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Is there a time limit for systemic menopausal hormone therapy?

ABSTRACT

In deciding whether it is time to stop hormone therapy, in addition to the patient's age we need to consider her preferences, symptoms, quality of life, time since menopause, hysterectomy status, and personal risks of osteoporosis, breast cancer, heart disease, stroke, and venous thromboembolism. This article presents the evidence for and against extending hormone therapy and a guide for making this highly individualized and shared decision.

KEY POINTS

Hormone therapy is the most effective treatment available for the vasomotor symptoms of menopause, and it also is effective and appropriate for preventing osteoporosis-related fracture in at-risk women under age 60 or within 10 years of menopause.

Oral hormone therapy is associated with a small but statistically significant increase in the risk of stroke and venous thromboembolism and breast cancer risk with combination therapy only.

Extended hormone therapy may be appropriate to treat vasomotor symptoms or prevent osteoporosis when alternative therapies are not an option.

The decision whether to continue hormone therapy should be revisited every year. Discussions with patients should include the perspective of absolute risk.

Dr. Kagan has served as a consultant and advisory board member for Amgen, Foundation for Osteoporosis Research and Education/American Bone Health, Merck, Noven Pharmaceuticals, Novo Nordisk, Own the Bone Advisory Board of the American Orthopaedic Association, Pfizer, Shionogi, Sprout Pharmaceuticals, and TherapeuticsMD. She has received grants and research support (fees to institution) from TherapeuticsMD and has served on speakers' bureaus for Novo Nordisk, Shionogi, Noven Pharmaceuticals, and Pfizer.

doi:10.3949/ccjm.83a.15161

THE DURATION OF HORMONE THERAPY needs to be an individualized decision, shared between the patient and her physician and assessed annually. Quality of life, vasomotor symptoms, current age, time since menopause, hysterectomy status, personal risks (of osteoporosis, breast cancer, heart disease, stroke, venous thromboembolism), and patient preferences need to be considered.

The North American Menopause Society (NAMS) and other organizations recommend that the lowest dose of hormone therapy be used for the shortest duration needed to manage menopausal symptoms.¹⁻⁴ However, NAMS states that extending the duration of hormone therapy may be appropriate in women who have persistent symptoms or to prevent osteoporosis if the patient cannot tolerate alternative therapies.¹

Forty-two percent of postmenopausal women continue to experience vasomotor symptoms at age 60 to 65.⁵ The median total duration of vasomotor symptoms is 7.4 years, and in black women and women with moderate or severe hot flashes the symptoms typically last 10 years.⁶ Vasomotor symptoms recur in 50% of women who discontinue hormone therapy, regardless of whether it is stopped abruptly or tapered.¹

FACTORS TO CONSIDER WHEN PRESCRIBING HORMONE THERAPY

Bone health

A statement issued in 2013 by seven medical societies said that hormone therapy is effective and appropriate for preventing osteoporosis-related fracture in at-risk women under age 60 or within 10 years of menopause.⁷

The Women's Health Initiative,⁸ a randomized placebo-controlled trial, showed a

statistically significant lower risk of vertebral and nonvertebral fracture after 3 years of use of conjugated equine estrogen with medroxyprogesterone acetate than with placebo:

- Hazard ratio 0.76, 95% confidence interval (CI) 0.69–0.83.

It also showed a mean increase of 3.7% ($P < .001$) in total hip bone mineral density. By the end of the trial intervention, women receiving either this combined therapy or conjugated equine estrogen alone saw a 33% overall reduction in hip fracture risk. The absolute risk reduction was 5 per 10,000 years of use.⁹

Karim et al,¹⁰ in a large observational study that followed initial hormone therapy users over 6.5 years, found that those who stopped it had a 55% greater risk of hip fracture and experienced significant bone loss as measured by bone mineral density compared with women who continued hormone therapy, and that the protective effects of hormone therapy disappeared as early as 2 years after stopping treatment.¹⁰

NAMS also recommends that women with premature menopause (before age 40) be offered and encouraged to use hormone therapy to preserve bone density and manage vasomotor symptoms until the age of natural menopause (age 51).^{1,11}

Cardiovascular health

Large observational studies have found that hormone therapy is associated with a 30% to 50% lower cardiovascular risk.¹² Randomized controlled trials of hormone therapy for 7 to 11 years suggest that coronary heart disease risk is modified by age and time since menopause.^{13,14}

