

In Perspective: Estrogen Therapy Safely and Effectively Reduces Total Mortality and Coronary Heart Disease in Recently Menopausal Women

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Editor's note: For several years before the publication of the WHI and HERS studies, observational studies had suggested a cardioprotective effect for postmenopausal hormone therapy. The results of the HERS and WHI trials were therefore unexpected, and led to a complete reversal in thinking. Subsequently, with careful review of studies like the WHI, as well as other published data, the pendulum of understanding has begun to swing back toward the center. In this issue of Menopause Management, Drs. Howard Hodis and Wendy Mack present their perspective on this evolving situation.

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Recent data from the Women's Health Initiative (WHI) support an extensive body of evidence that estrogen therapy (ET) reduces total mortality and coronary heart disease (CHD) in women less than age 60 who initiate ET in close proximity to menopause.¹ With the release of these data, the potential role of hormone therapy (HT), specifically ET, for the primary prevention of CHD in postmenopausal women is clearer, especially when appreciated in relation to other commonly used therapies.²⁻⁴

What is the magnitude of risk with postmenopausal ET?

All medications have risks and benefits. Hormones for postmenopausal

hormonal replacement are no exception. The hormone-related risks of greatest concern are breast cancer, stroke and venous thrombosis.

However, as with all approved medications that withstand the test of time, the risks associated with HT are small, and those associated with ET even smaller. In fact, the ET-related risks occur at an absolute frequency of <1 additional event per 1,000 women per year of therapy and are considered rare risks by World Health Organization criteria (Table 1).²

What are the most current ET data from WHI?

The benefits of HT are well appreciated^{3,4} and, as the most current data from WHI indicate,¹ the major remaining concern related to potential ET-associated risk is that of venous thromboembolic (VTE) events (Table 2). However, the overall risk for VTE events is rare with ET (0.8 additional events/1,000 women/year of conjugated equine estrogen [CEE] therapy) and it is even more rare in women under age 60 (0.4 additional events/1,000 women/year of CEE therapy).^{2,5} The VTE risks of CEE are similar to those of other commonly used medications, such as fenofibrate in diabetics.²

How does the risk-benefit profile of ET compare to that of other primary prevention therapies used in women?

Putting medications and standard therapies into clinical perspective is perhaps the most common approach to understanding overall utility and reasonable acceptance of risks and benefits. Two therapies recommended for the primary prevention of CHD in women are aspirin and lipid-lowering drugs. However, neither aspirin nor lipid-lowering therapy have been demonstrated to significantly reduce total mortality or CHD in women.² On the other hand, the cumulative data indicate that ET reduces CHD and total mortality in women <60 years old.²⁻⁴ The risks associated with ET in postmenopausal women <60 years are rare and of the same magnitude as those associated with aspirin and lipid-lowering therapy when used for primary prevention of CHD.² In addition, ET, specifically CEE, provides benefits beyond those obtained with other primary prevention therapies, such as prevention of fractures (Table 2).^{3,4}

Does lipid-lowering therapy reduce total mortality and CHD in women?

Lipid-lowering medications, predominantly statins, are among the mainstays for the primary prevention of CHD. As clinical trials have primarily enrolled men, the cumulative data across six randomized trials and data on 11,435 women are not sufficiently large to demonstrate that lipid lowering significantly reduces total mortality (relative risk [RR], 0.95; 95% confidence interval [CI], 0.62-1.46), CHD mortality (RR, 1.07; 95% CI, 0.47-2.40), CHD

Table 1. World Health Organization Council for International Organizations of Medical Sciences Frequency of Adverse Drug Reactions²

Category	Absolute Frequency	Percentage Frequency
Very common	≥1/10	≥10%
Common (frequent)	≥1/100 - <1/10	≥1% - <10%
Uncommon (infrequent)	≥1/1,000 - <1/100	≥0.1% - 1%
Rare	≥1/10,000 - <1/1000	0.01% - <0.1%
Very rare	<1/10,000	<0.01%

Table 2. Effect of Conjugated Equine Estrogen (CEE) Therapy on Major Outcomes for Women Younger than Age 60 from the Women's Health Initiative^{3,4}

Event	Percent difference in risk relative to placebo (95% CI)	Number of events/10,000 women/year of CEE therapy
Total mortality	-29 (0.46-1.11)	-11
Coronary heart disease	-37 (0.36-1.09)	-11
Stroke	-11 (0.47-1.69)	-2
New-onset diabetes mellitus	-12 (0.77-1.01)	-14
Fractures	-30 (0.59-0.83)	-56
Breast cancer*	-18 (0.65-1.04)	-8
Venous thromboembolism [†]	+37 (0.70-2.68)	+4

CI = confidence interval

*33% reduction in women who were at least 80% compliant with ET (RR=0.67; 95% CI, 0.47-0.97)

[†]Deep vein thrombosis and pulmonary embolism

events (RR, 0.87; 95% CI, 0.69-1.09) or nonfatal myocardial infarction (MI) (RR, 0.61; 95% CI, 0.22-1.68) when used for primary prevention of CHD in women.⁶

Does aspirin reduce total mortality and CHD in women?

