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# MENOPAUSE

## Does estrogen therapy carry more risk than benefit? The answer depends, new data suggest, on the age of the patient, route of administration, and type of progestin.

The past 12 months have yielded important new insights into the risks and benefits of menopausal hormone therapy (HT), including

- landmark reports from the Women's Health Initiative (WHI) regarding HT and the risk of coronary artery disease
- data from France on the route of HT and risk of thrombosis and on progestin selection and the risk of breast cancer
- data from the Mayo Clinic regarding HT use and subsequent risk of dementia and parkinsonism.



IN THIS ARTICLE



**BONUS**
A timeline of how WHI has shed light on the estrogen–heart relationship Pages 56, 57

## User age determines effects of HT on coronary artery disease

Rossouw JE, Prentice PL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA. 2007;297:1465–1477.

Manson JE, Allison MA, Rossouw JE, et al. Estrogen therapy and coronary-artery calcification. N Engl J Med. 2007;356:2591–2602.

The WHI clinical trials were designed in 1991 and 1992 primarily to determine whether oral menopausal HT protects against coronary artery disease (CAD), as a large body of literature based on observational studies had suggested. Most of those observational studies had involved unopposed oral estrogen.[1]

When the estrogen–progestin arm of the WHI was halted in 2002, investigators noted that use of conjugated equine estrogen (CEE) plus medroxyprogesterone acetate (MPA) overall was associated with a 29% increase in the risk of CAD (hazard ratio [HR], 1.29; 95% confidence interval [CI], 1.02–1.63) and a more than 200% increase in the risk of venous thromboembolism (HR, 2.11; 95% CI, 1.49–2.87), compared with placebo. Subsequent reports explored this connection from different angles (see the timeline on pages 56, 57).

In 2007, important—and, for some, startling—findings were published regarding HT and the risk of CAD, most notably:

- When estrogen users from both arms of the WHI trial were combined into

one group, those who were less than 10 years since the onset of menopause had a HR for CAD of 0.76 (95% CI, 0.5–1.16), and oral HT was associated with six fewer cases of CAD for every 10,000 woman-years of use. Similar findings were reported for women 50 to 59 years old. Among older WHI participants and those more distant from menopause, HT was associated with an elevated risk of CAD.

- In the same cohort, mean coronary artery calcium scores overall were more favorable among women receiving estrogen than among those randomized to placebo (*P*=.02). Among women who took the study medication most consistently (at least 80% adherent), an even greater reduction in coronary artery calcification was noted with estrogen use, which was associated with a 61% reduction in the risk of having extensive coronary artery calcification (*P*=.004). The authors concluded: "… estrogen therapy may have cardioprotective effects in younger (menopausal) women."

In contrast to earlier WHI reports, which failed to break out risks by user age, these recent publications are consistent with the earlier observational studies of HT and should reassure ObGyns that the patients most likely to experience menopausal symptoms (women in their 50s and early 60s) can use HT without increasing their risk of CAD.

## Transdermal estrogen carries a lower risk of VTE than oral administration

Canonico M, Oger E, Plu-Bureau G, et al; Estrogen and Thromboembolism Risk (ESTHER) Study Group. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: The ESTHER study. Circulation. 2007;115:840–845.

As I noted earlier in this article, the initial 2002 WHI report found that oral CEE plus MPA doubled the risk of venous thromboembolism (VTE). Although WHI clinical trials did not study transdermal estrogen, an important observational study comparing VTE risk between oral and transdermal estrogen therapy was conducted in France, where use of transdermal estrogen is more common than in the United States.

In a 2007 report from this large multicenter, case-control study (the Estrogen and Thromboembolism Risk study, or ESTHER), oral menopausal estrogen therapy was associated with a fourfold increase in the risk of VTE (including pulmonary embolism and deep venous thrombosis), compared with nonuse (*P*<.05), whereas use of transdermal estrogen was not associated with any increase in the risk of VTE.

### Type of progestin also played a role

This report also assessed VTE by the type of progestin used by women taking combination estrogen–progestin HT. Micronized progesterone and MPA did not affect the risk of VTE, but norethindrone acetate as well as other progestins not used in the United States did appear to elevate VTE risk.

### Transdermal estrogen is as effective as oral therapy

Like oral estrogen therapy, transdermal therapy effectively treats vasomotor symptoms, prevents loss of bone density, and treats genital atrophy.

Because transdermal menopausal estrogen therapy does not increase hepat-

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**Women in their 50s and early 60s can use HT without increasing their risk of CAD**

ic production of procoagulant factors, as does oral estrogen, it is biologically plausible that transdermal therapy is safer than oral therapy in terms of the risk of VTE.[6]

Combined with other evidence, the findings of this important French study suggest that ObGyns should consider transdermal therapy when helping menopausal women select a HT regimen.

## Micronized progesterone might not raise the risk of breast cancer

Fournier A, Berrino F, Clavel-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. Breast Cancer Res Treat. 2008;107:103–111.

In contrast to estrogen-only therapy, long-term use of combination estrogen–progestin HT is associated with a modestly elevated risk of breast cancer.[7–10]

In France, micronized progesterone is the progestin most commonly used in HT. In 2008, results from a large French case-control study suggested that—in contrast to combination HT that contains MPA or norethindrone acetate—use of combination HT formulated with micronized progesterone was not associated with an elevated risk of breast cancer.

