

**Cardiovascular Disease in Women: Update on Menopausal  
Hormone Therapy and Selective Estrogen Receptor Modulators (SERMs)**

**“Hormone Replacement Therapy” Risk-Benefit Balance: 1960s-1990s**

Hormone replacement therapy for menopausal women was widely advocated on the basis of perceived health benefits. By the 1990s, the most compelling argument for hormone replacement therapy was the belief, based on data from observational and cohort studies, that it prevented CHD.

SOURCES:

(1) Limacher MC. (2002). Hormones and heart disease: What we thought, what we have learned, and what we still need to know. *Transactions of the American Clinical & Climatological Association*, 113, 31-41.

(2) Grady et al. (1992). Hormone therapy to prevent disease and prolong life in postmenopausal women. *Annals of Internal Medicine*, 117, 1016-1037.

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**Effects of Postmenopausal Estrogen Therapy on CVD Risk Factors**

- A meta-analysis of 32 epidemiological studies published in 1992 found a 35% reduction in CHD risk in women using hormone therapy. Other meta-analyses have found even greater reductions of up to 45%
- Several mechanisms have been proposed to support a beneficial effect of estrogen on the cardiovascular system, including beneficial effects on lipid profile and coagulation, vasodilatory and antioxidant effects, and early restoration of endothelial integrity after injury

SOURCES:

(1) Grady et al. (1992). Hormone therapy to prevent disease and prolong life in postmenopausal women. *Annals of Internal Medicine*, 117, 1016-1037.

(2) Mendelsohn ME, Karas RH. (1999). The protective effects of estrogen on the cardiovascular system. *New England Journal of Medicine*, 340, 1801-1811.

(3) Espeland MA, et al. (1998). Effect of postmenopausal therapy on glucose and insulin concentrations. *Diabetes Care*, 21,1589-1595.

**Heart and Estrogen/Progestin Replacement Study (HERS): Cumulative Incidence of CHD Events**

- The Heart and Estrogen/Progestin Replacement study was the first randomized, blinded, placebo controlled trial testing the effects of hormone therapy in women with diagnosed coronary heart disease.
- 2763 women were enrolled; 1380 in the active treatment arm, and 1383 in the placebo arm
- At the end of an average of 4.1 years of follow-up, there was no difference between groups for endpoint of nonfatal MI, CHD death, or coronary revascularization.
- An increase in CHD events was found in year 1. The authors speculated this might be due to a prothrombotic, proarrhythmic, or proischemic effect of estrogen treatment that is balanced over time by beneficial lipid effects

SOURCE:

(1) Hulley S, et al. (1998). Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *Journal of the American Medical Association*, 280, 605-613.

**Women’s Health Initiative Estrogen and Progestin Arm: Absolute Excess Risk**

- The Women’s Health Initiative randomized 16,608 healthy postmenopausal women (average age 63 years) to conjugated equine estrogen .625 mg/d and medroxyprogesterone acetate 2.5 mg/d or placebo
- After a mean of 5.2 years of follow-up the study was stopped by the data and safety monitoring board because a global assessment of risks had outweighed potential benefits
- Risks and benefits were expressed in terms of excess events for 10,000 woman-years of hormone use
- Excess CHD events: 7/10,000 woman-years
- Excess stroke events : 8/10,000 woman-years
- Excess pulmonary emboli: 8/10,000 woman-years
- Excess invasive breast cancer: 8/10,000 woman-years

SOURCE:

(1) Writing Group for the Women’s Health Initiative Investigators. (2002). Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *Journal of the American Medical Association*, 288, 321-333.

**Women’s Health Initiative Estrogen and Progestin Arm: Absolute Benefits**

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- Risks and benefits were expressed in terms of excess events for 10,000 woman-years of hormone use
- Fewer colorectal cancers: 6/10,000 woman-years
- Fewer hip fractures: 5/10,000 woman-years

SOURCE:

(1) Writing Group for the Women’s Health Initiative Investigators. (2002). Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *Journal of the American Medical Association*, 288, 321-333.