Prophylactic use of aspirin for primary prevention of CHD is a common medical practice and is recommended by major health organizations.⁷ However, the Women's

Health Study (WHS) of 39,876 healthy women randomized to aspirin (100 mg every other day) or placebo for 10 years showed a null effect of aspirin on the primary trial end point of nonfatal MI, nonfatal stroke or cardiovascular death (RR, 0.91; 95% CI, 0.80-1.03).⁸ Total mortality and cardiovascular death from any cause were also unaffected by aspirin. Within the null finding was no significant effect on fatal or nonfatal MI (RR, 1.02; 95% CI, 0.84-

1.25), and a 17% (RR, 0.83; 95% CI, 0.69-0.99) reduction in stroke with aspirin relative to placebo.⁸ Although ischemic stroke was reduced by 24% (RR, 0.76, 95% CI, 0.63-0.93) with aspirin relative to placebo, hemorrhagic stroke was increased by 24% (RR, 1.24; 95% CI, 0.82-1.87) with aspirin.⁸

Bleeding diatheses were all significantly increased with aspirin versus placebo in the WHS.⁸ Any gastrointestinal bleeding was increased 22% (RR, 1.22; 95% CI, 1.10-1.34) with aspirin versus placebo, and gastrointestinal bleeding requiring blood transfusion was increased 40% (RR, 1.40; 95% CI, 1.07-1.83) with aspirin versus placebo.⁸ The absolute increased risk for any gastrointestinal bleeding was 8 additional cases/10,000 women/year of aspirin use.⁸

The other randomized controlled trials of aspirin that included women were of smaller size and shorter duration than the WHS, but showed similar magnitudes of risk with no overall reduction in cardiovascular events (Hypertension Optimal Treatment [n=8,883 women, 3.8 years]⁹ and Primary Prevention Project [n=2,583 women, 3.6 years]).^{8,10}

What is the effect of ET on total mortality and CHD?

The cumulative data across 23 randomized controlled trials of 39,049 women followed for 191,340 patient-years indicate a 32% (odds ratio [OR], 0.68; 95% CI, 0.48-0.96) significant reduction of CHD in women under age 60 years or less than 10 years since menopause when randomized to HT relative to placebo.¹¹ Under primary prevention conditions in the WHI, CEE significantly

Estrogen has effects on calcium metabolism at the arterial wall level, which could account for its unique ability to reduce calcium content of atherosclerotic plaques.^{19,20}

reduced several composite CHD outcomes by approximately 34%-45% in 3,310 postmenopausal women younger than age 60.¹²

In addition, the cumulative data indicate a 39% (OR, 0.61; 95% CI, 0.39-0.95) significant reduction in total mortality in women less than 60 years old who were randomized to HT relative to placebo.¹³ Recent WHI data show that CEE + medroxyprogesterone acetate (MPA) (hazard ratio [HR], 0.71; 95% CI, 0.46-1.11) and CEE alone (HR, 0.69; 95% CI, 0.44-1.07) each reduce total mortality 30% relative to placebo.¹ When both the WHI CEE and CEE + MPA data were combined, total mortality was significantly reduced (30%) relative to placebo (HR, 0.70; 95% CI, 0.51-0.96).¹

Unlike lipid-lowering therapy, ET reduces coronary artery calcium.¹⁴ The Coronary Artery Calcium Substudy of the WHI (WHI-CACS) adds to the growing evi-

dence that women who initiate ET in close proximity to menopause have lower rates of CHD than women who initiate ET distant from menopause.²⁻⁴ As a direct measure of calcium, a component of atherosclerosis, WHI-CACS provides insight into another mechanism by which ET reduces CHD.¹⁴ The effect of ET was greatest in the women who were most compliant with ET, consistent with the large body of evidence that ET reduces atherosclerosis, cardiovascular disease and total mortality in women under age 60.^{1-4,11-13,15}

WHI-CACS provides important information about a therapeutic effect of ET not seen with any other intervention for coronary artery disease; that is, the reduction of coronary artery calcium, a component of late-stage atherosclerosis lesions. It has been hypothesized for many years that calcium within atherosclerotic plaques is immutable. For example, over 1 to 4 years of randomized intervention, even aggressive lipid-lowering therapy has failed to slow the progression of coronary artery calcium accumulation.¹⁶⁻¹⁸ Estrogen has effects on calcium metabolism at the arterial wall level, which could account for its unique ability to reduce calcium content of atherosclerotic plaques.^{19,20}

Does statin therapy affect breast cancer risk in women?

