observational studies and the Women's Health Initiative clinical trial. Am J Epidemiol 2005; 162:404–414.
10. **Prentice RL, Langer RD, Stefanick ML, et al.** Combined analysis of Women's Health Initiative observational and clinical trial data on postmenopausal hormone treatment and cardiovascular disease. Am J Epidemiol 2006; 163:589–599.
11. **Anderson GL, Limacher M, Assaf AR, et al.** Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA 2004; 291:1701–1712.
12. **Rossouw JE, Prentice RL, Manson JE, et al.** Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA 2007; 297:1465–1477.
13. **Wassertheil-Smoller S, Hendrix SL, Limacher M, et al.** Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. JAMA 2003; 289:2673–2684.
14. **Anderson GL, Chlebowski RT, Rossouw JE, et al.** Prior hormone therapy and breast cancer risk in the Women's Health Initiative randomized trial of estrogen plus progestin. Maturitas 2006; 55:103–115.
15. **Cushman M, Kuller LH, Prentice R, et al.** Estrogen plus progestin and risk of venous thrombosis. JAMA 2004; 292:1573–1580.
16. **Chlebowski RT, Wactawski-Wende J, Ritenbaugh C, et al.** Estrogen plus progestin and colorectal cancer in postmenopausal women. N Engl J Med 2004; 350:991–1004.
17. **Cauley JA, Robbins J, Chen Z, et al.** Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. JAMA 2003; 290:1729–1738.

18. **Margolis KL, Bonds DE, Rodabough RJ, et al.** Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: results from the Women's Health Initiative Hormone Trial. Diabetologia 2004; 47:1175–1187.
19. **Heiss G, Wallace R, Anderson GL, et al, for the WHI investigators.** Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. JAMA 2008; 299:1036–1045.
20. **Manson JE, Hsia J, Johnson KC, et al.** Estrogen plus progestin and the risk of coronary heart disease. N Engl J Med 2003; 349:523–534.
21. **Chlebowski RT, Hendrix SL, Langer RD, et al.** Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative randomized trial. JAMA 2003; 289:3243–3253.
22. **Stefanick ML, Anderson GL, Margolis KL, et al.** Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. JAMA 2006; 295:1647–1657.
23. **Curb JD, Prentice RL, Bray PF, et al.** Venous thrombosis and conjugated equine estrogen in women without a uterus. Arch Intern Med 2006; 166:772–780.
24. **Bonds DE, Lasser N, Qi L, et al.** The effect of conjugated equine oestrogen on diabetes incidence: the Women's Health Initiative randomised trial. Diabetologia 2006; 49:459–468.
25. **Grodstein F, Stampfer MJ, Manson JE, et al.** Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. N Engl J Med 1996; 335:453–461.
26. **Morimoto LM, White E, Chen Z, et al.** Obesity, body size, and risk of postmenopausal breast cancer: the Women's Health Initiative (United States). Cancer Causes Control 2002; 13:741–751.
27. **Chilvers CE, Knibb RC, Armstrong SJ, Woods KL, Logan RF.** Postmenopausal hormone replacement therapy and risk of acute myocardial infarction—a case control study of women in the East Midlands, UK. Eur Heart J 2003; 24:2197–2205.
28. **Hulley S, Grady D, Bush T, et al.** Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA 1998; 280:605–613.
29. **Hsia J, Langer RD, Manson JE, et al.** Conjugated equine estrogens and coronary heart disease: the Women's Health Initiative. Arch Intern Med 2006; 166:357–365.
30. **Salpeter SR, Walsh JM, Greyber E, Salpeter EE.** Brief report: coronary heart disease events associated with hormone therapy in younger and older women. A meta-analysis. J Gen Intern Med 2006; 21:363–366.
31. **Hodis HN, Mack WJ, Lobo RA, et al.** Hormone therapy and progression of coronary-artery atherosclerosis in postmenopausal women. N Engl J Med 2003; 349:535–545.
32. **Hodis HN, Mack WJ, Lobo RA, et al.** Estrogen in the prevention of atherosclerosis: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 2001; 135:939–953.
33. **Salpeter SR, Walsh JM, Greyber E, Ormiston TM, Salpeter EE.** Mortality associated with hormone replacement therapy in younger and older women: a meta-analysis. J Gen Intern Med 2004; 19:791–804.
34. **Walsh JM, Pignone M.** Drug treatment of hyperlipidemia in women. JAMA 2004; 291:2243–2252.
35. **Hodis HN, Mack WJ.** Postmenopausal hormone therapy in clinical perspective. Menopause 2007; 14:944–957.
36. **Heart Protection Study Collaborative Group.** MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002; 360:7–22.
37. **Sacks FM, Pfeffer MA, Moye LA, et al.** The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med 1996; 335:1001–1009.
38. **Dale KM, Coleman CI, Henyan NN, Kluger J, White CM.** Statins and cancer risk: a meta-analysis. JAMA 2006; 295:74–80.
39. **Bonovas S, Filioussi K, Tsavaris N, Sitaras NM.** Use of statins and breast cancer: a meta-analysis of seven randomized clinical trials and nine observational studies. J Clin Oncol 2005; 23:8606–8612.
40. **Baigent C, Keech A, Kearney PM, et al; Cholesterol Treatment Trialists' (CTT) Collaborators.** Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005; 366: 1267–1278.
41. **Schmermund A, Achenbach S, Budde T, et al.** Effect of intensive versus standard lipid-lowering treatment with atorvastatin on the progression of calcified coronary atherosclerosis over 12 months: a multicenter, randomized, double-blind trial. Circulation 2006; 113:427–437.
42. **Raggi P, Davidson M, Callister TQ, et al.** Aggressive versus moderate lipid-lowering therapy in hypercholesterolemic postmenopausal women: Beyond Endorsed Lipid Lowering with EBT Scanning (BELLES). Circulation 2005; 112:563–571.
43. **Arad Y, Spadaro LA, Roth M, Newstein D, Guerci AD.** Treatment of asymptomatic adults with elevated coronary calcium scores with atorvastatin, vitamin C, and vitamin E: the St. Francis Heart Study randomized clinical trial. J Am Coll Cardiol 2005; 46:166–172.
44. **Manson JE, Allison MA, Rossouw JE, et al.** Estrogen therapy and coronary-artery calcification. N Engl J Med 2007; 356:2591–2602.
45. **Omenn GS, Goodman GE, Thornquist MD, et al.** Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. N Engl J Med 1996; 334:1150–1155.
46. **Bolland MJ, Barber PA, Doughty RN, et al.** Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial. BMJ 2008; 336:262–266.
47. **Amarenco P, Bogousslavsky J, Callahan A III, et al.** High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med 2006; 355:549–559.
48. **Ridker PM, Cook NR, Lee IM, et al.** A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med 2005; 352:1293–1304.
49. **Steering Committee of the Physicians' Health Study Research Group.** Final report on the aspirin component of the ongoing Physicians' Health Study. N Engl J Med 1989; 321:129–135.
50. **Keech A, Simes RJ, Barter P, et al.** Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet 2005; 366:1849–1861.
51. **DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication) Trial Investigators.** Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: randomised controlled trial. Lancet 2006; 368:1096–1105.
52. **Barrett-Connor E, Mosca L, Collins P, et al.** Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. N Engl J Med 2006; 355:125–137.
53. American Association of Clinical Endocrinologists (AACE) position statement on hormone replacement therapy (HRT) and cardiovascular risk. American Association of Clinical Endocrinologists Web site. www.aace.com/pub/pdf/guidelines/HRTCVRISKposition_statement.pdf. Accessed March 5, 2008.
54. Estrogen and progestogen use in peri- and postmenopausal women: March 2007 position statement of The North American Menopause Society. Menopause 2007; 14:168–182.

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Highlights from the latest WHI publications and the latest North American Menopause Society position statement on use of menopausal hormone therapy

ABSTRACT

This article updates clinicians on the use of menopausal hormone therapy (HT) by reviewing key recommendations and observations from the North American Menopause Society's (NAMS) 2007 position statement on HT use in peri- and postmenopausal women and then summarizing and interpreting three new reports from the Women's Health Initiative released after the NAMS statement.

In March 2007, the North American Menopause Society (NAMS) issued an updated evidence-based position statement on the risks and benefits of hormone therapy (HT) in peri- and postmenopausal women.[1] This article will briefly review the major conclusions of that position statement and review three new reports from the Women's Health Initiative (WHI) published after the NAMS position statement.[2–4] The objective is to update clinicians on current recommendations on the use of HT and to assess, together with the preceding article in this supplement by Hodis, emerging data that will inform future recommendations.

TAKE-HOME POINTS FROM THE UPDATED NAMS POSITION STATEMENT

The 2007 NAMS position statement on HT was developed by 14 expert clinicians and researchers who used previous NAMS position statements on the topic from 2002, 2003, and 2004 as a basis. The experts then reviewed all relevant subsequent evidence from a comprehensive literature search to determine areas of consensus and nonconsensus. Twenty-four areas of consensus and two areas of nonconsensus were identified, which represented a clear increase in consensus relative to the prior NAMS position statements. Thirty-two areas were identified as requiring further research.

Key recommendations and observations from the 2007 NAMS position statement are cited below, in many cases verbatim or near verbatim to preserve the intent.[1]

Highlights of the NAMS position statement

Terminology

NAMS proposes adoption of the following terminology:

- *Estrogen therapy (ET)* for use of unopposed estrogen
- *Estrogen-progestogen therapy (EPT)* for combined use of estrogen and progestogen
- *Hormone therapy (HT)* to include both ET and EPT
- *Progestogen* to include both progesterone and progestins.

Indications for HT

- Treatment of moderate to severe vasomotor symptoms
- Treatment of moderate to severe vulvovaginal symptoms. When ET is being used only for this symptom, NAMS recommends local (vaginal) delivery.

Use of a progestogen

- Because the primary purpose of progestogen use is to prevent the endometrial cancer associated with unopposed estrogen, only women with a uterus should take a progestogen along with estrogen.
- Lack of endometrial safety data prevents NAMS from recommending long-cycle progestogen (eg, 12 to 14 days every 3 to 6 months), progestogen intrauterine systems, or low-dose estrogen without progestogen.

Dr. Gass reported that she has received consulting fees from Wyeth Pharmaceuticals, Upsher-Smith, Eli Lilly, Procter & Gamble, Palatin Technologies, Esprit Pharma, Roche, Merck, and Novartis, and has received clinical trial funding from Wyeth, Boehringer Ingelheim, Procter & Gamble, Organon, and Roche.

Dr. Gass received an honorarium for participating in the roundtable that formed the basis of this supplement. The honoraria were paid by the *Cleveland Clinic Journal of Medicine* from the educational grant from Wyeth Pharmaceuticals underwriting this supplement. Wyeth had no input on the content of the roundtable or this supplement.

- A progestogen is usually not necessary with use of low-dose vaginal estrogen.[5] However, separate from the NAMS statement is a Cochrane review of the use of vaginally administered estrogens that recommends further investigation of long-term endometrial safety with use of vaginal estrogen beyond 6 months.[6]

Cardiac and cerebrovascular disease
- HT is not recommended for prevention of coronary heart disease (CHD) at any age, pending new data to the contrary.
- HT should not be used for prevention of stroke and should be discouraged in women who have an increased risk of stroke.

