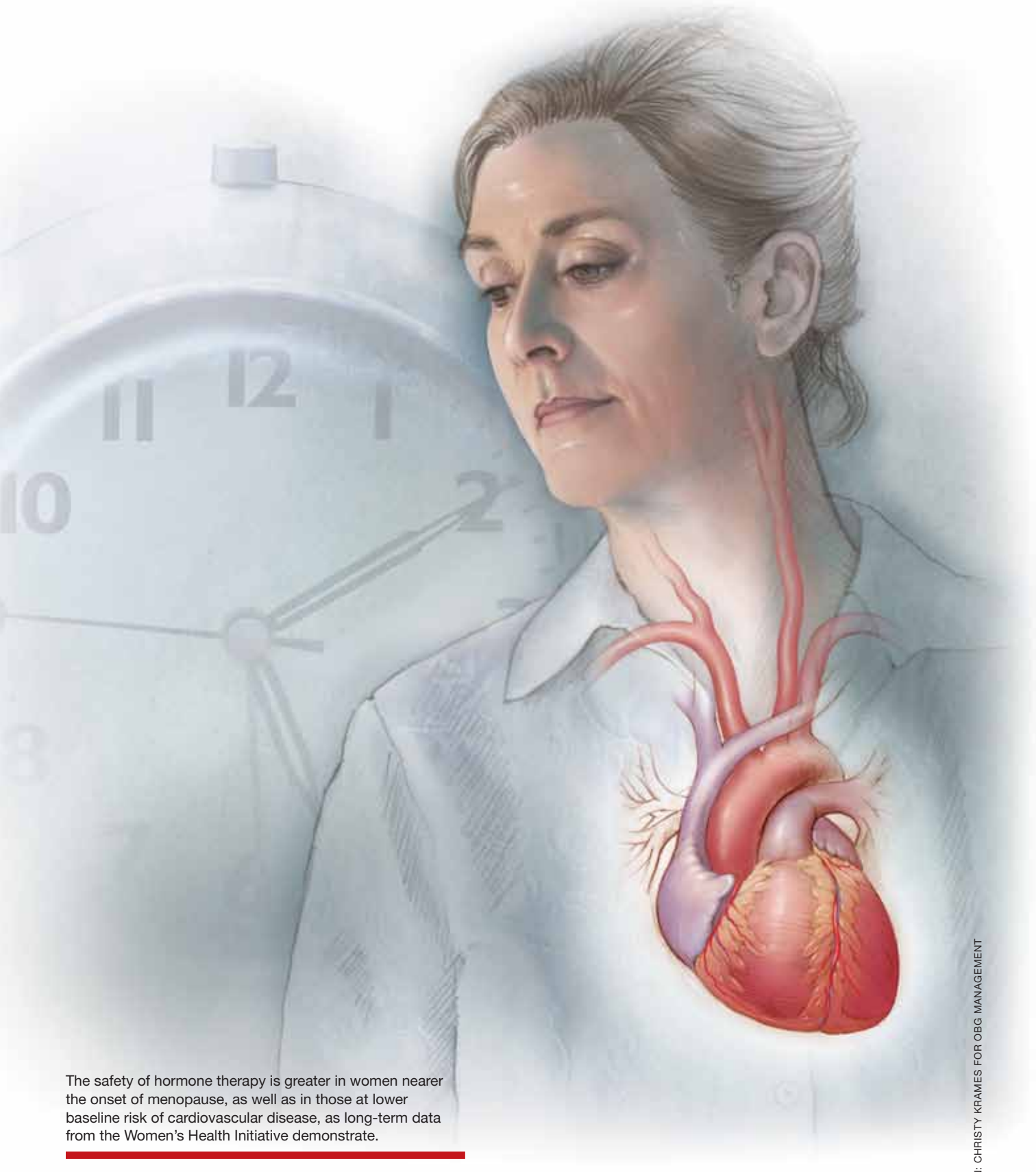

The safety of hormone therapy is greater in women nearer the onset of menopause, as well as in those at lower baseline risk of cardiovascular disease, as long-term data from the Women's Health Initiative demonstrate.

ILLUSTRATION: CHRISTY KRAMES FOR OBG MANAGEMENT

MENOPAUSE

The latest guidance on safe use of menopausal hormone therapy

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As new options for managing menopausal symptoms emerge, so do data on their efficacy and safety. In this article, I highlight the following publications:

- long-term follow-up data from the Women's Health Initiative (WHI) on the benefits and risks of hormone therapy (HT)
- a randomized trial of testosterone enanthate to improve sexual function among hysterectomized women
- guidance from the American College of Obstetricians and Gynecologists (ACOG) on the management of menopausal symptoms, including advice on individualization of therapy for older women
- a Swedish study on concomitant use of HT and statins.