Seven randomized controlled trials have reported the effect of statin therapy on breast cancer risk; the risk ranges from -10 to 75 additional breast cancers/10,000 women/year of statin therapy (Table 3). A recent meta-analysis reported data from

Table 3. Comparison of Relative and Absolute Risks of Breast Cancer in Randomized Controlled Trials of Statin and Estrogen-Alone Therapies

Study	No. of Breast Cancers (Annualized %)		Relative Risk	95% CI	No. Additional Breast Cancer Cases per 10,000 Women per Year of Therapy
	Placebo	Therapy			
STATIN					
PROSPER	11 (0.23)	18 (0.38)	1.65	0.78-3.49	15
AFCAPS/TexCAPS	9 (0.35)	13 (0.50)	1.44	0.62-3.36	15
4S 10-year follow-up	5 (0.11)	7 (0.17)	1.44	0.46-4.52	5
CARE	1 (0.07)	12 (0.84)	12.17*	2.48-59.80	77
LIPID	10 (0.22)	10 (0.22)	1.00	0.42-2.42	0
ALLHAT-LLT	37 (0.30)	34 (0.28)	0.93	0.58-1.48	-2
HPS	51 (0.40)	38 (0.30)	0.75	0.49-1.13	-10
CEE Alone					
WHI-E	161 (0.42)	129 (0.34)	0.82	0.65-1.04	-8 [†]
17β-E2 Alone					
WEST	5 (0.55)	5 (0.53)	1.00	0.30-3.50	-2

STATIN = HMG-CoA reductase inhibitor

CEE = oral daily conjugated equine estrogen (0.625 mg)

17β-E2 = oral daily 17β-estradiol (1 mg)

PROSPER = Prospective Study of Pravastatin in the Elderly Risk (Shepherd J, et al. *Lancet* 2002;360:1623-1630)

AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study (Clearfield M, et al. *J Women's Health Genet Based Med* 2001;10:971-981)

4S = Scandinavian Simvastatin Survival Study (Strandberg TE, *Lancet* 2004;364:771-7)

CARE = Cholesterol and Recurrent Events trial (Sacks FM, et al. *N Engl J Med* 1996;335:1001-09)

LIPID = Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID. *N Engl J Med* 1998;339:1349-57)

ALLHAT-LLT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT. *JAMA* 2002;288:2998-3007)

HPS = Heart Protection Study (Collins R, et al. *Lancet* 2004;363:757-67)

WHI-E = Women's Health Initiative Estrogen trial (Stefanick ML, et al. *JAMA* 2006;295:1647-57)

WEST = Women's Estrogen for Stroke Trial (Viscoli CM, et al. *N Engl J Med* 2001;345:1243-49)

**P* = 0.002

[†]Total breast cancer incidence statistically significantly reduced with CEE versus placebo in adherent subjects (HR, 0.67; 95% CI, 0.47-0.97). Statistically significant reduction of ductal (most common) breast cancer in subjects randomized to CEE versus placebo (HR, 0.71; 95% CI, 0.52-0.99).

five randomized controlled trials of statin therapy compared to placebo, indicating a 33% (OR, 1.33; 95% CI, 0.79-2.26) increased risk of breast cancer associated with statin use, or 7 additional breast cancer cases/10,000 women who used statin therapy.²¹ A previous meta-analysis of seven randomized controlled trials of statin therapy showed a 4% (RR, 1.04; 95% CI, 0.81-1.33) increased risk of breast cancer associ-

ated with statin use, or 2 additional breast cancer cases/10,000 women who used statin therapy.²² Site-specific cancers, especially breast cancer incidence, have not been reported in all lipid-lowering randomized controlled trials; thus, the breast-cancer-related risk remains unknown across all lipid-lowering medications. Although the oncogenicity of lipid-lowering medications, including statins, is complex

and incompletely understood, there is biological plausibility for induction of cancer in general, and for breast cancer specifically.²³⁻²⁵

What is the effect of ET on breast cancer risk in women?