Venous thromboembolism
- HT increases the risk of venous thrombosis and venous thromboembolism (VTE).

Diabetes mellitus
- Both ET and EPT reduced the risk of incident diabetes mellitus requiring treatment (by 12% and 21%, respectively, relative to placebo in the WHI).
- Evidence is insufficient to recommend HT solely for the prevention of diabetes mellitus.

Breast cancer
- EPT increased the risk of breast cancer in the WHI, but ET did not.
- Both ET and EPT increase breast cell proliferation, breast pain, and mammographic density. Diagnosis of cancer may be delayed.

Osteoporosis
- Both ET and EPT reduce the risk of postmenopausal fractures.
- HT is an option for reducing the risk of osteoporosis after the risks and benefits are weighed against those of other therapies.

Premature menopause and premature ovarian failure
- The absolute risks posed by ET and EPT may be lower in women with premature menopause or premature ovarian failure because of the lower incidence of CHD, stroke, and VTE in younger women. The risk-benefit ratio of HT is likely to be more favorable in this younger age group, but this has not yet been demonstrated.

Extended use of HT
- Extended use of HT may be considered in women who decide that menopausal symptom relief outweighs the risks of HT, particularly after an attempt to stop HT has failed.
- Extended use may be appropriate for women with vasomotor symptoms at high risk of osteoporosis-related fracture.
- Extended use may be considered for the prevention of further bone loss in women with established low bone mass when other therapies are contraindicated or are not well tolerated.

Caution on use of "bioidentical" hormones
- In the absence of further data, compounded "bioidentical" hormone preparations should be presumed to carry the known risks and benefits of HT.
- The lack of regulatory oversight with regard to purity and consistency of bioidenticals prompts caution in their use.

Areas of nonconsensus

The NAMS panel did not reach consensus on the best way to discontinue HT or on the relative safety of continuous versus sequential use of progestogen along with estrogen. Lack of data and conflicting data prevented consensus in these two areas.

UPDATES FROM THE WOMEN'S HEALTH INITIATIVE

Since the publication of the 2007 NAMS position statement, three additional important analyses have emerged from the WHI randomized trial. The first report, by Rossouw et al, examined the effects of HT on the risk of cardiovascular disease (CVD) and other outcomes according to age and time since menopause.[2] The second analysis, by Manson et al, was a post hoc study of the extent of coronary artery calcification in the 50- to 59-year-old group in the ET arm of the WHI.[3] The third analysis, by Heiss et al, reported health outcomes at 2.4 years after treatment was stopped in the EPT arm of the WHI.[4]

Cardiovascular results

The analysis by Rossouw et al of the CVD effects of HT by age and years since menopause has been reported in detail in the preceding paper by Hodis. In brief, the authors concluded that the data confirm a very low risk for women in their 50s who use HT for menopausal symptoms. The authors cautioned that the low risk from ages 50 to 59 does not guarantee lack of harm with prolonged use into older ages. Stroke and thrombosis risk were not dependent on years since menopause.

The WHI Coronary Artery Calcium Study was conducted in the ET arm approximately 1.3 years after the intervention (ET or placebo) was discontinued.[3] Participants had completed a mean 7.4 years of intervention. The 1,064 eligible and available partici-

pants were aged 50 to 59 at WHI baseline. They underwent computed tomography of the heart. More than half of the women had a coronary artery calcium (CAC) score of 0. Overall, the mean CAC score was 83.1 among those randomized to ET and 123.1 among those randomized to placebo (P = .02). Classic CVD risk factors such as smoking, diabetes, hypertension, and high cholesterol were also associated with increased CAC scores, but they did not significantly modify the effect of ET on CAC. The authors cautioned that because of the multiple and complex effects of estrogen in the cardiovascular system, further study should be completed before ET is used for prevention of CAC.

Postintervention assessment

The third key HT-related WHI paper[4] published since the 2007 NAMS position statement is the first to report the health events that occurred in the EPT arm since discontinuation of the study drugs.

Design and end points. The intervention phase of the WHI trial of EPT included 16,608 postmenopausal women (with intact uterus) aged 50 to 79 years at baseline who were randomized to treatment with EPT or placebo for a mean of 5.6 years before the treatment intervention was discontinued in July 2002 because the overall health risks of EPT were found to exceed the health benefits. Of these original participants, 15,730 women (95%) completed a planned postintervention follow-up consisting of semi-annual monitoring for adjudicated outcomes from July 2002 through March 2005. The mean duration of postintervention follow-up was 2.4 years.[4]

The primary outcomes of this postintervention analysis were CVD events and invasive breast cancer. These end points, together with endometrial cancer, colorectal cancer, stroke, pulmonary embolism, hip fracture, and death, were also factored into a global index of risks versus benefits with EPT.

Results. *CVD.* There was neither an elevated risk nor a decreased risk of CHD after discontinuation of EPT (hazard ratio [HR] = 0.95; 95% CI, 0.73 to 1.26). Risks that were elevated in the intervention phase, such as deep vein thrombosis (DVT) and stroke, disappeared after EPT was stopped. Women originally randomized to EPT had a similar rate of all CVD events compared with those who had been randomized to placebo (HR = 1.04; 95% CI, 0.89 to 1.21).

Breast and other cancers. The annualized incidence of invasive breast cancer in the postintervention period was 0.42% in the group that had been randomized to EPT versus 0.33% in the group randomized to placebo. This translated to a nonsignificant HR of 1.27 (95% CI, 0.91 to 1.78) for the postintervention period. In contrast, the annualized rate of all cancers (endometrial, colorectal, and breast combined) in the postintervention period was significantly higher in the EPT group (1.56%) than in the placebo group (1.26%) (HR = 1.24; 95% CI, 1.04 to 1.48). More extensive analysis of this finding is under way.

The cancer findings from this 2.4-year postintervention phase of the WHI parallel those from the 2.7-year postintervention phase of the Heart and Estrogen/progestin Replacement Study (HERS), in which between-group differences in the rates of breast and colon cancers approached null as the incidences of lung and other cancers increased in the group that had been randomized to EPT.[7]

Fractures. During the intervention phase, EPT was associated with a significant reduction in fractures; however, the EPT fracture benefit disappeared within the 2.4-year follow-up period.

Mortality. There was little difference in all-cause mortality between the treatment groups in the intervention phase. Although the difference was not statistically significant, there was a 15% higher mortality rate in the EPT group during the postintervention phase (HR = 1.15; 95% CI, 0.95 to 1.39). Contributing in part to this difference was an increased risk of mortality from lung cancer that requires further exploration.

Global index. The global index of risks versus benefits from enrollment to the present analysis remained significantly elevated (HR = 1.12; 95% CI, 1.03 to 1.21), suggesting more risk than benefit from use of EPT. The increase in the global index loses significance when the postintervention phase is considered alone (HR = 1.11; 95% CI, 0.99 to 1.27).

Conclusions. The researchers concluded that a number of outcome patterns observed with EPT in the intervention period of the WHI randomized trial did not persist during the 3-year postintervention follow-up:

- CHD, DVT, and stroke risks disappeared
- Hip fracture and total fracture benefits disappeared
- The composite risk of all cancers increased and was statistically significant in the postintervention phase, although the elevated risk of breast cancer was no longer statistically significant in the postintervention phase.

Summary of the new WHI reports

These three recent papers from the WHI suggest lower risks with short-term use of EPT in women ages 50 to 59 compared with older women. A delay in atherosclerosis and a decrease in all-cause mortality

were also noted in this age group. The postintervention follow-up findings of a rapid disappearance of most risks and benefits of EPT will be of interest to patients who want to know what to expect when they discontinue HT. The late development (in years 5 to 8) of an increase in the composite risk of all cancers merits further investigation.

REFERENCES

1. Estrogen and progestogen use in peri- and postmenopausal women: March 2007 position statement of The North American Menopause Society. Menopause 2007; 14:168–182.
2. **Rossouw JE, Prentice RL, Manson JE, et al.** Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA 2007; 297:1465–1477.
3. **Manson JE, Allison MA, Rossouw JE, et al.** Estrogen therapy and coronary-artery calcification. N Engl J Med 2007; 356:2591–2602.
4. **Heiss G, Wallace R, Anderson GL, et al, for the WHI investigators.** Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. JAMA 2008; 299:1036–1045.
5. The role of local vaginal estrogen for treatment of vaginal atrophy in postmenopausal women: 2007 position statement of The North American Menopause Society. Menopause 2007; 14:357–369.
6. **Suckling J, Lethaby A, Kennedy R.** Local oestrogen for vaginal atrophy in postmenopausal women. Cochrane Database Syst Rev 2003/2006; (4):CD001500.
7. **Hulley S, Furberg C, Barrett-Connor E, et al.** Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). JAMA 2002; 288:58–66.

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Update on nonhormonal approaches to menopausal management

ABSTRACT

The risk-benefit evaluation for managing vasomotor symptoms and other menopause-related health issues should be tailored to each individual woman, taking into account her own assessment of the most bothersome symptom(s) and her personal weighting of risks versus quality of life. For most symptomatic menopausal women, hormone therapy (HT) remains the best treatment, but various nonhormonal options are available for treating menopausal symptoms and bone loss in women who are unable or unwilling to take HT. Low doses of local vaginal estrogen remain an option for treatment of vaginal atrophy in these women. This article reviews alternatives to systemic HT for treating menopausal symptoms and related health issues.

As the life expectancy of women in the United States now exceeds 80 years,[1] many millions of US women will spend more than one-third to even one-half of their lives beyond menopause. While hormone therapy (HT) can effectively address many of the symptoms of menopause, women who are unwilling or unable to take HT need nonhormonal alternatives for treatment of menopausal symptoms as well as the estrogen-deficiency bone loss that ensues in many women. This article reviews current and experimental nonhormonal therapies for menopausal symptoms and related issues, such as midlife sexual dysfunction and maintenance of bone health.

DEFINING THE TERMINOLOGY OF MENOPAUSE

We begin the discussion of menopausal health with a clarification of some terms.[2]

Dr. Jenkins reported that she has received honoraria for teaching/speaking from Pfizer. **Dr. Sikon** reported that she has no financial relationships with commercial interests that are relevant to this article.

Each author received an honorarium for participating in the roundtable that formed the basis of this supplement. The honoraria were paid by the *Cleveland Clinic Journal of Medicine* from the educational grant from Wyeth Pharmaceuticals underwriting this supplement. Wyeth had no input on the content of the roundtable or this supplement.

Menopause refers to the final menstrual period and simply represents a point in time. Menopause can be diagnosed only a year after it occurs, when it is clear that the last menstrual period was truly the final one.

Perimenopause consists of three components: the period shortly before menopause (when the biological and clinical features of impending menopause begin), menopause itself (final menstrual period), and the year following menopause. Perimenopause is synonymous with *menopausal transition*.