The Women's Health Initiative and other randomized controlled trials suggest a lower risk of coronary heart disease in women who begin hormone therapy before age 60 and within 10 years of the onset of menopause, but an increased risk for women over age 60 and more than 10 years since menopause. However, several of these trends have not reached statistical significance (Table 1).^{13–15}

The Women's Health Initiative⁹ published its long-term follow-up results in 2013, with data on both the intervention phase (median of 7.2 years for estrogen-only therapy and 5.6 years for estrogen-progestin therapy) and the

post-stopping phase (median 6.6 years for the estrogen-only group and 8.2 years for the estrogen-progestin group), with a total cumulative follow-up of 13 years. The overall 13-year cumulative absolute risk of coronary heart disease was 4 fewer events per 10,000 years of estrogen-only therapy and 3 additional events per 10,000 years of estrogen-progestin therapy. Neither result was statistically significant:

- Hazard ratio with estrogen-only use 0.94, 95% CI 0.82–1.09
- Hazard ratio with estrogen-progestin use 1.09, 95% CI 0.92–1.24.

The Danish Osteoporosis Study was the first randomized controlled trial of hormone therapy in women ages 45 through 58 who were recently menopausal (average within 7 months of menopause).¹⁵ Women assigned to hormone therapy in the form of oral estradiol with or without norethisterone (known as norethindrone in the United States) had a statistically significant lower risk of the primary composite end point of heart failure and myocardial infarction after 11 years of hormone therapy, and this finding persisted through 16 years of follow-up (Table 1).

Stroke

Overall stroke risk was significantly increased with hormone therapy in the Women's Health Initiative trial (hazard ratio 1.32, 95% CI 1.12–1.56); however, the absolute increase in risk was small in both estrogen-alone and estrogen-progestin therapy users, 11 and 8 events, respectively, among 10,000 users. Younger women (ages 50–59) saw a nonsignificantly lower risk (2 fewer cases per 10,000 years of use).¹⁴ After 13 years of cumulative follow-up (combined intervention and follow-up phase), the risk of stroke persisted at 5 cases per 10,000 users for both arms, but only the estrogen-progestin results were statistically significant.⁹

The Danish Osteoporosis Study¹⁵ found no increased risk of stroke after 16 years of follow-up in recently menopausal women:

- Hazard ratio 0.89, 95% CI 0.48–1.65.

Venous thromboembolism

Data from both observational and randomized controlled trials demonstrate an increased risk of venous thromboembolism with oral hormone therapy, and the risk appears to

TABLE 1

Hormone therapy: Risk of coronary heart disease in randomized controlled trials

| Authors | Study description | Risk of coronary heart disease ^a | | |
|--------------------------------|---|---|---------------------|---------------|
| Salpeter et al ¹³ | Meta-analysis of 23 randomized controlled trials in 39,049 postmenopausal women | Subgroup | Odds ratio | 95% CI |
| | Mean duration of follow-up 4.8 years | Within 10 years of menopause and age < 60 | 0.68 | 0.48–0.96 |
| | Excludes Women's Health Initiative trial data | > 10 years of menopause and age > 60 | 1.03 | 0.91–1.16 |
| | Estrogen formulations include conjugated equine estrogen (CEE) and ethinyl estradiol | First year of hormone therapy and age < 60 | 0.22 | 1.12–1.92 |
| | Progesterone formulations include medroxyprogesterone acetate (MPA), gestodene, and micronized progesterone | First year of hormone therapy and age > 60 | 1.47 | 0.67–0.93 |
| | | Overall | 0.99 | 0.88–1.11 |
| Rossouw et al ¹⁴ | Secondary analysis of Women's Health Initiative, 27,347 US postmenopausal women | Subgroup | Hazard ratio | 95% CI |
| | Average age 64 | Within 10 years of menopause | 0.76 | 0.50–1.16 |
| | Average time since menopause 12 years | 10–19 years since menopause | 1.10 | 0.84–1.45 |
| | Intervention hormone therapies: CEE 0.625 mg/day or CEE + MPA 2.5 mg/day | ≥ 20 years since menopause | 1.28 | 1.03–1.58 |
| | | Age 50–59 | 0.93 | 0.65–1.33 |
| | | Age 60–69 | 0.98 | 0.79–1.21 |
| | | Age ≥ 70 | 1.26 | 1.00–1.59 |
| | | Overall | 1.07 | 0.92–1.23 |
| Schierbeck et al ¹⁵ | Danish Osteoporosis Study, 1,006 postmenopausal women | Analysis | Hazard ratio | 95% CI |
| | Average age 50 | 11 years of hormone therapy | 0.48 | 0.26–0.87 |
| | Average time since menopause 7 months | 16-year follow-up | 0.61 | 0.39–0.94 |
| | Intervention hormone therapy: 17-beta estradiol (BE) 2 mg/day or 17BE + norethisterone acetate 1 mg/day | | | |
| | Composite end point includes heart failure, cardiovascular death, and nonfatal myocardial infarction | | | |