After long-term follow-up of WHI participants, a "critical window" of HT timing is revealed

Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. JAMA. 2013;310(13):1353–1368.

After the initial 2002 publication of findings from the WHI trial of women with an intact uterus who were randomized to conjugated equine estrogens and medroxyprogesterone acetate or placebo, prominent news headlines claimed that HT causes myocardial infarction (MI) and breast cancer. As a result, millions of women worldwide stopped taking HT. A second impact of the report: Many clinicians became reluctant to prescribe HT.

Although it generated far less media attention, an October 2013 publication from the *Journal of the American Medical Association*, which details 13-year follow-up of WHI HT clinical trial participants, better informs clinicians and our patients about HT's safety profile.

During the WHI intervention phase, absolute risks were modest

Although HT was associated with a multifaceted pattern of benefits and risks in both

IN THIS ARTICLE

Further evidence that HT is safe when initiated soon after menopause

Tuomikoski P, Lyytinen H, Korhonen P, et al. Coronary heart disease mortality and hormone therapy before and after the Women's Health Initiative. Obstet Gynecol. 2014;124(5):947–953.

In Finland, all deaths are recorded in a national register, in which particular attention is paid to accurately classifying those thought to result from coronary heart disease (CHD). In addition, since 1994, all HT users have been included in a national health insurance database, enabling detailed assessment of HT use and coronary artery disease. Investigators assessed CHD mortality from 1995 to 2009 in more than 290,000 HT users, comparing them with the background population matched for year and age.

Use of HT was associated with reductions in the CHD mortality rate of 18% to 29% (for ≤1 year of use) and 43% to 54% (for 1–8 years of use). Similar trends were noted for EPT and ET. The HT-associated protection against CHD mortality was more pronounced in users younger than 60.

Tuomikoski and colleagues concluded, and I concur, that the observational nature of their data does not allow us to recommend HT specifically to *prevent* CHD. Nonetheless, these findings, along with long-term follow-up data from the WHI, make the case that, for menopausal women who are younger than 60 or within 10 years of the onset of menopause, clinicians may consider initiating HT to treat bothersome vasomotor symptoms, a safe strategy with respect to CHD.

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the estrogen-progestin therapy (EPT) and estrogen-only therapy (ET) arms of the WHI, absolute risks, as reflected in an increase or decrease in the number of cases per 10,000 women treated per year, were modest.

For example, the hazard ratio (HR) for coronary heart disease (CHD) during the intervention phase, during which participants were given HT or placebo (mean 5.2 years for EPT and 6.8 years for ET) was 1.18 in the EPT arm (95% confidence interval [CI], 0.95–1.45) and 0.94 in the ET arm (95% CI, 0.78–1.14). In both arms, women given HT had reduced risks of vasomotor symptoms, hip fractures, and diabetes, and increased risks of stroke, venous thromboembolism (VTE), and gallbladder disease, compared with women receiving placebo.

The results for breast cancer differed markedly between arms. During the intervention period, an elevated risk was observed with EPT while a borderline *reduced* risk was observed with ET.

Among participants older than 65 years at baseline, the risk of cognitive decline was increased in the EPT arm but not in the ET arm.

Hazard ratios for hormone therapy after 13-year follow-up in the WHI*

Hazard ratio	Estrogen-progestin therapy	Estrogen-only therapy
All-cause mortality	0.99	0.99
Age 50–59	0.88	0.78
Age 60–69	0.99	1.02
Age 70–79	1.04	1.06
Global index	1.06 (P = .05)	1.02
Breast cancer	1.28 (P<.05)	0.79 (P<.05)

*All P values >.05 (not statistically significant) unless stated otherwise.

Post intervention, most risks and benefits attenuated

An elevation in the risk of breast cancer persisted in the EPT arm (cumulative HR over 13 years, 1.28; 95% CI, 1.11–1.48). In contrast, in the ET arm, a significantly *reduced* risk of breast cancer materialized (HR, 0.79; 95% CI, 0.65–0.97) (**TABLE**).

To put into perspective the elevated risk of breast cancer observed among women randomly allocated to EPT, the attributable risk is less than 1 additional case of breast cancer diagnosed per 1,000 EPT users annually. Another way to frame this elevated risk: An HR of 1.28 is slightly higher than the HR conferred by consuming 1 glass of wine daily and lower than the HR noted with 2 glasses daily.[1] Overall, results tended to be more favorable for ET than for EPT. Neither type of HT affected overall mortality rates.

Age differences come to the fore

The WHI findings demonstrate a lower absolute risk of adverse events with HT in younger versus older participants. In addition, age and time since menopause appeared to affect many of the HRs observed in the trial. In the ET arm, more favorable results for

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Long-term follow-up of women who participated in the WHI clarifies the benefit-risk profile of systemic HT, underscoring that the benefit-risk ratio is greatest in younger menopausal women.