Postmenopause is the period beginning at the time of the final menstrual period (menopause), although it is recognized only after a year of amenorrhea. The *early postmenopausal phase* is the first 5 years after menopause, whereas all the time thereafter is referred to as the *late menopausal phase*.

MENOPAUSAL ASSESSMENT

Symptoms

The primary symptoms of perimenopause are:

- Vasomotor symptoms (eg, hot flashes, night sweats)
- Menstrual cycle changes (ie, oligomenorrhea, amenorrhea)
- Vaginal dryness.

Secondary symptoms include sleep disturbance, low sex drive and/or reduced sexual arousal, stress or urge urinary incontinence, mood changes, and somatic complaints.

Vasomotor symptoms, vaginal dryness, and dyspareunia (painful intercourse) contributing to sexual dysfunction have been correlated with the loss of sex hormones (particularly estrogen) associated with menopause, whereas the other symptoms listed above (sleep disturbance, urinary symptoms, mood changes, somatic symptoms) have not been linked definitively to menopause and may be a function of aging.[2]

Vasomotor symptoms are the predominant reason that women seek medical treatment around the time of menopause.[3] More than 75% of women report hot flashes within the 2 years surrounding menopause. Among these women who have hot flashes, 25%

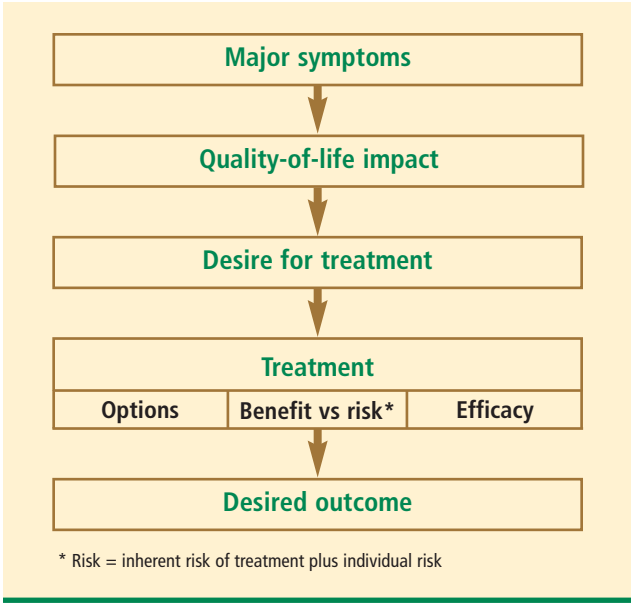

FIGURE 1. Key components of the menopausal assessment.

report that these symptoms remain for greater than 5 years, and 10% report that they remain for more than 10 years.[3] Vasomotor symptoms may be associated with sleep disturbance, mood swings, cognitive deficits, social impairment, a reduction in productivity, embarrassment, anxiety, and fatigue.

Individualizing the evaluation is imperative

Assessment of symptoms and their impact on quality of life is a key component of the menopausal evaluation **(Figure 1)**. During this visit, the most bothersome symptoms are elicited and the patient's desire for treatment to relieve symptoms is assessed. The risks and benefits of various treatment options, both hormonal and alternatives to HT, are discussed. The risk-benefit ratio will depend on the inherent risks of each treatment, the individual patient's risk profile, and the desired outcomes.

The overall patient must be considered in this assessment, which includes her personal history, family history, social history, and current medication use. Common factors affecting postmenopausal health—such as bone density; vaginal, bladder, and sexual function; cardiovascular health (including lipid profile, blood pressure, and tobacco use); thromboembolic risk; and cancer risk, including breast cancer—should be included in the assessment. For most women under the age of 60 years who have menopausal symptoms, HT remains the gold standard and recommended treatment, according to both the American Association of Clinical Endocrinologists[4] and the North American Menopause Society.[5] However, for women who cannot or will not take HT, there are other treatment options to consider.

ALTERNATIVE TREATMENTS FOR VASOMOTOR SYMPTOMS: FOCUS ON NONHORMONAL OPTIONS

Options for the treatment of vasomotor symptoms include lifestyle modification, HT, nonhormonal centrally acting agents, and complementary and alternative medicine. Lifestyle modifications to cope with hot flashes include dressing in layers, adjusting room temperature, and deep breathing and relaxation exercises. Complementary and alternative medical approaches to vasomotor symptoms have generally not been evaluated in well-designed studies or have been found ineffective, so they will not be discussed further here. HT was discussed at length in the previous articles in this supplement, and because of its perceived risks, some women are unwilling to use HT. For these women, and particularly for those with contraindications to HT—especially those with breast cancer treated with medications that promote severe vasomotor symptoms—nonhormonal alternatives for vasomotor symptom treatment clearly are needed. Centrally acting agents show the most promise in this regard.

The rationale for a nonhormonal approach

Development of vasomotor symptoms seems to be related to the withdrawal of gonadotropins and the instability of serotonin and norepinephrine in the hypothalamus.[6–9] A small increase in core temperature precedes a vasomotor symptom episode in approximately 70% of women. A narrowing of the hypothalamic thermoregulatory set point is followed by an increasing sensation of intense heat and peripheral vasodilation, leading to an exaggerated response (ie, severe sweating and flashing) to the very small rise in core temperature. This pathophysiology of vasomotor symptoms is the basis for the use of alternatives to HT, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs).

In general, studies of nonhormonal pharmacologic agents are limited by small numbers of patients, short duration of therapy, and high placebo response rates **(Table 1)**. Because of a lack of head-to-head trials, the relative efficacy of nonhormonal therapies cannot be determined at this time. As with HT, a dose-response relationship with respect to efficacy and side effects has been observed with nonhormonal therapies.

TABLE 1
Clinical trials of commonly used nonhormonal centrally acting agents for vasomotor symptoms

Drug	No. of trials	Effect	Dosage	No. of pts	Duration	Study design
SSRIs						
Citalopram	3	Reduced severity/ frequency (2 of 3 trials)	10–30 mg	18–122	4 wk–9 mo	PC, DB (1 of 3)
Fluoxetine	2	Reduced severity/ frequency (1 of 2 trials)	10–30 mg	68–150	4 wk–9 mo	PC, DB (1 of 2); PC, DB, R (1 of 2)
Sertraline	1	Subjective improvement	25–250 mg	15	Not reported	Retrospective, uncontrolled
Fluvoxamine	1	Reduced frequency	50 mg (given with estrogen)	42	8 wk	Open trial, estrogen alone as control
Paroxetine	5	Reduced severity/ frequency (5 of 5 trials)	10–37.5 mg	22–165	4–9 wk	PC, DB, R (2 of 5)
SNRIs						
Venlafaxine	6	Reduced severity/ frequency (3 of 6 trials)	25–150 mg	28–191	4–12 wk	PC, DB, R (2 of 6)
Desvenlafaxine[20,21]	2	Reduced severity/ frequency (2 of 2 trials)	50–200 mg	541–620	12–52 wk	PC, DB, R (2 of 2)
Duloxetine[19]	1	Reduced frequency	60–120 mg	20	8 wk	Open-label
Anticonvulsants						
Gabapentin[22,23]	6	Reduced severity/ frequency (6 of 6 trials)	900–2,700 mg	20–371	5–12 wk	PC, DB, R (3 of 6); C, R (1 of 6)
Alpha$_2$-adrenergic agonists						
Clonidine	8	Reduced severity/ frequency (5 of 8 trials)	0.5–1.5 mg	10–194	6–13 wk	PC, DB (8 of 8)

SSRIs = selective serotonin reuptake inhibitors; SNRIs = serotonin-norepinephrine reuptake inhibitors; PC = placebo-controlled, DB = double-blind; R = randomized; C = controlled
Adapted from Rapkin[13] with additions of more recent studies indicated by the referenced study citations within table body.

SSRIs

As detailed in **Table 1**, studies of SSRIs have usually been only weeks in duration, have often been uncontrolled or retrospective in design, and have generally enrolled small numbers of patients, making it difficult to draw valid conclusions from their data.[10–13] Overall, the results with SSRIs are mixed with respect to efficacy in reducing the incidence and severity of vasomotor symptoms.

Most studies of SSRIs for this indication have been performed with paroxetine, which has the highest affinity for the norepinephrine receptor among the SSRIs. Fluoxetine and paroxetine have each been studied in randomized controlled trials in menopausal women with vasomotor symptoms, and each has resulted in a reduction in the frequency and severity of those symptoms compared with placebo.[11,12] The North American Menopause Society (NAMS), in its 2004 position statement on management of menopause-related vasomotor symptoms,[5] and the National Institutes of Health[2] have recognized fluoxetine and paroxetine as possible alternatives to HT for the treatment of vasomotor symptoms.

One cautionary note is required with SSRI use in this setting: because SSRIs are strong inhibitors of CYP2D6, an enzyme important in the metabolism of tamoxifen,[14] the potential for interactions between SSRIs and tamoxifen must be recognized. In breast cancer patients with the CYP2D6 genotype, paroxetine reduced plasma levels of the active metabolite of tamoxifen.[15]

SNRIs

Studies of SNRIs have also enrolled few patients, with treatment durations of 4 to 52 weeks **(Table 1)**.[10,13]

Venlafaxine has been the most widely studied of the SNRIs, but the longest follow-up in studies of venlafaxine has been only 12 weeks.[10,13,16–18] It has been

shown to reduce the frequency and severity of vasomotor symptoms in several studies, and two of its studies had randomized controlled designs.[16,18] In its 2004 position statement, NAMS recognizes low-dose venlafaxine (37.5 to 75.0 mg) as a nonhormonal alternative for the treatment of vasomotor symptoms.[5]

Duloxetine has been assessed in a single published clinical trial for vasomotor symptoms, a small, 8-week, open-label investigation that demonstrated a small reduction in the frequency of vasomotor symptoms with its use.[19]

Desvenlafaxine succinate, the active metabolite of venlafaxine, was approved by the US Food and Drug Administration (FDA) in February 2008 for the treatment of major depressive disorder. It is currently under FDA review for treatment of menopause-related vasomotor symptoms and is expected to be the first FDA-approved nonhormonal agent for the treatment of menopausal vasomotor symptoms. Among the centrally acting agents studied for treatment of vasomotor symptoms, desvenlafaxine has been assessed in the largest randomized controlled trials to date.

In a randomized trial of 541 menopausal women with hot flashes, both dosages of desvenlafaxine tested (100 and 150 mg/day) were associated with a sustained significant reduction in the incidence of moderate to severe vasomotor symptoms compared with placebo over the 12 to 26 weeks of treatment.[20] Withdrawal of desvenlafaxine was associated with a recurrence of symptoms, which the study authors argue is proof that the drug was responsible for the reduced incidence of vasomotor symptoms, despite the large placebo effect observed in the study.

Another randomized trial compared four dosages of desvenlafaxine (50, 100, 150, or 200 mg/day) with placebo in 707 healthy postmenopausal women who experienced at least 50 moderate to severe hot flashes per week.[21] Among the 620 evaluable women, the best results overall were seen with the 100-mg dose of desvenlafaxine, which was associated with a 64% reduction from baseline in the average daily number of hot flashes at week 12. Compared with the placebo group, significantly greater percentages of patients achieved a 75% or greater reduction in the number of hot flashes from baseline in the 100-, 150-, and 200-mg dose groups at week 4, and in the 100- and 200-mg dose groups at week 12.