In women taking menopausal estrogen, the appropriate dosage of micronized progesterone to prevent endometrial hyperplasia is 100 mg nightly or 200 mg for 12 or more nights each month.

### Avoid micronized progesterone in patients with peanut allergy

Because micronized progesterone contains peanut oil, patients with a history of peanut allergy should not use it.

## Continued analysis of WHI data has refined our understanding of estrogen's effects on the heart

### 2002

**July. The first report from the WHI involving use of CEE–MPA in women with an intact uterus was published.[1]**

Notable observations: WHI enrolled women 50 to 79 years old at baseline (mean age at screening was 63 years), and the published report stated, "No noteworthy interactions with age…were found for the effect of estrogen plus progestin on CHD [coronary heart disease]."[1] This publication did not report hazard ratios for CHD by age group or time since menopause.

### 2003

**April. In an editorial published in *Circulation*,[3] Dr. JoAnn Manson, a Harvard internist and epidemiologist and a WHI investigator, asked, "Why then do the results from the observational studies and the randomized clinical trials on the association between HT and CAD seem to send different messages?"**

Notable observations: Dr. Manson pointed out that more than two thirds of women in the WHI were at least 60 years old and may have had subclinical CAD.

**August. A more detailed report on estrogen–progestin and the risk of CAD was published.[2]**

Notable observations: Although the risks of CHD appeared to increase with the number of years since menopause, this interaction was not found to be statistically significant.[2]

# Estrogen's effects on cognition depend on, again, age at use

Rocca WA, Bower JH, Maraganore DM, et al. Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause. Neurology. 2007;69:1074–1083.

Rocca WA, Bower JH, Maraganore DM, et al. Increased risk of parkinsonism in women who underwent oophorectomy before menopause. Neurology. 2008;70:200–209.

One intriguing possibility entertained in recent years is that HT prevents dementia, although data so far have been conflicting. A large, high-quality observational study performed in Utah and published in 2002 provided evidence that HT use by young menopausal women prevents cognitive decline later in life, particularly when HT is used over the long term.[11]

In contrast, the WHI Memory Study found that HT increases the risk of mild cognitive impairment and dementia.[12] However, that study enrolled an older subgroup of WHI participants (65 to 79 years old at randomization).

### Very young estrogen-deprived women stand to benefit from HT

Over the past year, Rocca and colleagues at the Mayo Clinic in Minnesota published two reports assessing the risk of neurologic disease among several thousand Midwestern women who had undergone oophorectomy (unilateral or bilateral) before reaching menopause. A history of oophorectomy, especially in women younger than 38 years, was associated with a significantly increased risk of cognitive impairment and dementia. However, when estrogen therapy was prescribed until at least 50 years of age following bilateral oophorectomy, no increased risk of cognitive impairment was found.

Using similar methods, the same research group at Mayo found that oophorectomy before menopause was associated with a significantly increased risk of parkinsonism (symptoms that did not

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## 2004

**April. First report from the estrogen-only arm of the WHI.**

Notable observations: Oral estrogen use in women who had undergone hysterectomy carried a risk of CAD similar to that of placebo (HR, 0.91; 95% CI, 0.75–1.12).[4] This publication did not report HRs for CAD by age.

## 2006

**February. Additional findings on estrogen-only HT were published.**

Notable observations: Among women 50 to 59 years old at baseline, the risk of myocardial infarction or coronary death was lower with estrogen use (HR, 0.63; 95% CI, 0.36–1.08, *P*>.05), and the risk of undergoing coronary artery revascularization (coronary artery bypass grafting or percutaneous coronary intervention) was significantly lower than with placebo (HR, 0.55; 95% CI, 0.35–0.86).[5]

## 2007

**April. A subanalysis was published that combined *both arms* of the WHI.**

Notable observations: Estrogen users who were less than 10 years since the onset of menopause had an HR for CAD of 0.76 (95% CI, 0.5–1.16).

**June. A separate subanalysis was published assessing estrogen use and coronary artery calcification in WHI participants who had undergone hysterectomy and who were 50 to 59 years old at baseline.**

Notable observations: Overall, mean coronary artery calcium scores were more favorable among women receiving estrogen than among those randomized to placebo (*P*=.02).

**of arterial inflow and venous outflow of abdominal, pelvic, scrotal contents and/or retroperitoneal organs; complete study) with an obstetric US code?**

**A** Yes. You may report a duplex-Doppler scan with an obstetric US procedure because there are no bundles within the National Correct Coding Initiative that preclude your doing so. But your diagnosis code will be taken from the obstetric complications chapter (e.g., **654.13**, *tumors of body of uterus*), which may create a mismatch in the diagnosis/procedure check in the payer's computer. This doesn't mean you won't be paid for the nonobstetric sonogram being linked to an obstetric complication, but you might have to submit additional information with the claim.

Also, understand that the duplex procedures are only reported when you are trying to characterize the pattern and direction of blood flow in arteries or veins. This year, CPT clarified that, although evaluation of vascular structures using both color and spectral Doppler is reportable separately, color Doppler alone, when performed for identification of anatomic structures in conjunction with a real-time US exam, cannot be reported separately.

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meet the formal criteria for Parkinson's disease) as well as an increased risk, which did not attain statistical significance, of Parkinson's disease itself.

Taken in totality, the evidence suggests that when HT is initiated in young menopausal women, protection against dementia and other neurologic disease may result. These findings parallel the evidence on the risk of CAD during HT use presented at the beginning of this article. ■

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