Did long-term follow-up of WHI participants reveal any mortality increase among women who received HT?

No. Cumulative 18-year follow-up data from 2 randomized WHI clinical trials between 1993 and 1998 (followed through December 2014) indicate that use of systemic HT did not impact the risk of all-cause or cause-specific mortality, including cardiovascular or cancer mortality.

Manson JE, Aragaki AK, Rossouw JE, et al; for the WHI Investigators. Menopausal hormone therapy and long-term all-cause and cause-specific mortality: the Women's Health Initiative randomized trials. JAMA. 2017;318(10):927–938.

EXPERT COMMENTARY

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FAST TRACK

All-cause mortality was similar in the pooled cohort (EPT and ET groups), with a rate of 27.1% in the HT group and 27.6% in the placebo group

A 2013 report from the Women's Health Initiative (WHI), the large National Institutes of Health–funded placebo-controlled randomized trial of postmenopausal hormone therapy (HT) with oral estrogen (for women with hysterectomy) or estrogen-progestin (for women with an intact uterus), with 13 years of cumulative follow-up, documented the safety of systemic HT when initiated by women younger than 60 years of age or within 10 years of menopause onset.[1]

Dr. Kaunitz reports that he serves as a consultant for Allergan, Inc, AMAG Pharmaceuticals Inc, Bayer Healthcare Pharmaceuticals, Pfizer Inc, Sebela Pharmaceuticals Inc, and Shionogi Inc; receives research grants (funds paid to University of Florida) from Bayer Healthcare Pharmaceuticals, Millendo Therapeutics, and TherapeuticsMD; and receives royalties from UpToDate.

Now, with 18 years of cumulative follow-up data available (intervention and extended postintervention phases), the WHI investigators present all-cause and cause-specific mortality outcomes from the 2 HT trials.

Details of the study

A total of 27,347 WHI participants (baseline mean age, 63.4 years; 80.6% white) used oral estrogen-progestin therapy (EPT) or placebo for a median of 5.6 years (n = 16,608) or estrogen-only therapy (ET) or placebo for a median of 7.2 years (n = 10,739). Each hazard ratio (HR) reported below refers to 18-year cumulative follow-up.

All-cause mortality. In the overall pooled cohort (EPT and ET groups), all-cause mortality was similar, with a rate of 27.1% in the HT group and 27.6% in the placebo group (HR, 0.99; 95% confidence interval [CI], 0.94–1.03). The mortality end points included deaths from all causes; cardiovascular disease (coronary heart disease, stroke, and other cardiovascular diseases); cancer (breast, colorectal, and other cancers); and other (Alzheimer disease, other dementia, chronic obstructive pulmonary disease, injuries and accidents, and other).

Stratifying by baseline participant age (comparing women aged 50–59 years with those aged 70–79 years), the HR for all-cause

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mortality in the pooled cohort during the intervention phase was 0.61 (95% CI, 0.43–0.87), and during the cumulative 18-year follow-up, the HR was 0.87 (95% CI, 0.76–1.00).

Cause-specific mortality. Neither cardiovascular disease mortality nor total cancer mortality was significantly impacted by HT use. In the pooled cohort, cardiovascular disease mortality was 8.9% in the HT group and 9.0% in the placebo group (HR, 1.00; 95% CI, 0.92–1.08), with no differences between the EPT and the ET trials. Cancer mortality rates in the pooled cohort also were similar, with 8.2% in the HT group and 8.0% in the placebo group (HR, 1.03; 95% CI, 0.95–1.12).

With respect to breast cancer mortality, the impact of HT diverged for EPT and ET. For the EPT group, the HR for breast cancer mortality was 1.44 (95% CI, 0.97–2.15; $P = .07$), while for the ET group the HR was 0.55 (95% CI, 0.33–0.92; $P = .02$).

Study strengths and weaknesses

The WHI represents the largest randomized placebo-controlled trials of HT. The current WHI trials report provides new, cumulative 18-year follow-up data on all-cause and cause-specific mortality in women treated with HT or placebo.

The authors noted, however, that the use of only one HT dose, formulation, and route of administration in each trial may limit the generalizability of the study results to other HT preparations. For example, the WHI did not examine the transdermal route of estrogen administration. Likewise, the WHI did not examine use of progestational agents other than medroxyprogesterone acetate. In addition, while almost all cohort deaths were captured through the National Death Index for the data analyses, specificity of cause of death may vary across outcomes. Further, since multiple outcomes and subgroups were examined, clinicians should interpret cause-specific mortality rates with caution.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Given the complex impact of HT, all-cause mortality represents an important summary outcome in assessing the safety of 5 to 7 years of HT use. This report's reassuring findings regarding the safety of HT support the guidance from The North American Menopause Society and the Endocrine Society, which endorse the use of HT for symptomatic recently menopausal women without contraindications.[2,3]

›› **ANDREW M. KAUNITZ, MD**

References

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