The most common side effects associated with desvenlafaxine were nausea, dizziness, and insomnia. The most common symptoms that occurred upon discontinuation were dizziness, nausea, and headache.[21] The rate of discontinuation with desvenlafaxine was lowest in the group assigned to 50 mg, which suggests a dose-related effect in terms of side effects. It should be noted that desvenlafaxine in this study was started at full dosage without titration and was discontinued abruptly, practices that are not typical with the use of venlafaxine and may account for the above-mentioned side effects.

SNRIs are weak inhibitors of CYP2D6 and therefore represent a good nonhormonal alternative for vasomotor symptoms in breast cancer patients being treated with tamoxifen.

Anticonvulsants

Gabapentin is an anticonvulsant that has been assessed in several trials for the treatment of vasomotor symptoms, showing superior efficacy to placebo in all placebo-controlled trials **(Table 1)**. Its mechanism of action against hot flashes is uncertain, but it has been theorized that gabapentin may modulate calcium currents.[5]

In addition to the placebo-controlled trials mentioned above, gabapentin has been assessed in comparison with estrogen[22] and in combination with antidepressants.[23] One study randomized 60 postmenopausal women with moderate to severe hot flashes to treatment with conjugated estrogens (0.625 mg/day), gabapentin (titrated to 2,400 mg/day), or placebo for 12 weeks.[22] Gabapentin and estrogen were similarly effective in reducing the study's primary outcome measure—hot flash composite score at 12 weeks—and each was significantly superior to placebo in this regard.

Another study assessed gabapentin in combination with antidepressants (mostly venlafaxine or paroxetine) in 118 women with inadequate hot flash control, 91 of whom were evaluable at 5 weeks.[23] Three-fourths of the study population had a history of breast cancer, and two-thirds were taking tamoxifen or an aromatase inhibitor at entry. Women were randomized either to remain on their antidepressant and have gabapentin added or to be weaned off their antidepressant and switched to gabapentin monotherapy. Gabapentin alone was associated with a statistically significant 50% median reduction in hot flash frequency from baseline, with no additional efficacy induced by continuation of the antidepressant. Negative mood changes and nervousness by week 2 were noted in the women who discontinued their antidepressants, although there was no change in quality-of-life evaluations.

The most common side effects of gabapentin in this clinical setting have been somnolence, disorientation, and headache. Notably, the effective dosages

of gabapentin studied in women with vasomotor symptoms were higher (900 to 2,700 mg/day) than is sometimes possible to achieve in real-world practice, so the clinical relevance of these studies may be somewhat limited. Nevertheless, the NAMS position statement recognizes gabapentin as an alternative to HT for treating vasomotor symptoms.[5]

Alpha$_2$-adrenergic receptor agonists

The alpha$_2$-adrenergic receptor agonist clonidine has been used for treatment of hot flashes, but its efficacy has been modest at best in small trials of short duration **(Table 1)**. The total daily doses used ranged from 0.5 mg to 1.5 mg, and side effects of dry mouth and dizziness were reported to cause relatively high discontinuation rates. While clonidine is an option, it should be reserved for patients who are intolerant of the other nonhormonal options discussed above.

Special considerations in breast cancer patients

Women with breast cancer merit special consideration, for several reasons. First, their cancer constitutes a contraindication to HT, so they are leading candidates for nonhormonal approaches to vasomotor symptom control. Second, chemotherapy itself may induce menopausal symptoms. Finally, vasomotor symptoms are often induced by other common (and longer-term) breast cancer therapies, including aromatase inhibitors (ie, anastrozole, exemestane, letrozole) in addition to tamoxifen, as mentioned above. Because SSRIs are strong inhibitors of CYP2D6, which is critical to tamoxifen metabolism, the SNRIs or gabapentin are preferred nonhormonal options in women taking tamoxifen.

Vitamin E: Scant evidence for symptom improvement, but a role in VTE prevention?

Vitamin E was frequently recommended in the past as a possible nonhormonal alternative to treat vasomotor symptoms, but small clinical trials have shown that it is not much more likely than placebo to be effective for this indication. Evidence from the Women's Health Study indicates, however, that any value of vitamin E supplementation in this population may lie in reducing the risk of venous thromboembolism (VTE).[24] In this large placebo-controlled trial, randomization to 600 IU of alpha-tocopherol every other day was associated with modest reductions in VTE overall and more significant reductions among the subgroup of women at highest risk for VTE—ie, those with a history of prior VTE or a prothrombotic mutation.

TABLE 2
Treatment options for vaginal dryness and atrophy

Nonhormonal options for vaginal dryness (nonprescription)

Moisturizers
(eg, Replens, Silk-E, RepHresh [lowers vaginal pH])

Lubricants
(eg, K-Y Jelly, Lubrin, Astroglide)

Oils
(vitamin E, olive oil)

Vaginal estrogen therapy options for vaginal atrophy*

Estrogen vaginal creams
(estradiol [Estrace Vaginal], conjugated estrogens [Premarin Vaginal])
—Daily for 2 weeks, then 1–3 times per week

Estradiol hemihydrate vaginal tablet (Vagifem)
—Daily for 2 weeks, then 2 times per week

Estradiol vaginal ring (Estring)
—Once every 3 months

* All of these local estrogen preparations are equally effective at recommended doses. Estrogen absorption appears to be highest with the creams, followed by the tablet, followed by the ring.

ALTERNATIVES TO SYSTEMIC ESTROGEN FOR OTHER MENOPAUSAL HEALTH ISSUES

Vaginal atrophy

Nonhormonal vaginal lubricants and moisturizers **(Table 2)** are considered first-line nonhormonal therapies for vaginal atrophy, according to a 2007 NAMS position statement on vaginal atrophy in postmenopausal women.[25] Nonhormonal lubricants do not restore the integrity of the vagina, however. Beyond these options, low-dose local vaginal estrogen delivery **(Table 2)** is effective and well tolerated for vaginal atrophy, according to the same NAMS statement. Topical low-dose vaginal estrogen limits systemic absorption and generally does not require the use of progestogen.[25] Focusing estrogen therapy to localized vaginal administration is recommended when a woman complains only of vaginal atrophic symptoms.

New research is helping to define just how "low" low-dose topical therapy can go while still providing efficacy. A recent placebo-controlled trial compared 10-μg and 25-μg strengths of estradiol-containing vaginal tablets for vaginal atrophy in 230 postmenopausal women.[26] Over the 12-week study, both doses of estradiol significantly improved vaginal maturation, lowered vaginal pH, and reduced the severity of vaginal symptoms compared with placebo.

Although improvements were greater with the 25-μg dose, the results suggest that 10-μg topical estradiol is an effective option for women with vaginal atrophy who wish to minimize their exposure to estrogen.

Although there is insufficient evidence to support endometrial surveillance in asymptomatic women using vaginal estrogen, such surveillance may be indicated in women at high risk for endometrial cancer, in those requiring a higher dose for vaginal atrophy relief, and in those with spotting or breakthrough bleeding.[25]

Sexual dysfunction

Sexual dysfunction is not directly caused by the menopausal transition but is multifactorial, involving physical health, mental health, relationship dynamics, and partner availability, among other factors. The two most common complaints relating to sexual dysfunction in women at midlife are lack of desire and hypoarousal.

A number of therapies are currently under investigation for treatment of female sexual dysfunction at midlife. These include the same low-dose vaginal estrogen preparations used for vaginal atrophy as well as newer approaches currently in clinical testing, such as the melanocortin receptor agonist bremelanotide[27,28] and topical alprostadil,[29] both of which act by inducing sexual arousal. In a study of premenopausal women with sexual arousal disorder, bremelanotide increased both genital arousal and sexual desire.[30]

The most widely studied pharmacotherapy approach to sexual dysfunction has been testosterone replacement. A recent Cochrane review assessed the results of 23 trials that evaluated the addition of testosterone to HT (estrogen with or without progestogen) in 1,957 peri- and postmenopausal women.[31] It found that adding testosterone to HT has a beneficial effect on sexual function in postmenopausal women but also confers the adverse effect of reducing levels of high-density lipoprotein cholesterol. The authors concluded that the impact of testosterone therapy on other health outcomes in estrogenized postmenopausal women is unclear, as is the existence of a benefit in sexual function for perimenopausal women.

In addition to systemic testosterone, a transdermal testosterone patch has been studied for treatment of sexual dysfunction in postmenopausal women; FDA evaluation of the patch is awaiting the availability of long-term safety data, although the testosterone patch for women is available in Europe.

According to a 2005 NAMS position statement on testosterone therapy,[32] postmenopausal women presenting with symptoms of decreased sexual desire that causes personal distress may be candidates for testosterone therapy. The NAMS statement further clarifies that all other identifiable causes of sexual dysfunction should be considered and ruled out as appropriate. Because of a lack of safety and efficacy data on the use of testosterone therapy in unestrogenized women, testosterone therapy alone cannot be recommended in women not taking concomitant estrogen.[32]

Bone health

Many alternatives to systemic HT exist for maintaining bone health, including calcium and vitamin D supplementation, bisphosphonates, selective estrogen receptor modulators, calcitonin, recombinant human parathyroid hormone, and ultralow-dose transdermal estradiol. Beyond calcium and vitamin D supplementation, the most appropriate options for most women will likely be bisphosphonates or transdermal estradiol.

Ultralow-dose (0.014 mg/day) transdermal estradiol has been shown to significantly increase bone mineral density (BMD) at both the hip and the spine in postmenopausal women compared with placebo.[33] However, the only agent that has demonstrated fracture risk reduction in women who do not otherwise have osteoporosis is standard-dose estrogen therapy (eg, 0.625 mg conjugated equine estrogens). Lower doses of estrogen, which may maintain bone density, do not have data on fracture risk reduction. Although lower doses of estrogen have been found to increase BMD, there is a dose-dependent response, with higher doses producing more of an increase.[34,35]

Bisphosphonates. The oral bisphosphonates, alendronate and risedronate, have proven efficacy in reducing hip fracture rates in women who already have osteoporosis. Risedronate recently gained FDA approval for administration in a regimen involving two 75-mg tablets taken on a monthly (consecutive-day) basis, and a 150-mg monthly risedronate tablet is expected soon.

Zoledronic acid, an injectable bisphosphonate, recently gained FDA approval for administration as a once-yearly intravenous infusion after this regimen was shown in a large 3-year placebo-controlled trial to significantly reduce the risk of morphometric spine, hip, nonvertebral, wrist, and rib fractures in postmenopausal women with osteoporosis.[36] In this trial, atrial fibrillation was more common in women treated with zoledronic acid than in those who received placebo. However, any link between zoledronic acid and atrial fibrillation is uncertain, since episodes of atrial fibrillation tended to occur more than 30 days after the infusion and since circulating active levels of zoledronic acid persist for only up to 1 week. (A history of arrhyth-

mia or atrial fibrillation is not listed in FDA-approved labeling as a contraindication to zoledronic acid.) Also, there was no increased risk of jaw osteonecrosis in subjects treated with zoledronic acid.[36]

Intravenous dosing can be helpful when patients have intolerable gastrointestinal side effects or other contraindications to oral dosing, as well as to ensure adherence.