**Women’s Health Initiative: Estrogen Alone in Postmenopausal Women Compared to Placebo: Major Clinical Outcomes**

In the estrogen-only arm of the WHI, no increase in CHD or breast cancer was demonstrated after an average of 6.8 years of follow-up. However, stroke risk did significantly increase, and consequently, total CVD risk was slightly increased

The chart below shows the relative risks:

	Stroke	Colorectal Cancer	Total Mortality	CHD	Breast Cancer	Hip Fracture
Hazard Ratio	1.39	1.08	1.04	0.91	0.77	0.61

SOURCE:

(1) Women's Health Initiative Steering Committee. (2004). Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: The Women's Health Initiative randomized controlled trial. *Journal of the American Medical Association*, 291, 1701-1712.

#### **Hormone Therapy Risk-Benefit Balance: 2004**

- Randomized trials have shown no benefit of postmenopausal hormone therapy for CHD
- Although not all possible preparations, doses, and routes of administration of hormone therapy have been studied, results of randomized trials have not shown any difference between preparations, and have shown similar results both for healthy women, and for those with CHD
- Hormone therapy should not be started or continued for the prevention or treatment of CHD
- Initiation of hormone therapy for menopausal symptoms should be done with careful consideration of associated risk, including those related to CVD

#### **SOURCES:**

(1) ACOG Task Force for Hormone Therapy. (2004). Summary of balancing risks and benefits. *Obstetrics & Gynecology*, 104 (4 Suppl), 1S-129S.

(2) Mosca L, et al. (2004). Evidence-based guidelines for cardiovascular disease prevention in women. *Circulation*, 109, 672-693.

#### **Menopausal Hormone Therapy, SERMs and CVD: Summary of Major Randomized Trials**

- Use of estrogen plus progestin associated with a small but significant risk of CHD and stroke
- Use of estrogen without progestin associated with a small but significant risk of stroke
- Use of all hormone preparations should be limited to short term menopausal symptom relief
- Use of a selective estrogen receptor modulator (raloxifene) does not affect risk of CHD or stroke, but is associated with an increased risk of fatal stroke

#### **SOURCES:**

(1) Hulley S, et al. (1998). Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *Journal of the American Medical Association*, 280, 605-613.

(2) Writing Group for the Women's Health Initiative Investigators. (2002). Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *Journal of the American Medical Association*, 288, 321-333.

(3) Women's Health Initiative Steering Committee. (2004). Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: The Women's Health Initiative randomized controlled trial. *Journal of the American Medical Association*, 291, 1701-1712.

(4) ACOG Task Force for Hormone Therapy. (2004). Summary of balancing risks and benefits. *Obstetrics & Gynecology*, 104 (4 Suppl), 1S-129S.

(5) Barrett-Connor E, et al. (2006). Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. *New England Journal of Medicine*, 355, 125-37.

#### **Raloxifene Use for the Heart (RUTH) Trial: Primary and Secondary CVD Outcomes**

- The RUTH trial randomized 10,101 postmenopausal women with a mean age of 67.5 years to the selective estrogen receptor modulator (SERM) raloxifene 60 mg daily, or placebo.

- Median follow-up was 5.6 years.
- Raloxifene had no significant effect on primary coronary events, CHD fatality, or strokes.
- Raloxifene use was associated with an increase in fatal stroke and venous thromboembolism that reached statistical significance.
- Raloxifene reduced the risk of invasive breast cancers and vertebral fractures.

The following chart shows the number of events by category:

	CHD events	Fatal CHD	Stroke	Fatal Stroke
Raloxifene	533	253	249	59
Placebo	553	273	224	39

SOURCE:

(1) Barrett-Connor E, et al. (2006). Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. *New England Journal of Medicine*, 355, 125-37.