^aCardiovascular death and nonfatal myocardial infarction.

CI = confidence interval

be highest during the first few years of use.¹ The pooled cohort from the Women's Health Initiative had 18 additional cases of venous thromboembolism per 10,000 women in estrogen-progestin users compared with nonusers, and 7 additional cases in those using estrogen-only therapy.

Breast health

Observational studies and randomized controlled trials have provided data on longer use of hormone therapy and breast cancer risk, but the true magnitude of this risk is unclear.

The Danish Osteoporosis Study,¹⁵ in a younger cohort of women, showed no increased risk of breast cancer after 16 years of follow-up:

- Hazard ratio 0.90, 95% CI 0.52–1.57.

The Women's Health Initiative⁹ showed a statistically nonsignificant lower risk of breast cancer in women of all ages exposed to conjugated equine estrogen alone for 7.1 years (6 fewer cases per 10,000 women-years of use), and after 6 years of follow-up this developed statistical significance:

- Hazard ratio 0.79, 95% CI 0.65–0.97.

In contrast, those using conjugated equine estrogen plus medroxyprogesterone acetate had a statistically nonsignificant increase in the risk of new breast cancer after 3 to 5 years:

- 3-year relative risk 1.26, 95% CI 0.73–2.20
- 5-year relative risk 1.99, 95% CI 1.18–3.35
- Absolute risk 8 cases per 10,000 women-years of use.

The increased risk of breast cancer significantly declined within 3 years after stopping hormone therapy.

However, even after stopping hormone therapy, there remains a statistically small but significant increased risk of breast cancer, as demonstrated in the postintervention 13-year follow-up data on breast cancer risk and estrogen-progestin use from the Women's Health Initiative⁹:

- Hazard ratio 1.28, 95% CI 1.11–1.48
- Absolute cumulative risk 9 cases per 10,000 women-years of use.

The Nurses' Health Study, an observational study, prospectively followed 11,508 hysterectomized women on estrogen therapy and found that breast cancer risk increased with longer duration of use. An analysis by

Chen et al¹⁶ found a trend toward increased breast cancer risk after 10 years of estrogen therapy, but this did not become statistically significant until 20 years of ongoing estrogen use. The risk of estrogen receptor-positive and progesterone receptor-positive breast cancer became statistically significant earlier, after 15 years. The relative risk associated with using estrogen for more than 15 years was 1.18, and the risk with using it for more than 20 years was 1.42.¹⁶

To put this in perspective, Chen et al¹⁷ found a similar breast cancer risk with alcohol consumption. The relative risk of invasive breast cancer was 1.15 in women who drank 3 to 6 servings of alcohol per week, 1 serving being equivalent to 4 oz of wine, which contains 11 g of alcohol.

Mortality

Studies have suggested that hormone therapy users have a lower mortality rate, even with long-term use.

A meta-analysis¹⁸ of 8 observational trials and 19 randomized controlled trials found that younger women (average age 54) on hormone therapy had a 28% lower total mortality rate compared with women not taking hormone therapy:

- Relative risk 0.72, 95% credible interval 0.62–0.82.

The Women's Health Initiative¹⁹ suggested that the mortality rate was 30% lower in hormone therapy users younger than age 60 than in similar nonusers, though this difference did not reach statistical significance.

- Relative risk with estrogen-only therapy: 0.71, 95% CI 0.46–1.11
- Relative risk with combined estrogen-progestin therapy 0.69, 95% CI 0.44–1.07.