Ibandronate is another bisphosphonate that has been shown to reduce the risk of vertebral fractures. It is administered as a once-monthly oral dose or as an intravenous injection given every 3 months. Although these less-frequent dosing regimens can be more convenient for patients and the injectable form can eliminate gastrointestinal side effects, widespread use of ibandronate has been limited somewhat by a lack of evidence for reduction of nonvertebral and hip fractures.[37]

Raloxifene is the only selective estrogen receptor modulator (SERMs, which the FDA recently requested be called "estrogen agonists/estrogen antagonists") approved for the prevention and treatment of osteoporosis in postmenopausal women. Raloxifene reduced the vertebral fracture rate by 40% to 50% over 2 to 4 years of use but did not reduce nonvertebral fracture rates. Raloxifene also reduces the risk of invasive breast cancer development.[38,39] It has not been shown to lower the risk of coronary events or overall stroke risk but was instead associated with an increased risk of VTE and fatal stroke.

Synthetic recombinant human parathyroid hormone (PTH[1–34]; teriparatide) is currently the sole available agent in the new class of bone anabolic agents, although others are on the horizon. PTH(1–34) is given as a once-daily subcutaneous injection for up to 2 years of therapy. It is associated with a reduction in the risk of vertebral and nonvertebral fractures and is indicated for postmenopausal women (and men) with osteoporosis who are at high risk for fracture, as well as those in whom other medications have failed or are not tolerated.

Although rat studies revealed a potential increased risk for osteosarcoma with PTH(1–34) use, this has not been seen in any human studies or in postmarketing surveillance. As the risk was dependent on dose and duration of therapy, use of PTH(1–34) is not recommended for more than 2 years or in patients at increased risk for osteosarcoma.

Concomitant use of PTH(1–34) with a bisphosphonate seems to blunt its effect and is therefore to be avoided. Resumption of bisphosphonate use after 2 years of PTH(1–34) therapy seems to prevent the loss of densitometric gains that ensues upon cessation of PTH(1–34).[40]

Calcitonin is an older agent administered mainly as a nasal spray. It reduces vertebral fracture risk in postmenopausal women and is FDA-approved for the treatment, but not prevention, of osteoporosis. Calcitonin has questionable mild analgesic effects in compression fracture treatment. Because of its expense and inferior efficacy relative to other therapies, it is generally reserved for patients who cannot tolerate other agents.[41]

Therapies on the horizon for osteoporosis prevention and/or treatment in postmenopausal women include strontium ranelate, third-generation SERMs or estrogen agonists/antagonists (ie, bazedoxifene and lasofoxifene), and combination estrogen/SERM therapies.

SUMMARY

The risk-benefit assessment for management of vasomotor symptoms and other menopause-related health issues should be tailored to formulate the most efficacious and safe treatment plan for each individual woman. The most appropriate management is guided by the individual patient's own assessment of her most bothersome symptom(s) and her preferences and comfort level regarding various risks and quality-of-life issues. To best inform these patient choices, physicians must strive to clearly and accurately present the risks and benefits of the various available treatment options.

For most symptomatic menopausal women, HT remains the best treatment. However, for women unable or unwilling to take HT, there are alternatives for the treatment of vasomotor symptoms and bone loss. Low doses of local vaginal estrogen remain an option for treatment of genitourinary atrophy, even in women in whom systemic HT may be contraindicated.

Reassessment of current data and ongoing clinical trials will assist clinicians and patients in decision-making regarding menopausal HT. Nonhormonal therapies for menopausal symptoms should be used to provide effective treatment options for those menopausal patients unwilling or unable to take HT.

REFERENCES

1. **Anderson RN.** United States life tables, 1997. Natl Vital Stat Rep 1999; 47:1–37.
2. **NIH State-of-the-Science Panel.** National Institutes of Health State-of-the-Science Conference Statement: management of menopause-related symptoms. Ann Intern Med 2005; 142:1003–1013.
3. **Utian WH.** Psychosocial and socioeconomic burden of vasomotor symptoms in menopause: a comprehensive review. Health Qual Life Outcomes 2005; 3:47.
4. American Association of Clinical Endocrinologists (AACE) position statement on hormone replacement therapy (HRT) and cardiovascular risk. American Association of Clinical Endocrinologists Web site. www.aace.com/pub/pdf/guidelines/HRTCVRISKposition_statement.pdf. Accessed March 5, 2008.

5. **North American Menopause Society.** Treatment of menopause-associated vasomotor symptoms: position statement of The North American Menopause Society. Menopause 2004; 11:11–33.
6. **Deecher DC.** Physiology of thermoregulatory dysfunction and current approaches to the treatment of vasomotor symptoms. Expert Opin Investig Drugs 2005; 14:435–448.
7. **Bachmann GA.** Menopausal vasomotor symptoms: a review of causes, effects and evidence-based treatment options. J Reprod Med 2005; 50:155–165.
8. **Freedman RR.** Pathophysiology and treatment of menopausal hot flashes. Semin Reprod Med 2005; 23:117–125.
9. **Berendsen HH.** The role of serotonin in hot flashes. Maturitas 2000; 36:155–164.
10. **Nelson HD, Vesco KK, Haney E, et al.** Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis. JAMA 2006; 295:2057–2071.
11. **Loprinzi CL, Sloan JA, Perez EA, et al.** Phase III evaluation of fluoxetine for treatment of hot flashes. J Clin Oncol 2002; 20:1578–1583.
12. **Stearns V, Beebe KL, Iyengar M, Dube E.** Paroxetine controlled release in the treatment of menopausal hot flashes: a randomized controlled trial. JAMA 2003; 289:2827–2834.
13. **Rapkin AJ.** Vasomotor symptoms in menopause: physiologic condition and central nervous system approaches to treatment. Am J Obstet Gynecol 2007; 196:97–106.
14. **Jin Y, Desta Z, Stearns V, et al.** CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. J Natl Cancer Inst 2005; 97:30–39.
15. **Stearns V, Johnson MD, Rae JM, et al.** Active tamoxifen metabolite plasma concentrations after coadministration of tamoxifen and the selective serotonin reuptake inhibitor paroxetine. J Natl Cancer Inst 2003; 95:1758–1764.
16. **Loprinzi CL, Kugler JW, Sloan JA, et al.** Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. Lancet 2000; 356:2059–2063.
17. **Barton D, La VB, Loprinzi C, Novotny P, Wilwerding MB, Sloan J.** Venlafaxine for the control of hot flashes: results of a longitudinal continuation study. Oncol Nurs Forum 2002; 29:33–40.
18. **Evans ML, Pritts E, Vittinghoff E, et al.** Management of postmenopausal hot flushes with venlafaxine hydrochloride: a randomized, controlled trial. Obstet Gynecol 2005; 105:161–166.
19. **Joffe H, Soares CN, Petrillo LF, et al.** Treatment of depression and menopause-related symptoms with the serotonin-norepinephrine reuptake inhibitor duloxetine. J Clin Psychiatry 2007; 68:943–950.
20. **Kagan R, Constantine G, Olivier S.** Treatment with desvenlafaxine succinate (DVS) results in a sustained reduction in number of severe hot flushes (HFs) in menopausal women [abstract]. Menopause 2007; 14:1084. Abstract S-13.
21. **Speroff L, Gass M, Constantine G, Olivier S, for the Study 315 Investigators.** Efficacy and tolerability of desvenlafaxine succinate treatment for menopausal vasomotor symptoms: a randomized controlled trial. Obstet Gynecol 2008; 111:77–87.
22. **Reddy SY, Warner H, Guttuso T Jr, et al.** Gabapentin, estrogen, and placebo for treating hot flushes: a randomized controlled trial. Obstet Gynecol 2006; 108:41–48.
23. **Loprinzi CL, Kugler JW, Barton DL, et al.** Phase III trial of gabapentin alone or in conjunction with an antidepressant in the management of hot flashes in women who have inadequate control with an antidepressant alone: NCCTG N03C5. J Clin Oncol 2007; 25:308–312.
24. **Glynn RJ, Ridker PM, Goldhaber SZ, Zee RY, Buring JE.** Effects of random allocation to vitamin E supplementation on the occurrence of venous thromboembolism: report from the Women's Health Study. Circulation 2007; 116:1497–1503.
25. **North American Menopause Society.** The role of local vaginal estrogen for treatment of vaginal atrophy in postmenopausal women: 2007 position statement of The North American Menopause Society. Menopause 2007; 14:355–369.
26. **Bachmann G, Lobo RA, Gut R, Nachtigall L, Notelovitz M.** Efficacy of low-dose estradiol vaginal tablets in the treatment of atrophic vaginitis: a randomized controlled trial. Obstet Gynecol 2008; 111:67–76.
27. **Pfaus J, Giuliano F, Gelez H.** Bremelanotide: an overview of preclinical CNS effects on female sexual dysfunction. J Sex Med 2007; 4(Suppl 4):269–279.
28. **Safarinejad MR.** Evaluation of the safety and efficacy of bremelanotide, a melanocortin receptor agonist, in female subjects with arousal disorder: a double-blind placebo-controlled, fixed dose, randomized study. J Sex Med 2008; 5:887–897.
29. **Heiman JR, Gittelman M, Costabile R, et al.** Topical alprostadil (PGE1) for the treatment of female sexual arousal disorder: in-clinic evaluation of safety and efficacy. J Psychosom Obstet Gynaecol 2006; 27:31–41.
30. **Diamond LE, Earle DC, Heiman JR, et al.** An effect on the subjective sexual response in premenopausal women with sexual arousal disorder by bremelanotide (PT-141), a melanocortin receptor agonist. J Sex Med 2006; 3:628–638.
31. **Somboonporn W, Davis S, Seif MW, Bell R.** Testosterone for peri- and postmenopausal women. Cochrane Database Syst Rev 2005; (4):CD004509.
32. **North American Menopause Society.** The role of testosterone therapy in postmenopausal women: position statement of The North American Menopause Society. Menopause 2005; 12:497–511.
33. **Ettinger B, Ensrud KE, Wallace R, et al.** Effects of ultralow-dose transdermal estradiol on bone mineral density: a randomized clinical trial. Obstet Gynecol 2004; 104:443–451.
34. **Genant HK, Lucas J, Weiss S, et al.** Low-dose esterified estrogen therapy: effects on bone, plasma estradiol concentrations, endometrium, and lipid levels. Estratab/Osteoporosis Study Group. Arch Intern Med 1997; 157:2609–2615.
35. **Lindsay R, Gallagher JC, Kleerekoper M, Pickar JH.** Effect of lower doses of conjugated equine estrogens with and without medroxyprogesterone acetate on bone in early postmenopausal women. JAMA 2002; 287:2668–2676.
36. **Black DM, Delmas PD, Eastell R, et al.** Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007; 356:1809–1822.
37. **MacLean C, Newberry S, Maglione M, et al.** Systematic review: comparative effectiveness of treatments to prevent fractures in men and women with low bone density or osteoporosis. Ann Intern Med 2008; 148:197–213.
38. **Vogel VG, Constantino JP, Wickerham DL, et al.** Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. JAMA 2006; 295:2727–2741.
39. **Barrett-Connor E, Mosca L, Collins P, et al.** Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. N Engl J Med 2006; 355:125–137.
40. **Black DM, Bilezikian JP, Ensrud KE, et al.** One year of alendronate after one year of parathyroid hormone (1-84) for osteoporosis. N Engl J Med 2005; 353:555–565.
41. **Chesnut CH III, Silverman S, Andriano K, et al.** A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. PROOF Study Group. Am J Med 2000; 109:267–276.