### **Interventions that are not useful/effective and may be harmful for the prevention of heart disease**

- Hormone therapy and selective estrogen-receptor modulators (SERMs) should not be used for the primary or secondary prevention of CVD

SOURCES:

(1) Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, Newby LK, Piña IL, Roger VL, Shaw LJ, Zhao D, Beckie TM, Bushnell C, D'Armiento J, Kris-Etherton PM, Fang J, Ganiats TG, Gomes AS, Gracia CR, Haan CR, Jackson EA, Judelson DR, Kelepouris E, Lavie CJ, Moore A, Nussmeier NA, Ofili E, Oparil S, Ouyang P, Pinn VW, Sherif K, Smith SC, Sopko G, Chandra-Strobos N, Urbina EM, Vaccarino V, Wenger NK. (2011). Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 Update: A Guideline From the American Heart Association. *Circulation*, 123, 1243-1262.

(2) Lee IM, Cook NR, Gaziano JM, Gordon D, Ridker PM, Manson JE, Hennekens CH, Buring JE. (2005). Vitamin E in the primary prevention of cardiovascular disease and cancer: the Women's Health Study: A randomized controlled trial. *Journal of the American Medical Association*, 294(1), 56-65.

(3) Lonn E, Bosch J, Yusuf S, Sheridan P, Pogue J, Arnold JM, Ross C, Arnold A, Sleight P, Probstfield J, Dagenais GR; HOPE and HOPE-TOO Trial Investigators. (2005). Effects of long-term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial. *Journal of the American Medical Association*, 293(11), 1338-47.

(4) Bønaa KH, Njølstad I, Ueland PM, Schirmer H, Tverdal A, Steigen T, Wang H, Nordrehaug JE, Arnesen E, Rasmussen K; NORVIT Trial Investigators. (2006). Homocysteine lowering and cardiovascular events after acute myocardial infarction. *New England Journal of Medicine*, 354(15), 1578-88.

(5) Loscalzo J. (2006). Homocysteine trials - Clear outcomes for complex reasons. *New England Journal of Medicine*, 354, 1629 – 1632.

The Women's Health Study, a 10-year randomized double-blind, placebo controlled trial of nearly 40,000 healthy women aged 45 years and older showed no cardiovascular benefit or risk to vitamin E supplementation (600 IU every other day) (1). The HOPE and HOPE-TOO trials performed in patients with CHD equivalent risk also found no benefit (2).

Multiple trials have shown no CHD benefit or a trend to harm for folic acid supplementation in patients with coronary artery disease or significant CHD risk (3), (4).

### **What the Experts Are Saying About Hormone Therapy And Cardiovascular Disease**

- NIH – “New analyses from the Women's Health Initiative (WHI) confirm that combination hormone therapy *increases* the risk of heart disease in healthy postmenopausal women. Researchers report a trend toward an increased risk of heart disease during the first two years of hormone therapy among women who began therapy within 10 years of menopause.”

–“WHI Study Data Confirm Short-Term Heart Disease Risks of Combination Hormone Therapy for Postmenopausal Women,” *NIH News*, Monday, February 15, 2010.

#### **SOURCES:**

(1) National Institutes of Health. “Menopausal Hormone Therapy Information.” Available at: <http://www.nih.gov/PHTindex.htm>.

(2) Toh SD, Hernández-Díaz S, Logan R, Rossouw JE, & Hernán MA. (2010). Coronary heart disease in postmenopausal recipients of estrogen plus progestin therapy: Does the increased risk ever disappear? A randomized trial. *Annals of Internal Medicine*, 152(4), 211-217.

### **What the Experts Are Saying About Hormone Therapy And Cardiovascular Disease**

American Congress of Obstetricians & Gynecologists (ACOG):

- “Menopausal HT should not be used for the primary or secondary prevention of CHD at the present.”
- “Hormone therapy use should be limited to the treatment of menopausal symptoms at the lowest effective dosage over the shortest duration possible and continued use should be reevaluated on a periodic basis.”

#### **SOURCE:**

(1) ACOG Committee Opinion No. 420, November 2008: Hormone therapy and heart disease. *Obstetrics & Gynecology*, 112(5), 1189-92.

