Outcomes during and after stopping HT: a comprehensive look at WHI data

Differences between initiation of therapy in younger vs older menopausal women and between ET and EPT are clarified


Summary. Earlier findings from the randomized placebo-controlled oral conjugated equine estrogens (CEE) plus medroxyprogesterone acetate (MPA) and CEE-alone Women’s Health Initiative (WHI) trials, which enrolled women ages 50 to 79 years, are well known to NAMS members. Now, investigators have published an analysis of outcomes for both trials based on extended (median 13 years) cumulative follow-up with stratification by age.

Among women randomized to CEE+MPA versus placebo, small but statistically significant elevations in risk of invasive breast cancer (HR, 1.24), stroke (1.37), pulmonary embolism (1.98), as well as reductions in risk of colorectal cancer (0.62), hip fracture (0.67), and diabetes (0.81) were noted during the intervention phase. With the exception of breast cancer, the altered risk of these outcomes attenuated during the postintervention phase. Among women randomized to CEE versus placebo, small but statistically significant elevations in risk of stroke (1.35) as well as statistically significant reductions in hip fracture (0.67) and diabetes (0.86) were observed during the intervention phase, with the altered risk of these outcomes again attenuating during the postintervention phase. Cumulatively, randomization to CEE was associated with a significantly reduced risk of invasive breast cancer (0.79). Neither CEE+MPA nor CEE-alone significantly impacted all-cause mortality during or after the intervention phase. Women age 50 to 59 years randomized to CEE-alone had significantly more favorable all-cause mortality and fewer myocardial infarctions.

Comment #1. Menopausal hormone therapy (HT) remains the most effective treatment for vasomotor symptoms, which are experienced by more than 50% of menopausal women, with bothersome symptoms most likely to occur in late perimenopausal and recently menopausal women. Mean duration of bothersome symptoms is greater than 10 years.¹ These long-term observations regarding participants in the WHI HT trials remind us that the risk: benefit ratio of menopausal hormone therapy (HT) is most favorable when initiated in younger rather than in older menopausal women, and for
estrogen-only compared with estrogen-progestin therapy.

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Reference


Dr. Kaunitz’s commentary is adapted from a summary to be published in Journal Watch Women’s Health.

Comment #2. We applaud the authors from the WHI Writing group for the extensive updating and review of both the WHI CEE+MPA and the WHI CEE studies. Now that this data is available, it would be an excellent time to have outside review from varied clinical disciplines to examine the very details of the studies that are still questioned, including the attending subgroup analysis. For example, in the CEE-alone study over 80% of the participants had hysterectomies prior to age 49 and half of those were done prior to age 40. The data for this group should be available and analyzed for years since last period. This information might offer further support for the timing hypothesis. Women in the CEE-alone group presently placed in the 50 to 59 cohort include 83% who were hysterecomized prior to age 49. A total of 39.8% of these women were rendered menopausal prior to age 40. Therefore, these latter participants were all 10 years or more beyond their last period. Analyzing outcomes by years since last period rather than by age group might strengthen the timing hypothesis.

Similarly, the CEE-alone study was halted by the increase in cerebrovascular thrombotic events. However, 53% of these women were hypertensive at baseline. It would be informative to separate this group to compare the 47% normotensive women with the hypertensive women as to cardiovascular and stroke hazard ratios. This is particularly cogent since hypertension is a relative contraindication for oral estrogen therapy.

This brings up another issue. Large population studies such as these are invaluable for an overall public health point of view. However, they do not apply to individuals. Indeed, it is subanalysis that the clinician has to apply to each individual patient when evaluating risk and benefit. The woman with a high risk for bone loss may not be the same woman at risk for cardiovascular disease.

This same concept of subanalysis review should be applied to the overview of outcomes and the CEE-only results should not be combined with the CEE+MPA results. They are separate studies with different populations with separate placebo groups and must be analyzed for their varied outcomes. Perhaps overall conclusions for therapy would be very different and more directly applicable to individualizing treatment if this subanalysis were widely performed and open to a wider clinical review.

Those of us who take care of the menopausal woman thank the authors for publishing these findings. It is helpful to recognize that the older menopausal woman is at risk with hormone therapy. It is equally reassuring and should be stressed that the younger menopausal woman is at low risk with estrogen therapy, and even when the treated patient’s risk is greater than placebo, the risk ratios are very small. Perhaps we should be stressing that 9,900 women per 10,000 had almost 7 years of exceptional health.

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Comment #3. The report from Manson et al in JAMA provides a well written comprehensive overview of intervention and postintervention follow-up (13 years total) from the WHI1,2 and
helps place into context, for practitioners and patients, the differences in findings between estrogen alone (ET) and estrogen combined with progestogen (EPT) and that age makes a difference in risks and outcomes if taking HT. Findings are presented by age, by ET or EPT, and by time since menopause, which makes the detailed analysis much more practical to determine individual risks.

- Hormone therapy remains a reasonable choice for symptomatic postmenopausal women who want short-term relief from hot flashes but should not be used to prevent chronic disease in women at any age as, on balance, the risks including increases in heart disease and breast cancer outweighed the benefits unless used for relief of moderate to severe menopausal symptoms.
- Women under age 60 had the most benefits and fewest risks.
- EPT carried more risk than ET, largely due to the increased the risk of breast cancer and dementia in women over 65.
- EPT and ET increased the risk of stroke, venous thromboembolic events, gallstones, and urinary incontinence.
- Both decreased the risk of hip fractures, diabetes, and hot flashes with improvement in health-related quality of life.
- Women on ET had a reduced risk of breast cancer and those under the age of 60 had small but significant reductions in all-cause mortality and myocardial infarction.
- Symptomatic menopausal women ages 50 to 54 years had "substantial reductions in symptoms" when receiving treatment during both trials compared with placebo.
- Women 70 to 79 years old who had vasomotor symptoms at baseline on treatments in both trials had high risks for CHD compared with women receiving placebo, whereas younger women did not.