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Putting the latest data into practice:

Case studies and clinical considerations in menopausal management

Dr. Holly Thacker: In light of the updates that Drs. Hodis and Gass have presented on hormone therapy (HT) for menopausal women and that Drs. Jenkins and Sikon have presented on nonhormonal options for menopausal management, let's start our roundtable by considering a couple of case studies that will give us the chance to apply the latest data in a practical way.

CASE 1: A SYMPTOMATIC 67-YEAR-OLD IN WHOM HORMONE THERAPY WAS ABRUPTLY STOPPED

Dr. Margaret McKenzie: A 67-year-old menopausal woman presents for the evaluation of hot flashes, vaginal dryness causing dyspareunia, and decreased libido. She was previously on estrogen-progestogen therapy (EPT), consisting of daily conjugated equine estrogens and medroxyprogesterone acetate, for 15 years starting at the time of natural menopause. Her gynecologist discontinued this HT abruptly at the time of the initial release of data from the Women's Health Initiative trial, and the patient is now seeking another opinion about resuming HT. When she presents, she has been off HT for less than 6 months. Would you restart HT in this patient?

> When HT is stopped, it is as if a newly menopausal state is being created. Providers need to think about ensuing changes in bone and genitourinary status as well as quality of life.
> —*Dr. Andrea Sikon*

Dr. Andrea Sikon: The abrupt discontinuation certainly contributes to her symptoms. The short duration of time off HT is important, and would lead me to restart HT after an updated review of risk factors. She had been on it for 15 years and has done fine, so she appears to be an ideal candidate to restart.

Dr. McKenzie: What specific questions would you ask when doing your risk assessment? How would you evaluate this patient to determine whether she is a good candidate to continue HT?

Dr. Thacker: I would obtain a family history. Using a population-based risk assessment such as the Gail model, I would calculate her absolute risk of breast cancer based on her duration of EPT use. I might offer her a lower-dose regimen. A conjugated equine estrogen dosage of 0.3 mg/day may be as effective in a 67-year-old woman as 0.625 mg/day is in a younger woman in terms of relieving vasomotor symptoms, depending on individual metabolism. We do have evidence from the HOPE trial that 0.3 mg/day is effective for relief of vasomotor symptoms.[1] In addition, data from the Nurses' Health Study show no increased risk of stroke with 0.3 mg/day, as opposed to the increased risk with 0.625 mg/day, and there are other data showing that the risk of stroke is possibly related to dosage.[2]

At the same time, we do not yet have long-term data to show that the lower dose is necessarily safer and we do not have data on bone fracture risk with the lower dose, so I would want to know this patient's bone mineral density (BMD). I would also want to know about her cardiovascular risk profile, including

See inside front cover for author affiliations.

Drs. McKenzie, Sikon, and Hodis reported that they have no financial relationships with commercial interests that are relevant to this article. **Dr. Thacker** reported that she has received honoraria for teaching/speaking from Procter & Gamble, Sanofi-Aventis, Bayer, Wyeth Pharmaceuticals, Novartis, and Esprit Pharma. **Dr. Gass** reported that she has received consulting fees from Wyeth Pharmaceuticals, Upsher-Smith, Eli Lilly, Procter & Gamble, Palatin Technologies, Esprit Pharma, Roche, Merck, and Novartis, and has received clinical trial funding from Wyeth, Boehringer Ingelheim, Procter & Gamble, Organon, and Roche. **Dr. Jenkins** reported that she has received honoraria for teaching/speaking from Pfizer.

Each author received an honorarium for participating in the roundtable that formed the basis of this supplement. The honoraria were paid by the *Cleveland Clinic Journal of Medicine* from the educational grant from Wyeth Pharmaceuticals underwriting this supplement. Wyeth had no input on the content of the roundtable or this supplement.

her lipid profile, and I would want more details about her sexual function.

Dr. McKenzie: I will supply a few more case details. This patient's body mass index (BMI) was 24 kg/m^2. She exercised regularly. Her BMD was normal for her age. She was taking a statin to treat hyperlipidemia. She was a nonsmoker, and her family history was unremarkable. Does any of this information change the way that you would counsel her?

Dr. Howard Hodis: Knowing her BMI and that she was on a statin, I would have even less of a problem reinitiating HT.

Case continued

Dr. McKenzie: Well, EPT was reinitiated in this patient at a lower dose (0.45/1.5 mg), and she was satisfied. At her most recent visit, several years later, the possibility of reducing her dose of HT was offered; however, the patient is happy with her quality of life and accepts whatever risk that continued HT may bring. She inquired about transdermal testosterone to restore her sex drive, and it was agreed that if it receives US marketing approval for women with decreased libido, a 24-week trial would be attempted.

Dr. Hodis: If you look at the data, this patient not only may enhance her quality of life by continuing HT but might extend it as well.

Dr. Thacker: Many patients inquire about using testosterone only, without estrogen, for treating dyspareunia and low libido. Clinicians must understand that testosterone is aromatized to estrogen. If a patient is on a high dose of oral estrogen, I would consider switching to transdermal estrogen before trying testosterone, whose use in women remains off-label in the United States. But the patient in our case has been doing well for several years on low-dose estrogen and she still has her ovaries.

Dr. Margery Gass: Some colleagues and I completed a study, which was presented at a recent Endocrine Society meeting,[3] in which transdermal testosterone was just as effective without estrogen in increasing libido. But this remains moot for general clinical practice unless the transdermal testosterone patch is approved in this country (as it is already approved for use in women in Europe).

I am surprised at how many women are referred to me who should have already been on HT for menopausal symptoms but whose physicians were unduly influenced by the initial WHI data.
—Dr. Margaret McKenzie

Dr. Hodis: Would any of you be worried about this patient's fracture risk after having HT stopped following 15 years of use? Data show that the rate of bone loss after abrupt cessation of HT is just as great as when a woman is going through menopause.

Dr. Gass: Yes, and that is exactly the point. The woman should be assessed under these circumstances just as she would be at menopause, using the same risk factors.

Dr. Thacker: I think that underscores that there is risk in stopping treatment, just as there is in taking treatment or not taking treatment, and all of these risks should be considered. Many times, once a patient is off HT, some clinicians forget to check the patient's BMD or to do a complete genital examination.

Dr. Sikon: Many providers who do not specialize in women's health may forget that when HT is stopped, it is as if a newly menopausal state is being created. Providers need to think about ensuing changes in bone and genitourinary status as well as quality-of-life concerns.

Dr. McKenzie: In today's clinical environment, there is awareness of the importance of long-term bone health because patients are living longer. The use of BMD measurements in practice is clearly expanding.

Dr. Thacker: It is worth noting that all of the drugs used to treat osteoporosis have been studied primarily in women who already have osteoporosis. The therapy with the most data to support a reduction in the risk of all types of fracture is HT. These data are very impressive, and although fracture prevention would not be the sole reason for using HT, it can make the overall risk-benefit assessment easier, particularly if it can be determined whether or not an individual patient is at high risk of venous thromboembolism (VTE).

CASE 2: A SYMPTOMATIC 47-YEAR-OLD WITH A HISTORY OF BREAST CANCER

Dr. McKenzie: A 47-year-old postmenopausal woman with a 7-year history of breast cancer presents for the management of hot flashes, irritability, and reduced sleep. In addition, recent onset of vaginal dryness is causing dyspareunia that is not alleviated by lubricants. Her breast cancer was estrogen receptor (ER)/progesterone receptor (PR)–positive, and she received tamoxifen therapy for 5 years (now completed) following the

initial diagnosis and management. How would you approach the management of this patient?

Dr. Marjorie Jenkins: I would first try to determine the severity of her hot flashes and how much her symptoms are affecting her quality of life. She may say that she is still having hot flashes, but how frequent are they? Do they cause nighttime awakening and subsequent fatigue?

Dr. McKenzie: The reason this patient presented was to ask for some form of relief because her symptoms were affecting her quality of life. Her dyspareunia was getting worse. She was trying various lubricants without success. At the same time, she expressed fear because her tumor was ER/PR-positive. Most cancer survivors have recurrence in the back of their mind even though they are in remission.

Dr. Jenkins: Was she asking specifically about HT or about help to relieve her symptoms?

Dr. McKenzie: She was asking for help for her symptoms.

Dr. Jenkins: I would consider low-dose vaginal estrogen to address her dyspareunia. I would also consider a serotonin-norepinephrine reuptake inhibitor, such as venlafaxine, to treat her hot flashes and irritability, along with lifestyle modifications, although the latter do not have evidence-based support. If these measures failed to offer relief, I would reconsider the risks and benefits of low-dose HT. I would call her oncologist for input if I planned to start vaginal estrogen, low-dose topical testosterone, or any type of hormonal treatment. I would make sure that the patient knew that her oncologist was working as part of the team responsible for her management.

The WHI was not a menopausal treatment trial, and its data are being misapplied to women who are different from WHI enrollees, in that they are younger and more symptomatic.

—Dr. Holly Thacker

Dr. Thacker: I concur. When I see hormonally sensitive breast cancer patients with vaginal symptoms, particularly when they are taking tamoxifen, I often talk to them about local estrogen before vaginal atrophy becomes severe. Once the atrophy becomes severe, local estrogen, even in low doses, may be absorbed systemically (increasing the risk of endometrial hyperplasia) until the the vagina becomes re-estrogenized and stratified with healthy squamous epithelium. Once this restratification takes place, there are generally no systemic hormonal effects with low-dose local vaginal estrogen, but it is best to avoid severe atrophy in the first place. I like to start local estrogen early if I know that the oncologist wants to use an aromatase inhibitor in a breast cancer survivor. I prescribe the low-dose vaginal form frequently in my practice, and order transvaginal ultrasonography liberally if there is concern about the endometrium.

Additionally, I would offer this patient venlafaxine or, more specifically, desvenlafaxine, as the literature has shown that the latter agent is associated with an improvement in sleep.[4] (Currently, desvenlafaxine has been approved by the US Food and Drug Administration [FDA] solely to treat major depression; however, it has been studied in nondepressed women with hot flashes and is expected to be the first nonhormonal agent to receive FDA approval specifically to treat hot flashes.)

Dr. Gass: This patient still has her uterus in place. Data show that estrogens have a first-pass uterine effect, and this gives me pause because estrogen levels could well be higher in the uterus than in the bloodstream. Because of those data, as well as the absence of long-term safety data, the use of estrogen in this patient would cause me concern.