After an average of 7.1 years of randomized treatment in the WHI trial, breast cancer was decreased with CEE therapy by 18% relative to placebo (HR, 0.82; 95% CI,

0.65-1.04), resulting in 8 fewer cases of breast cancer/10,000 women/year of CEE therapy (Table 3).²⁶ The reduction in breast cancer incidence with CEE relative to placebo was seen across the entire 50- to 79-year age range.²⁷ More important, breast cancer was significantly reduced (by 33%) in the women who were at least 80% compliant with ET (RR=0.67; 95% CI, 0.47-0.97).²⁶ In addition, breast cancer incidence was significantly reduced (by 29%) in those women who developed ductal carcinoma, the most common form of the disease (HR, 0.71; 95% CI, 0.52-0.99).²⁶ In the Women's Estrogen for Stroke Trial, breast cancer incidence did not differ in women treated with 17 β -estradiol alone compared to placebo (Table 3).²⁸

Does duration of ET affect the risk-benefit profile?

It has been argued that the long-term risks associated with ET are unknown and that the adverse effects of ET increase as a woman ages. However, this argument can be made for all therapies used in the primary prevention of CHD since no CHD prevention has been studied over decades under randomized controlled trial conditions. In fact, ET is one of the longest studied primary prevention therapies (average, 7.1 years of randomized controlled trial experience), longer than any statin trial. Additionally, HT and ET have the most information derived from observational studies in which women used HT for 10 to 40 years. The WHI, other trials and observational studies (including the WHI observational study) demonstrate significant trends in the re-

Table 4. Coronary Heart Disease in the Women's Health Initiative Trial and the Women's Health Initiative Observational Study According to Duration of Postmenopausal Hormone Therapy*²⁻⁴

Duration of Use (years)	Clinical Trial		Observational Study	
	HR [†]	95% CI	HR [§]	95% CI
CEE	ET			
<2	1.07	0.68-1.68	1.20	0.49-2.24
2-5	1.13	0.79-1.61	1.09	0.75-1.60
>5	0.80	0.57-1.12	0.73	0.61-0.84
CEE+MPA	EPT			
<2	1.68	1.15-2.45	1.12	0.48-2.74
2-5	1.25	0.87-1.79	1.05	0.70-1.58
>5	0.66	0.36-1.21	0.83	0.67-1.01

*Adjusted for age, race, body mass index, educational level, smoking, age at menopause and physical activity

[†]Hazard Ratio, relative to placebo

[§]Hazard Ratio, relative to nonusers of hormone therapy

CEE = conjugated equine estrogen; CEE + MPA = conjugated equine estrogen plus medroxyprogesterone acetate; ET = estrogen therapy; EPT = estrogen+progesterone therapy

duction of total mortality and CHD with time, indicating benefit on these outcomes with duration of therapy (Table 4).²⁻⁴ Most important, there is no evidence to indicate that if a woman initiates ET at age 50 her risks from ET will increase as she ages. The assumption that adverse CHD events with ET will increase with time (in fact, the WHI has shown the opposite)^{12,27} contradicts the paradigm of prevention since with all preventive therapies, the earlier initiated the greater the benefit. All that the WHI can tell us is that women who initiate ET at age 60 or younger will have greater benefit than risk, and women over 60 will have greater risk when initiating ET.

Summary and Conclusions

The cumulative data indicate that in

postmenopausal women <60 years old ET significantly reduces total mortality and CHD. In addition, the risks of concern for ET, such as stroke and breast cancer, were not elevated in postmenopausal women <60 years old. VTE associated with ET is rare and the risk is no greater than that with other commonly used medications. The risks and benefits of ET compare favorably to those of aspirin and lipid-lowering therapy for the primary prevention of CHD. With the risks and benefits of ET in clinical perspective, the cumulative data indicate that ET is a potentially effective therapy for the primary prevention of CHD if initiated in postmenopausal women <60 years old.

The evidence for a preventive role of ET in certain postmenopausal women is stronger than ever.²⁻⁴ The WHI has not only confirmed the

known benefits of ET from observational studies but has also shown the relative safety of ET under randomized controlled conditions in women under age 60. The WHI confirms 40 years of consistent observational data showing that women who initiate ET in close proximity to menopause have a significant reduction in total mortality and CHD. In addition, the WHI has shown that ET (CEE) reduces breast cancer risk with efficacy similar to that of selective estrogen-receptor modulators,²⁹ and the remaining risk (VTE associated with ET) is rare (<1/1,000).

The Early versus Late Intervention Trial with Estradiol, funded by the National Institute on Aging, is designed to specifically address the "timing of initiation hypothesis,"²⁻⁴ providing further insight into the effect of ET in young versus older postmenopausal women.³⁰ Although the privately funded Kronos Early Estrogen Prevention Study does not have a comparative older group of women, it will provide insight into the effects of several HT regimens in young postmenopausal women.

Until shown otherwise, women and healthcare providers can feel comfortable that the cumulative data, including those from the WHI, indicate that ET, in particular CEE, is safe and effective in reducing total mortality and CHD in women who initiate ET in close proximity to menopause. ■

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