Because the safety of HT is greater in women nearer the onset of menopause, as well as in those at lower baseline risk of cardiovascular disease (CVD), individualized risk assessment may improve the benefit-risk profile and safety of HT. One approach to decision-making for women with bothersome menopausal symptoms is the MenoPro app, a free mobile app from the North American Menopause Society, with modes for both clinicians and patients.

all-cause mortality, MI, colorectal cancer, and the global index (CHD, invasive breast cancer, pulmonary embolism, colorectal cancer, and endometrial cancer) were observed in women aged 50 to 59 years at baseline. In the EPT arm, the risk of MI was elevated only in women more than 10 years past the onset of menopause at baseline. Both HT regimens, however, were associated with increased risks of stroke, VTE, and gallbladder disease.

EPT increased the risk of breast cancer in all age groups. However, the lower *absolute* risks of adverse events in younger women, together with the generally more favorable HRs for many outcomes in the younger women, resulted in substantially lower rates of adverse events attributable to HT in the younger age group, compared with older women.

As far as CHD is concerned, the impact of age (or time since menopause) on the vascular response to HT in women and in nonhuman models has generated support for a "critical window" or timing hypothesis, which postulates that estrogen reduces the development of early stages of atherosclerosis while causing plaque destabilization and other adverse effects when advanced atherosclerotic lesions are present. Recent studies from Scandinavia provide additional support for this hypothesis (see the sidebar on page 38).

FAST TRACK

Estrogen may reduce the early stages of atherosclerosis while causing plaque destabilization and other adverse effects when advanced lesions are present

In hysterectomized women, supraphysiologic doses of testosterone improve parameters of sexual function

Huang G, Basaria S, Travison TG, et al. Testosterone dose-response relationships in hysterectomized women with or without oophorectomy: effects on sexual function, body composition, muscle performance, and physical function in a randomized trial. Menopause. 2014;21(6):612–623.

No formulation of testosterone is approved by the US Food and Drug Administration (FDA) for use in women. Nonetheless, in the United States, many menopausal women hoping to boost their sexual desire are prescribed, off-label, testosterone formulations indicated for use in men, as well as compounded formulations.[2]

Investigators randomly allocated women who had undergone hysterectomy to 12 weeks of transdermal estradiol followed by 24 weekly intramuscular injections of placebo or testosterone enanthate at doses of 3.0 mg, 6.0 mg, 12.5 mg, or 25.0 mg while continuing estrogen. At the outset of the trial, all women had serum free testosterone levels below the range for healthy premenopausal women.

CONTINUED ON PAGE 40

CONTINUED FROM PAGE 39

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Although this well-executed study was small and short-term, it confirms that, in menopausal women receiving estrogen, testosterone can enhance parameters of sexuality. It is unfortunate that the dose needed to achieve this benefit results in markedly supraphysiologic serum testosterone levels.

One important caveat raised by this trial: It did not specifically recruit participants with low sexual desire. Therefore, it remains unknown whether lower doses of testosterone might provide benefits in women with low baseline libido. Regrettably, no randomized trials have addressed the long-term benefits and risks of use of testosterone among menopausal women.

Among the 62 women who received testosterone, serum testosterone levels increased in a dose-related fashion. Among those allocated to the highest dose, serum total testosterone levels at 24 weeks were 5 to 6 times higher than values in healthy premenopausal women. Compared with women who received placebo, those who received the highest testosterone dose had better measures of sexual desire, arousal, and frequency of sexual activity. Excess hair growth was significantly more common in women who received the 2 highest doses of testosterone.

ACOG offers valuable guidance on management of menopausal symptoms

FAST TRACK

Some women aged 65 years and older may continue to need systemic HT for the management of vasomotor symptoms

ACOG Practice Bulletin No. 141: management of menopausal symptoms. American College of Obstetricians and Gynecologists. Obstet Gynecol. 2014;123(1):202–216.

Despite findings from new studies, optimal management of menopausal symptoms remains controversial. In January 2014, ACOG issued guidance regarding conventional systemic and vaginal HT, recently approved treatments, and compounded HT.

For the management of vasomotor symptoms, ACOG indicated that systemic HT (including oral and transdermal routes), alone or combined with a progestin, is the most effective treatment for bothersome menopausal vasomotor symptoms. The ACOG Practice Bulletin also pointed out that systemic EPT increases the risk for VTE and breast cancer and that, compared with oral estrogen, transdermal estrogen may carry a lower risk for VTE.