With breast cancer patients in particular, I try everything else to treat vaginal dryness before adding estrogen. I believe that if a patient is having dyspareunia despite the use of adequate lubricants, something else is the problem. In many cases these women have not had intercourse for months because they have been undergoing treatment for breast cancer, and they can have hallmark pain syndromes or constriction of the vagina that may require treatments besides just estrogen. If all else failed, I would prescribe vaginal estrogen on a temporary basis. Women who stay sexually active after menopause can do perfectly fine without treatment, but those who have periods of abstinence and then try to resume sexual activity typically run into problems.

Dr. Hodis: Would you have concern about breast cancer recurrence with estrogen reinitiation, based on the literature?

Dr. Gass: I have seen recurrences out to 20 years after the initial cancer. If the cancer does recur, the woman will always have a nagging doubt that it could have been avoided if she had not used estrogen.

Dr. Thacker: We have many breast cancer survivors in our practice. It is an easier decision to give estrogen to women who have had bilateral mastectomy with

reconstruction for a stage I breast cancer and have already had a hysterectomy or bilateral salpingo-oophorectomy. But we otherwise try to avoid it unless the patient has first tried everything else and is miserable from her vaginal symptoms.

Dr. Gass: When a patient is diagnosed with breast cancer, I gently encourage her to continue sexual activity through the course of treatment, explaining that she may be far better off later. It may avoid a lot of problems if we can proactively get that message across.

Dr. Jenkins: That is a great point, and there is evidence that increased sexual activity decreases vaginal atrophy and assists in maintaining vaginal elasticity and the ability of urogenital congestion with arousal. Although lubricants and moisturizers do work well, they may require repeated application, and inelasticity is still a problem for some patients. It is somewhat of a "use it or lose it" proposition.

Dr. Thacker: Recurrent urinary tract infections (UTIs) are a problem as well. Patients see urologists, undergo multiple endoscopies, and are treated with antibiotics, sometimes chronically, yet often they are not even offered local vaginal estrogen, which reduces recurrent UTIs. Local estrogen should be considered in any woman with vaginal atrophy and recurrent UTIs.

I wonder how many more women would select HT if we told them about the 30% reduction in mortality despite the possibility of breast cancer diagnosis and DVT risks.
—Dr. Howard Hodis

Case continued

Dr. McKenzie: To return to our case, this patient's vagina was, in fact, severely constricted because she had not been sexually active for a while. Her BMI was initially greater than 25 kg/m^2, but she lost weight and became more symptomatic as she did so. She then stopped having sex because it was painful.

When she presented initially, she had a package of black cohosh with her and was willing to try it for her symptoms but was apprehensive after reading the disclaimers in the package. A 47-year-old who has already been diagnosed with ER-positive breast cancer is generally anxious about using any therapies that may be associated with an increased risk of breast cancer.

After examination of her vagina, her oncologist was consulted and suggested that her serum estradiol levels be measured; they were less than 20 pg/mL. We then agreed to a trial of estradiol vaginal tablets, vaginal dilators, and an increase in her sexual activity. She has been on vaginal estradiol for 2 years and is functioning very well. Her hot flashes improved spontaneously as her body adapted to her new weight.

BEYOND THE CASES: OTHER CHALLENGES IN MENOPAUSAL MANAGEMENT

HT discontinuation, dose reduction in real-world practice

Dr. Thacker: The first case we covered touched on both discontinuation of HT and HT dosage reduction. These are issues that come up often in clinical practice; what lessons does the panel have to share on these issues?

Dr. Gass: I find that there is a small subset of women who are highly symptomatic and are probably always going to be miserable whenever they try to go off HT. For some, if they are highly symptomatic at menopause, they tend to stay that way. They may try to go off, but a year later, they come back and say, "I am just too miserable."

Dr. McKenzie: In my practice, I have noticed patients who end up staying on higher doses of HT for a long period because they do not tolerate weaning. If you take them down to 0.625 mg of estrogen, their hot flashes resume, so they seem to require 0.9 mg.

Dr. Thacker: I have a very small subset of those women too. I wonder if their metabolism is different; maybe 0.9 mg of conjugated equine estrogens is to them what 0.3 mg is to other women. As women get older, perhaps metabolic changes are one reason that many can reduce their hormone dosage. It is very challenging. I tell my students that it is much easier trying to determine how much thyroid hormone replacement to give a patient than how much estrogen.

When does transdermal estrogen make sense?

Dr. Sikon: I would be interested in the rest of the panel's views on management of a woman in her early postmenopausal years who is symptomatic and has been on oral HT and is also a smoker. Would you switch her to transdermal estrogen or continue her oral HT and continue aggressive smoking cessation counseling?

Dr. Thacker: Many practitioners think that a smoker cannot take any type of HT because they equate it to oral/hormonal contraceptives, which increase the risk of heart attack in smokers over age 35, but hormonal contraceptives are different in that they involve a much higher dose of hormone. In my practice, the cases when I will offer transdermal estrogen are generally when a patient has gastrointestinal upset, known gallbladder disease, elevated triglycerides, or a prior

deep vein thrombosis (DVT), even though I will tell the patient that the HT-associated risks are still possible with transdermal therapies. Many women are inappropriately and inaccurately told that compounded transdermal therapies are "risk free."

Dr. McKenzie: Transdermal estrogen is also an option for patients who are poor pill takers or are already taking too many pills. Many of my patients are on transdermal estrogen for the convenience that it offers. It is unfortunate that transdermal progesterone cream does not protect the endometrium in all patients; for women with a uterus, an oral progestogen needs to be prescribed. However, two transdermal patches containing progestogens have been shown to be efficacious in protecting the endometrium.

How should a history of DVT affect decision-making?

Dr. McKenzie: What do you do when a patient has a history of postoperative DVT and is already on HT? How many of the panel would discontinue the HT as opposed to continuing it?

Dr. Hodis: If it were a history of spontaneous DVT, I would feel uncomfortable continuing HT. A few years ago, a clinical trial was stopped early because women with a prior spontaneous DVT who were randomized to HT had a substantial increase in DVT incidence relative to those randomized to placebo.[5] In the case of provoked or postoperative DVT, it may be a tougher call.

Dr. Thacker: I think that DVT is the greatest risk with HT, even though the media are more focused on breast cancer risk. The risk of breast cancer with estrogen alone is debatable, at least with oral conjugated estrogen, which was associated with a decreased risk in women who had undergone hysterectomy in the Women's Health Initiative (WHI).[6]

When I see a woman with a history of DVT in my practice, I check her homocysteine levels and check for factor V Leiden and prothrombin gene mutation. If I find an inherited hypercoagulability disorder, I tell the patient that her risk of DVT with any type of hormone product is not just multiplicative, it is logarithmic. If the patient already requires lifelong anticoagulation, then I am a bit more comfortable with prescribing HT and I usually will try the transdermal route first; however, I always consider nonhormonal treatment alternatives first.

Dr. Gass: The WHI was supposed to have excluded women with a history of DVT, but a few such women were enrolled, and it was demonstrated that they were at higher risk of DVT recurrence if randomized to HT. The majority of DVT episodes in the WHI were spontaneous, not related to surgical procedures.

Dr. Jenkins: I have a patient who had been on low-dose HT for 30 years and underwent lumbar spine surgery. She had a somewhat prolonged recovery, so her lack of mobility and her age clearly increased her risk of DVT. So she was taken off HT and became miserable from the resulting hot flashes and sleep disturbance. We thoroughly discussed the risks and benefits of restarting HT, and because she was taking warfarin, we felt comfortable restarting the HT.

Women with spontaneous DVT are a different case, however, and I have an issue with restarting oral or transdermal HT in those cases. However, if we discuss the data with these patients and document the significant risks of HT in their cases, some may want to accept the increased risk in order to improve their quality of life, and that may be reasonable if they are truly fully informed.

Women know their priorities. Each woman has specific concerns and bases her personal decision about HT on these specific concerns. Our job is to educate them about the risks and benefits.

—Dr. Margery Gass

Dr. Thacker: What about a woman who has been on oral contraceptives for several years and has not had a DVT? Is the safe use of oral/hormonal contraceptives something you take into account, Dr. Gass, in your decision whether to prescribe HT?

Dr. Gass: Yes, that can be reassuring. Twenty-seven percent of EPT participants and 49% of estrogen therapy (ET) participants in the WHI randomized trial had used hormones in the past, so it was as if they were already tested for an early risk of blood clots.[7]

What role for SERMs (estrogen agonists/antagonists)?

Dr. Thacker: I would like to discuss the use of estrogen agonists/estogen antagonists, formerly known as selective estrogen receptor modulators (SERMs), such as raloxifene. Raloxifene now has an indication for breast cancer prevention as well as for reduction of vertebral fractures. I don't know if there is adequate recognition among practitioners that SERMs appear to be associated with the same risk of DVT that estrogen is, and a greater risk of fatal stroke.

Dr. Jenkins: I find the lack of hip fracture data with raloxifene concerning, because hip fracture carries

the highest 5-year mortality of any type of fracture. Raloxifene therefore is not a first-line agent for bone loss in my practice. But we also have to consider the patient's risk of breast cancer and whether or not she has been on tamoxifen and now needs an agent to protect her against fracture. The question is whether we should consider starting these patients on raloxifene versus a bisphosphonate.

Dr. Thacker: Dr. Gass, do you think that raloxifene is safe for the endometrium? For years, we did not know the full effects of tamoxifen on the endometrium; it took experience with millions of patients to find out that tamoxifen increases the risk of endometrial cancer.

Dr. Gass: I do think that raloxifene is safer. I use it in my practice primarily for women younger than age 65 who are not yet at high risk for hip fracture but are still concerned about breast cancer. Although this concern diminishes as women age without having developed breast cancer, for younger women, who may see their friends getting breast cancer, it is a major concern. So if a patient is a good candidate for a bone loss agent and also has concern about breast cancer, raloxifene can be a good option, especially since we do not know what the implications are of taking bisphosphonates for 30 years. Questions about that are starting to be raised, so I think it is good to consider a sequential approach for some of these patients. A sequential approach might involve use of HT in a symptomatic menopausal woman, followed by use of raloxifene after the woman no longer has menopausal symptoms but is concerned about spine fracture protection and breast cancer risk reduction, followed by bisphosphonate use as she gets older and is at increased risk for stroke/VTE and for hip fracture.

The challenge of educating younger doctors about HT

Dr. Thacker: I think we need to find ways to translate the data on HT to younger generations of physicians, because the closer one is to graduating from medical school, the less likely he or she is to offer HT to an otherwise healthy, severely symptomatic woman younger than age 60.

Dr. McKenzie: Absolutely, and I think the real challenge is to reach younger physicians who go into private practice, who generally have the fewest opportunities to stay on top of the latest evidence. We must offer evidence-based education programs on this topic to physicians in the community to ensure that they are equipped to understand and explain the real risks and benefits of HT in order to individualize treatment decisions.

As a physician at a tertiary care center, I am surprised at the number of women referred to me who should have already been on HT for menopausal symptoms, but their physicians were unduly influenced by the initial WHI publication. They need to thoroughly evaluate their patients, assess their risks, assess any new medical problems, try to educate them, and then tailor therapy to improve their patients' quality of life.

