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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.

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- 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 paper⁴ 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.

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