### **Ongoing Studies About Hormone Therapy: Does the Timing and Type of Estrogen Matter?**

- **KEEPS:** **K**ronos **E**arly **E**strogen **P**revention **S**tudy
  - 660 women aged 48-52, randomized to placebo, oral conjugated equine estrogen, or transdermal 17 beta-estradiol with placebo or pulsed progesterone for 12 days/month
  - Endpoint: Progression of atherosclerosis measured by carotid intima media thickness and coronary artery calcification
- **ELITE:** **E**arly versus **L**ate **I**ntervention **T**rial with **E**stradiol
  - 504 women either less than 6 years from menopause or more than 10 years from menopause randomized to oral 17 beta-estradiol or placebo, with progesterone gel or placebo
  - Endpoint: Progression of atherosclerosis measured by carotid intima media thickness

#### **SOURCES:**

(1) Miller VM, et al. (2009). Using basic science to design a clinical trial: Baseline characteristics of women enrolled in the Kronos Early Estrogen Prevention Study (KEEPS). *Journal of Cardiovascular Translational Research*, 2, 228-239.

(2) Clinical trial: ELITE: Early Versus Late Intervention Trial With Estradiol. Available at: <http://clinicaltrials.gov/ct2/show/NCT00114517>.

### **Estrogen Alone Caused Stroke in Women's Health Initiative**

- Women randomized to conjugated equine estrogen (CEE) for an average of 6.8 years had statistically significantly more strokes (HR 1.39)
- Statistical analysis did not show that the risk of stroke was affected by age of initiation of therapy
- Follow-up studies showed the risk of stroke was no longer elevated once CEE was discontinued

#### **SOURCES:**

(1) Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, Bonds D, Brunner R, Brzyski R, Caan B, Chlebowski R, Curb D, Gass M, Hays J, Heiss G, Hendrix S, Howard BV, Hsia J, Hubbell A, Jackson R, Johnson KC, Judd H, Kotchen JM, Kuller L, LaCroix AZ, Lane D, Langer RD, Lasser N, Lewis CE, Manson J, Margolis K, Ockene J, O'Sullivan MJ, Phillips L, Prentice RL, Ritenbaugh C, Robbins J, Rossouw JE, Sarto G, Stefanick ML, Van Horn L, Wactawski-Wende J, Wallace R, Wassertheil-Smoller S; Women's Health Initiative Steering Committee. (2004). Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *Journal of the American Medical Association*, 291(14), 1701-12.

(2) LaCroix AZ, Chlebowski RT, Manson JE, et al. (2011). Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy. *Journal of the American Medical Association*, 305(13), 1305-1314.

### **Estrogen Alone Did Not Effect CHD Events in WHI; After Cessation of Estrogen, Younger Women Who Had Taken CEE Had Fewer CHD Events**

#### **SOURCES:**

(1) Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, Bonds D, Brunner R, Brzyski R, Caan B, Chlebowski R, Curb D, Gass M, Hays J, Heiss G, Hendrix S, Howard BV, Hsia J, Hubbell A, Jackson R, Johnson KC, Judd H, Kotchen JM, Kuller L, LaCroix AZ, Lane D, Langer RD, Lasser N, Lewis CE, Manson J, Margolis K, Ockene J, O'Sullivan MJ, Phillips L, Prentice RL, Ritenbaugh C, Robbins J, Rossouw JE, Sarto G, Stefanick ML, Van Horn L, Wactawski-Wende J, Wallace R, Wassertheil-Smoller S; Women's Health Initiative Steering Committee. (2004). Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *Journal of the American Medical Association*, 291(14), 1701-12.

(2) LaCroix AZ, Chlebowski RT, Manson JE, et al. (2011). Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy. *Journal of the American Medical Association*, 305(13), 1305-1314.

### **The Heart Truth Professional Education Campaign Website**

[www.womenshealth.gov/heart-truth](http://www.womenshealth.gov/heart-truth)

### **Million Hearts Campaign Website**

[millionhearts.hhs.gov](http://millionhearts.hhs.gov)

**“Get involved and share your commitment to help prevent 1 million heart attacks and strokes in the next five years.”**