Correcting misperceptions: WHI was not a treatment trial

Dr. Thacker: I believe that many practitioners and especially students do not realize that the WHI was a trial designed to assess prevention of chronic diseases. It was not a menopausal treatment trial, and often its data are being misapplied to women who are different from the ones enrolled in the WHI, in that they are younger and more symptomatic.

Too many people associate menopause only with hot flashes without considering the increased risk of serious diseases that may occur at this time.
—Dr. Marjorie Jenkins

Dr. Gass: It is correct that the WHI was not a treatment trial, but that was how HT was being used by some physicians and patients prior to the WHI. Physicians in this country were giving some 65-year-old women HT for osteoporosis and dementia. These practices needed to be supported with data, and that was the impetus behind the trial. Along the same lines, it is important how we present the risks to patients. If HT is being used as a therapy for a woman suffering from menopausal symptoms, she might be willing to accept more risk than if it is being used like a vitamin pill, to promote general health, in which case the risks should be virtually nil because the woman is healthy and without complaints.

Dr. Thacker: Yes, and that is why I think the earlier discussion of comparable risks of breast cancer, stroke, and VTE with aspirin, SERMs, fibric acid derivatives, and statins helps to put the risks of HT in perspective. It appears that physicians and patients tolerate very similar risks with commonly used nonhormonal medicines in women but do not tolerate any risks with HT, even in symptomatic women. In my opinion, this is a medical travesty. It is important to recognize that there are few absolutes in medicine that apply to all patients. The only universal recommendations I make to all patients are to wear seatbelts and not to smoke.

Dr. Hodis: What I find notable is that with HT we

see a reduction in mortality regardless of the risks that we have described. As the observational data show, if we start HT and continue it, there is a reduction in mortality of 30% or even greater, and the clinical trial data tend to support this benefit. So why do we shy away from HT? Because we are worried about a small increase in breast cancer diagnoses or a small increase in DVT? That is an issue I am grappling with.

Dr. Thacker: Similarly, how do you reconcile the observational data with aspirin? In the Nurses' Health Study, the aspirin users had lower mortality, but in all of the randomized controlled trials in midlife women, we do not see a reduction in cardiovascular risk with aspirin, let alone a reduction in mortality. So, the people who self-select for treatment are obviously different from those enrolled in randomized trials. The randomized controlled trial may be our gold standard, but it is not necessarily the only evidence to consider.

Dr. Hodis: But there *is* a concordance between observational studies and randomized trials with respect to overall mortality and HT. The data from a meta-analysis of 30 randomized trials[8] are consistent with the data from observational studies, even though they do identify risks. I wonder how many more women would select HT if we told them about the 30% reduction in mortality despite the possibility of breast cancer diagnosis and DVT risks.

To neglect treating a woman going through menopausal symptoms because menopause is a normal life event is akin to withholding assistance from women during childbirth.
—Dr. Holly Thacker

Dr. Gass: Women will select according to their own agenda.

Dr. Hodis: Yes, in the end, it is all individualized.

Dr. Gass: Indeed, because women have specific concerns, such as breast cancer, fracture risk, or Alzheimer disease, and they base their personal decisions on these specific concerns. I educate them about the risks and benefits, and they pretty much decide for themselves. They know their priorities.

Age and the risk-benefit assessment with HT

Dr. Thacker: Does the panel have any comments on the recent position statement from the American Association of Clinical Endocrinologists concluding that the benefits of HT exceed the risks in symptomatic women younger than age 60?

Dr. Hodis: My only comment is to ask why it took them so long to come to that conclusion.

Dr. Thacker: We could say the same for the North American Menopause Society (NAMS). It was not until its 2007 position statement on the use of ET and EPT in perimenopausal and postmenopausal women that NAMS moved beyond the issue of a time limit for HT—the "lowest dose for the shortest amount of time" mantra—and recommended the type of reevaluation used with any other treatment.

It seems as if practitioners are less willing to tolerate the risks of HT in older women than to tolerate the risks of hormonal contraceptives in younger women. Perhaps that is because hormonal contraceptives prevent pregnancy and the risks associated with it, yet this same value is not afforded to the symptoms and other effects suffered by postmenopausal women. I think we did afford HT similar value as hormonal contraceptives in the 1980s and 1990s, when we were trying to promote the potential health benefits of HT before we had bisphosphonates and statins and before we realized the risks of VTE with HT, risks that were identified much sooner with hormonal contraceptives. Since then the medical community has overcorrected by too often dismissing HT, overemphasizing the risks and ignoring very important quality-of-life issues, including sex and sleep disturbances, in the process.

Dr. Jenkins: Also, too many people associate menopause only with hot flashes, without taking into account the increased risk of serious diseases that may occur at this time, such as osteoporosis and heart disease.

Dr. Thacker: That may be because menopause is a normal event. It can be a great time of life for many women; in fact, it is associated with lower rates of depression, unless there is a prolonged symptomatic perimenopause. Menopause is certainly not a disease, and NAMS has been very good at recognizing and promoting it as a normal phase of life. But to neglect treating a woman going through menopausal symptoms just because menopause is a normal life event would be akin to withholding assistance for women during childbirth, which is another natural event.

We fail from a medical perspective if we do not take care of symptomatic women, because they will then turn to people who are not physicians and who offer unregulated therapies. These people may deliver the right message—that menopausal women deserve to feel well and look good—but the way they tell women to treat menopausal symptoms is not science-based.

Risks and benefits of hormone therapy: The importance of timing

The benefits of HT (ET or EPT) vary based on the time of therapy initiation and the duration of use.

Early menopausal years

Starting HT in the early menopausal years is associated with relief of vasomotor symptoms, prevention of urogenital atrophy (and resulting dyspareunia), and reduction of the rapid bone loss that is prevalent in untreated women during the first 5 to 7 years following menopause. Use of HT during the early menopausal years may also be associated with a reduction in the risk of coronary heart disease.

The risks of HT during the early menopausal years include VTE, greater risk of increased breast density, and increased risk of gallbladder disease. The increased risk of breast cancer in women on short-term HT remains debatable.

In general, the benefits of HT outweigh the risks in symptomatic menopausal women under the age of 60.

Duration of use

The duration of use is closely related to the risks and benefits of HT. The natural progression in most women is for vasomotor symptoms to decrease over time. With continued use of HT for 5 years or more, there are skeletal benefits, urogenital benefits, vasomotor symptom relief, and potential cardiovascular benefits if the patient was initially healthy when therapy was started. The risks with continued use of HT for more than 5 years remain VTE, stroke, and increased risk of breast cancer diagnosis.

Ages 60 to 69

For women 60 to 69 years old, the benefits of HT are vasomotor symptom relief (for those who remain symptomatic), prevention of urogenital atrophy, and prevention of bone loss and fracture. The risks are essentially the same as in younger women (VTE, stroke, and breast cancer), but these risks are increased compared with younger women, and HT dosage reduction should be considered.

Ages 70 to 79

Among women 70 to 79 years old, the skeletal and urogenital benefits of HT continue and the risks change slightly, to VTE, stroke, and coronary heart disease. The risks are increased particularly in women who have not been on systemic HT and who are starting HT at an advanced age, which is generally discouraged. Local vaginal estrogen should be considered in any woman with symptomatic urogenital atrophy.

Clinical considerations

The timing of HT initiation (relative to menopause) is a very important factor in the benefit-risk ratio. The patient's age at menopause is also important. The benefits of HT outweigh the risks for most women in the early menopausal phase.

Recommendations for long-term therapy should consider the patient's baseline risk factors, family history, duration of prior hormone use, the differential effects of ET and EPT, and the onset of new medical conditions.

At one time, we were overtreating women and not individualizing therapy, but to me it is even more worrisome to withhold therapies unless women are so highly symptomatic that they consider ending their life. We are continuing to discover the risks and benefits of HT and how to further tailor it. We have many newer, lower-dose HT options, and we are expecting the first nonhormonal therapy for menopausal vasomotor symptoms, desvenlafaxine. We are fortunate to have bone agents and local vaginal therapies for women without vasomotor symptoms. With both hormonal and nonhormonal options, we must keep the risks and benefits of any therapy in perspective.

CONCLUSIONS

Dr. Thacker: This has been a great discussion, and although we do not all agree on every point, I would like to conclude by summarizing some key points on which I think we do all agree **(see sidebar above)**. Menopause is a normal life event, but for some women who are symptomatic, and for a smaller percentage who will be symptomatic for the rest of their lives, HT is the gold standard, although it does not treat all symptoms and has some well-defined risks. We do have other options on the horizon for relief of vasomotor symptoms, for bone health, and for urogenital atrophy.

Following the data on the effects of HT on cardiovascular health will be particularly interesting. Although there is not support for using HT specifically for cardiovascular prevention, there are provocative data that in the symptomatic woman who has self-selected it, HT has cardiovascular benefit and reduces the risk of diabetes.

A woman on HT who has not had "early harm" does not need to arbitrarily discontinue therapy based on any time limit, as long as she is being periodically reevaluated and is offered individualized options.

REFERENCES

1. **Utian WH, Shoupe D, Backmann G, Pinkerton JV, Pickar JH.** Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens and medroxyprogesterone acetate. Fertil Steril 2001; 75:1065–1079.

2. **Grodstein F, Manson JE, Colditz GA, Willett WC, Speizer FE, Stampfer MJ.** A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. Ann Intern Med 2000; 133:933–941.
3. **Davis S, Studd J, Bouchard C, Kroll R, Moufarege A, Von Schoultz B.** The effect of a testosterone transdermal system on hypoactive sexual desire disorder in postmenopausal women not receiving systemic estrogen therapy, the APHRODITE study. Abstract presented at: 86th Annual Meeting of the Endocrine Society; June 16–19, 2004; New Orleans, LA.
4. **Speroff L, Gass M, Constantine G, Olivier S; Study 315 Investigators.** Efficacy and tolerability of desvenlafaxine succinate treatment for menopausal vasomotor symptoms: a randomized controlled trial. Obstet Gynecol 2008; 111:77–87.
5. **Høibraaten E, Qvigstad E, Arnesen H, Larsen S, Wickstrøm E, Sandset PM.** Increased risk of recurrent venous thromboembolism during hormone replacement therapy: results of the randomized, double-blind, placebo-controlled Estrogen in Venous Thromboembolism Trial (EVTET). Thromb Haemost 2000; 84:961–967.
6. **Anderson GL, Limacher M, Assaf AR, et al.** Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA 2004; 291:1701–1712.
7. **Stefanick ML, Cochrane BB, Hsia J, Barad DH, Liu JH, Johnson SR.** The Women's Health Initiative postmenopausal hormone trials: overview and baseline characteristics of participants. Ann Epidemiol 2003; 13:S78–S86.
8. **Salpeter SR, Walsh JM, Greyber E, Ormiston TM, Salpeter EE.** Mortality associated with hormone replacement therapy in younger and older women: a meta-analysis. J Gen Intern Med 2004; 19:791–804.

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