Some insurers deny coverage of HT for women older than 65 years

A classification of medications from the American Geriatrics Society known as "the Beers List" [the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults] includes oral and transdermal estrogen, with or without a progestin.[3] Along with many of the clinicians reading this Update, I routinely receive notices from insurance companies that, based on the Beers List, they will no longer provide reimbursement for systemic HT in patients who are older than 65 years. In this regard, I believe that one of the most important components of ACOG's Practice Bulletin is the following text:

> The decision to continue HT should be individualized and be based on a woman's symptoms and the risk-benefit ratio, regardless of age. Because some women aged 65 years and older may continue to need systemic HT for the management of vasomotor symptoms, the American College of Obstetricians and Gynecologists recommends against routine discontinuation of systemic estrogen at age 65 years. As with younger women, use of HT and estrogen therapy should be individualized, based on each woman's risk-benefit ratio and clinical presentation.

CONTINUED ON PAGE 42

CONTINUED FROM PAGE 40

WHAT THIS EVIDENCE MEANS FOR PRACTICE

ACOG's Practice Bulletin provides useful guidance for clinicians regarding treatment of menopausal symptoms. Besides clarifying that systemic HT should not be arbitrarily discontinued at age 65 and that FDA-approved HT is preferable to compounded HT, this publication details newer (including nonhormonal) formulations for treating menopausal symptoms as well as traditional HT formulations, including useful dosing information.

Three new options for menopausal HT

The ACOG Practice Bulletin describes 3 formulations for the treatment of menopausal symptoms that have recently become available:

- In women with a uterus and with bothersome vasomotor symptoms, an alternative to EPT is oral tablets combining conjugated equine estrogen (0.45 mg) with 20 mg of the selective estrogen receptor modulator (SERM) bazedoxifene.
- The oral SERM ospemifene (60 mg) is effective for relief of dyspareunia associated with vulvovaginal atrophy (also known as genitourinary syndrome of menopause).
- Paroxetine mesylate (7.5 mg) is the only FDA-approved nonhormonal formulation for management of vasomotor symptoms and is dosed lower than regimens used to treat psychiatric conditions.

Steer patients clear of compounded formulations

Every week I encounter patients who have recently visited physicians who prescribe and sell compounded bioidentical hormones. In addressing this issue, ACOG provides a useful service to women and their clinicians:

> Because of a lack of FDA oversight, most compounded preparations have not undergone any rigorous clinical testing for either safety or efficacy, so the purity, potency, and quality of compounded preparations are a concern. In addition, both underdosage and overdosage are possible because of variable bioavailability and bioactivity. Evidence is lacking to support superiority claims of compounded bioidentical hormones over conventional menopausal HT.... **Conventional HT is preferred, given the available data.**

FAST TRACK

Most compounded hormone therapy preparations have not undergone any rigorous clinical testing for safety or efficacy

Is menopausal HT safe in statin users?

Berglind IA, Andersen M, Citarella A, Linder M, Sundström A, Kieler H. Hormone therapy and risk of cardiovascular outcomes and mortality in women treated with statins. Menopause. 2015;22(4):369–376.

Hodis HN, Mack WJ. Hormone therapy and risk of all-cause mortality in women treated with statins [comment]. Menopause. 2015;22(4):363–364.

Since the initial publications of findings from the WHI, clinicians have been cautioned not to prescribe menopausal HT in women at elevated risk for CVD. In this study from Sweden, investigators enrolled women 40 to 74 years old who initiated statin use between 2006 and 2007 due to known CVD (secondary prevention) or in the absence of known CVD (primary prevention). Women were followed for a mean of 4 years after beginning statins until the end of 2011.

Of 40,958 statin users, 7% used HT (mean age of HT users and nonusers was 61 and 62 years, respectively). Overall, 70% of statin use was for primary prevention. Deaths from CVD occurred in 5 and 18 patients per 10,000 person-years among HT users and nonusers, respectively (HR, 0.38). All-cause mortality occurred in 33 and 87 patients per 10,000 person-years among HT users and nonusers, respectively (HR, 0.53). These reduced risks of mortality noted in women who used concomitant statins achieved statistical significance. Whether statins were

used for primary or secondary prevention, the incidence of cardiovascular events was similar in HT users and nonusers.

Why these findings diverge from those of the WHI

The findings of this large prospective cohort study are consistent with findings from other large observational studies—though they diverge from WHI findings. As Berglind and colleagues note, few WHI participants used statins at baseline. Also in contrast with the WHI, in which all HT was based on conjugated estrogen, all HT users in this Swedish study used oral or transdermal estradiol, as conjugated estrogen is not available in Sweden (and appears to be associated with an elevated risk of CVD, compared with other estrogens[4]).

WHAT THIS EVIDENCE MEANS FOR PRACTICE

This important study provides strong evidence that, for menopausal women with bothersome vasomotor symptoms or an elevated risk for osteoporosis, concomitant use of statins should not be considered a contraindication to HT.

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