The Danish Osteoporosis Study,¹⁵ at 16 years of follow-up, similarly demonstrated a 34% lower mortality rate in hormone therapy users, which was not statistically significant:

- Relative risk 0.66, 95% CI 0.41–1.08.

A Cochrane review²⁰ in 2015 found that the subgroup of women who started hormone therapy before age 60 or within 10 years of menopause saw an overall benefit in terms of survival and lower risk of coronary heart disease: RR 0.70, 95% CI 0.52–0.95 (moderate-quality evidence).

Extended hormone therapy may be appropriate to control symptoms or to prevent osteoporosis if the patient cannot tolerate other therapies

■ TYPE OF FORMULATION

Compared with estrogen-progestin therapy, estrogen-only therapy has a more favorable risk profile in terms of coronary heart disease and breast cancer, although stroke risk remains elevated in users of conjugated equine estrogen with or without medroxyprogesterone acetate.

There is limited evidence directly comparing different formulations of hormone therapy, although they all effectively treat vasomotor symptoms.¹

Oral vs transdermal formulations

Canonico et al,²¹ in a meta-analysis of observational studies, found that oral estrogen was associated with a higher risk of venous thromboembolism than transdermal estrogen:

- Relative risk with oral estrogen 2.5, 95% CI 1.9–3.4
- Relative risk with transdermal estrogen 1.2, 95% CI 0.9–1.7.

The **Estrogen and Thromboembolism Risk (ESTHER) study**²² was a multicenter case-control study of women ages 45 to 70 that assessed risk of venous thromboembolism in oral vs transdermal estrogen users. Compared with women not taking hormone therapy, current users of oral estrogen had a significantly higher risk of venous thromboembolism, while transdermal estrogen users did not:

- Odds ratio with oral estrogen 4.2, 95% CI 1.5–11.6
- Odds ratio with transdermal estrogen 0.9, 95% CI 0.4–2.1.

The **Kronos Early Estrogen Prevention Study (KEEPS)**²³ did not support these findings. This 4-year randomized controlled trial, published in 2014, was designed to assess the risk of atherosclerosis progression with early menopause initiation of placebo vs low-dose oral hormone therapy (conjugated equine estrogen 0.45 mg daily with cyclical micronized progesterone) or transdermal hormone therapy (estradiol 50 µg/week with cyclical micronized progesterone).

In the 727 women in the study, there was one transient ischemic attack in the oral hormone therapy group, one unconfirmed stroke in the transdermal hormone therapy group, and one case of venous thromboembolism in

TABLE 2

Hormone therapy: Contraindications and precautions

Contraindications. In general, estrogen therapy should not be used in women with any of the following conditions:

- Undiagnosed abnormal genital bleeding
- Known, suspected, or history of cancer of the breast
- Known or suspected estrogen-dependent neoplasia including endometrial cancer
- Active deep vein thrombosis, pulmonary embolism, or history of these conditions
- Active arterial thromboembolic disease (for example, stroke, myocardial infarction) or a history of these conditions
- Known anaphylactic reaction or angioedema in response to any ingredient in the medication
- Known liver impairment or disease
- Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders
- Known or suspected pregnancy

Caution should also be exercised in women with:

- Gallbladder disease (oral estrogen therapy)
- Hypertriglyceridemia (> 400 mg/day) (oral estrogen therapy)
- Diabetes
- Hypoparathyroidism (risk of hypocalcemia)
- Benign meningioma
- Intermediate or high risk of breast cancer
- High risk of heart disease
- Migraine with aura (can be used, but may exacerbate condition)
- Asthma (rare chance of exacerbation)
- Epilepsy
- Porphyria
- Systemic lupus erythematosus
- Hepatic hemangioma

Based on information in reference 3.

each group, findings that were underpowered for statistical significance. Both oral and transdermal hormonal therapy had neutral effects on atherosclerosis progression, as assessed by arterial imaging. Transdermal hormone therapy was associated with improvements in mark-