Short-term hormone therapy remains useful for women with bothersome hot flashes, particularly if under age 60, with more benefits seen in ET users (hysterectomized women). Use of EPT or ET should be individualized based on each woman's risk-benefit ratio; time from menopause and degree of symptomatology. Despite benefits, the long-term use of combined EPT for chronic disease prevention is not warranted. We tolerate less risk when using medicine for prevention of disease than we do for treatment of problems. However, for some women, the quality of life improvements may outweigh risks, particularly in younger, healthier women. Transdermal products or micronized progesterone may decrease risks compared to the product tested in the WHI (CEE 0.625/MPA 2.5 mg). Caution should be exercised in older women with persistent menopausal symptoms as an increased risk of heart disease was found.

Combination EPT: For 10,000 women on EPT
Ages 50 to 59: 12 more adverse events (AEs) than placebo
Ages 60 to 69: 22 additional AE
Ages 70 to 79: 38 more AEs
Estrogen alone was safer: for 10,000 women
Ages 50 to 59: decrease in AE by 19
Ages 60 to 69: decrease in AE by 1
Ages 70 to 79: increased AEs by 51

For women who are not candidates for hormone therapy, nonhormonal treatment options may be helpful. The FDA has just approved 7.5 mg of paroxetine salt for treatment of hot flashes. Other SSRIS such as escitalopram, SSNRs such as desvenlafaxine and venlafaxine, and gabapentin have been found in large, randomized, double-blind trials to relieve hot flash frequency and severity more than placebo.

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References


Comment #4. Like many of you, I spend a great deal of time and energy tracking new menopause and hormone therapy findings and translating, to the best of my ability, those findings for both patients and practitioners. One of the inherent frustrations in this endeavor, over the past decade, has been trying to standardize the findings from multiple reports of multiple outcomes from the WHI. Some reports included absolute risk and stratification by age and years since menopause, while others have not. In some instances, as the data evolved, the relative risk or significance of a particular finding shifted from publication to publication. It made for a certain degree of dissonance as speakers at the same meeting selected different values to present, or inconsistencies in reports made it difficult to draw consistent conclusions for clinical counseling.

Today is a new day. This WHI report by Manson et al finally provides a clear summation of the WHI findings with a consolidated, consistent, and cohesive rendering of the results from the WHI clinical trials, extending from the initial reports through 13 cumulative years of follow up. To our benefit—and to those who look to us for guidance—this report literally puts us all on the same page (or rather, pages—the main report is 16 pages long with dense tables better approached with a magnifying glass than my reading glasses; the supplement, which is indeed complementary, weighs in at another 21 pages.) This is not a quick read, but the time to review the report line by line is time indeed well spent. Then you can go about the real work ahead: updating those Power Point slides!

What news do we learn? These were some of the standouts for me:

- The risk for invasive breast cancer with CEE+MPA remained elevated during the postintervention and cumulative follow up compared with the placebo group. This has important clinical implications for patient monitoring and follow up.
- The risk for invasive breast cancer with CEE-alone was significantly decreased in the cumulative follow up (overall combined phases). This is intriguing and leads to the question of how long might this unanticipated benefit of CEE persist?
- While endometrial cancer had neither increased nor decreased in the initial 2002 WHI report, in the cumulative follow up there is a 33% reduction in endometrial cancer. This is reassuring news for women taking the same hormone regimen as studied in the WHI.
- Of note is the persistent 19% reduction of hip fracture risk in the CEE+MPA group during the cumulative follow up. Again, this is an unanticipated longer-term benefit of combined therapy as the positive bone effects of HT are expected to decline shortly after discontinuation.
- A particularly helpful component is the detailing of the absolute risks and benefits for women ages 50 to 59 per 10,000 women-years of treatment with CEE+MPA versus CEE-alone (page 1363). These numbers allow for a consistent presentation to women considering HT and to the clinicians who prescribe it (maybe a new NAMS Patient Information Page could be generated!).
- The diverging safety profile between combined therapy and CEE-alone is confirmed. This strengthens our resolve
to establish the safety of additional modes of endometrial protection.

- While the reduced risks overall for younger (ages 50 to 59 year-old) women are highlighted, especially those on CEE-alone therapy, the primary role of HT for symptom relief rather than prevention continues to be emphasized.

At the end of the day, this report provides a much-needed summary of the WHI experience to date. As in the past, however, remain mindful that this updated chapter may not be the end of the HT story.

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The level of evidence indicated for each study is based on a grading system that evaluates the scientific rigor of the study design, as developed by the US Preventive Services Task Force. A synopsis of the levels is presented below.

- **Level I**: Properly randomized, controlled trial.
- **Level II-1**: Well-designed controlled trial but without randomization.
- **Level II-2**: Well-designed cohort or case-control analytic study.
- **Level II-3**: Multiple time series with or without the intervention (e.g., cross-sectional and uncontrolled investigational studies).
- **Level III**: Meta-analyses; reports from expert committees; descriptive studies and case reports.

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