TABLE 3

Estrogen formulations available in the United States

| | Ultra-low dose | Low dose | Standard dose | High dose |
|----------------------|---|--------------|---------------------|----------------------------|
| Oral formulations | | | | |
| Conjugated estrogen | Not available (NA) | 0.3, 0.45 mg | 0.625 mg | 0.9, 1.25 mg |
| Esterified estrogen | NA | 0.3 mg | 0.625 mg | 1.25, 2.5 mg |
| Estropipate | NA | NA | 0.75, 1.5 mg | 3 mg |
| Estradiol acetate | NA | 0.45 mg | 0.9 mg | 1.8 mg |
| 17-beta estradiol | 0.25 mg | 0.5 mg | 1, 2 mg | NA |
| Topical formulations | | | | |
| Estradiol patch | 0.014 mg/day (14 µg/day) | 0.025 mg/day | 0.0375, 0.05 mg/day | 0.06, 0.075, 0.1 mg/day |
| Gels, pumps, sprays | Various brands of estradiol available in all dosing options | | | |
| Vaginal formulation | | | | |
| Femring ^a | NA | NA | 0.05 mg/day | 1 mg/day |

^a Femring is the only vaginal formulation in the United States that provides standard/high-dose systemic levels of estrogen. All other vaginal estrogen formulations are indicated to treat only the genitourinary symptoms of menopause through local vaginal effects.

Benefits are more likely to outweigh risks when hormone therapy is started before age 60 or within 10 years of menopause

ers of insulin resistance and was not associated with an increase in triglycerides, C-reactive protein, or sex hormone-binding globulin, as would be expected with transdermal circumvention of the first-pass hepatic effect.

■ BALANCING THE RISKS AND BENEFITS FOR THE PATIENT

The most effective treatment for vasomotor symptoms in women at any age is hormone therapy, and the benefits are more likely to outweigh risks when initiated before age 60 or within 10 years of menopause.⁷ The Women's Health Initiative randomized study was limited to 5.6 to 7.2 years of hormone therapy (13 years of cumulative follow-up), and the Danish Osteoporosis Study was limited to 11 years of use (16 years cumulative follow-up).

The coronary heart disease outcomes for longer durations of therapy remain uncertain. There is a small but statistically significant increased risk of stroke and venous thromboembolism with oral hormone therapy, and breast cancer risk is associated with long-term estrogen-progestin use.

Patients on hormone therapy should be

evaluated annually regarding the need for ongoing therapy. Persistent moderate-severe vasomotor symptoms, quality of life benefits of hormone therapy, contraindications to its use (Table 2), and patient preference need to be assessed as well as baseline risks of cardiovascular disease, breast cancer, and fracture.

Risk calculators may facilitate the shared decision-making process. Examples are:

- The American College of Cardiology/American Heart association risk calculator for cardiovascular disease²⁴ (www.cvrisk-calculator.com)
- The World Health Organization Fracture Risk Assessment Tool (FRAX)²⁵ (www.shef.ac.uk/FRAX/tool.jsp)
- The Gail model for breast cancer risk²⁶ (www.cancer.gov/bcrisktool/).
- MenoPro, a menopause decision-support algorithm and companion mobile app developed by NAMS to help direct treatment decisions based on the 10-year risk of atherosclerotic cardiovascular disease (www.menopause.org/for-professionals/-i-menopro-i-mobile-app).²⁷

The discussion of the risks of hormone

therapy with patients should incorporate the perspective of absolute risk. For example, a woman wishing to continue estrogen-progestin therapy should be told that the Women's Health Initiative data suggest that, after 5 years of use, breast cancer risk may be increased by 8 additional cases per 10,000 users per year. According to the World Health Organization, this magnitude of risk is defined as rare (less than 1 event per 1,000 women).²⁸

A strategy of prescribing the lowest dose to achieve the desired clinical benefits is prudent and recommended.¹⁻³ **Table 3** outlines the estrogen formulations now available in the United States, with their doses and formulations.

Unless contraindications develop (**Table 2**), patients may elect to continue hormone therapy if its benefits outweigh its risks. The

American College of Obstetricians and Gynecologists (ACOG) 2014 practice recommendations for management of menopausal symptoms³¹ and the 2015 NAMS statement both recommend that hormone therapy not be discontinued based solely on a woman's age.²⁹

Hormone therapy is on the Beer's list of potentially inappropriate medications for older adults,³⁰ which remains a hurdle to its long-term use and seems to be at odds with these ACOG and NAMS statements.

Patients who choose to discontinue hormone therapy need to be monitored for persistent bothersome vasomotor symptoms, bone loss, osteoporosis, and the genitourinary syndrome of menopause (previously referred to as vulvovaginal atrophy)³¹ and offered alternative therapies if needed. ■

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