

# Cardiovascular CORNER

## Post-Intervention Findings from the Women's Health Initiative Estrogen Plus Progestin Trial: Implications for Clinical Practice

JoAnn E. Manson, MD, DrPH  
Shari S. Bassuk, ScD

What happens to a woman's health risks after she stops taking menopausal hormone therapy (HT)? Until recently, there was limited scientific evidence to address this question. New findings from the Women's Health Initiative (WHI) estrogen-plus-progestin trial—which randomized 16,608 postmenopausal women ages 50 to 79 years (average, 63 years) to a daily combination of conjugated equine estrogens (CEE; 0.625 mg) plus medroxyprogesterone acetate (MPA; 2.5 mg) or to placebo for a mean of 5.6 years and then followed these women for a mean of 2.4 years after treatment ended—now help to provide an answer.<sup>1</sup> As shown in the Table (p. 28), the good news is that the elevated risks for coronary heart disease (CHD), stroke and venous thromboembolism associated with the active use of CEE plus MPA declined substantially or disappeared after discontinuation of therapy. The bad news is that many of the benefits of therapy, including amelioration of hot flashes<sup>2</sup> and protection against osteoporotic fractures and colorectal cancer, also dissipated. Moreover, a slightly elevated risk for breast cancer persisted, and a suggestion of higher risks for lung cancer, total cancer and total mortality emerged.

What are the implications of the post-intervention findings for clinical decision-

making? These findings reinforce current guidelines for hormone use, which state that HT is appropriate primarily for short-term relief of moderate to severe vasomotor symptoms of menopause (hot flashes or night sweats) but should not be used for chronic disease prevention.<sup>3-7</sup> HT is best used for less than 5 years, unless a woman has experienced premature menopause. (For vaginal dryness, consider topical estrogen, which has minimal systemic absorption.) Although fracture prevention has also historically been considered an important benefit of HT, the reality is that a woman would need to take hormones for many, many years to maintain bone protection when fracture risk is greatest. (The average age of women who break a hip is close to 80 years.<sup>8</sup>) Because the potential harms of long-term use of estrogen plus progestin—including rising risks for breast and lung cancer, as well as stroke—outweigh the bone benefits, most experts no longer recommend HT as a first line of defense against osteoporosis.

It should be noted that the post-intervention findings of the WHI are for the entire cohort and are thus heavily weighted by the data from older participants. Post-intervention results that are stratified by age or time since menopause onset are not yet available. However, continued follow-up of the cohort will enable the accumulation of sufficient endpoints for meaningful analyses in younger participants (women ages 50-59 at trial entry). Such analyses are expected to refine clinical decision-making further, as accumulating research suggests that timing of initiation is relevant to the benefit-to-risk ratio and safety profile of HT.<sup>9</sup> The risks for CHD, stroke and venous thromboembolism related to active hormone use are low in recently menopausal women (those less than 10 years past their final menstrual periods) who are in good cardiovascular health. On the other hand, these risks are higher in older women and in those with adverse cardiovascular profiles. For example, among women who entered the WHI trial with a better cholesterol profile, assignment to HT led to a 40% lower risk for incident CHD, whereas among those who entered with an adverse cholesterol profile, assignment to HT resulted in a 73% higher risk.<sup>10</sup> Indeed, the overall balance of benefits and risks of HT appears quite favorable for younger women

**Table.** Clinical Outcomes: Estrogen plus Progestin versus Placebo in the Women's Health Initiative Estrogen-plus-Progestin Trial and Post-Intervention Observational Follow-Up\*

Outcome	Clinical Trial Phase (mean length, 5.6 years)	Post-Intervention Follow-Up Phase (mean length, 2.4 years)	Overall Combined Phases (mean length, 8.0 years)
	RR† (95% CI†)	RR (95% CI)	RR (95% CI)
Coronary heart disease	1.22 (0.99–1.51)	0.95 (0.73–1.26)	1.11 (0.94–1.31)
Stroke	1.34 (1.05–1.71)	1.16 (0.83–1.61)	1.28 (1.05–1.56)
Venous thromboembolism	1.98 (1.52–2.59)	0.95 (0.63–1.44)	1.62 (1.30–2.03)
All cardiovascular disease events	1.13 (1.02–1.25)	1.04 (0.89–1.21)	1.10 (1.01–1.20)
Breast cancer	1.26 (1.02–1.55)	1.27 (0.91–1.78)	1.27 (1.06–1.51)
Colorectal cancer	0.62 (0.43–0.89)	1.08 (0.66–1.77)	0.75 (0.57–1.00)
All cancers	1.03 (0.92–1.15)	1.24 (1.04–1.48)	1.09 (0.99–1.20)
Hip fracture	0.67 (0.47–0.95)	0.92 (0.64–1.34)	0.78 (0.60–1.00)
Vertebral fracture	0.68 (0.48–0.96)	0.96 (0.64–1.44)	0.78 (0.60–1.01)
All fractures	0.76 (0.69–0.83)	0.91 (0.78–1.06)	0.80 (0.73–0.86)
All-cause mortality <sup>§</sup>	0.97 (0.81–1.16)	1.15 (0.95–1.39)	1.04 (0.91–1.18)
Global index <sup>¶</sup>	1.12 (1.02–1.24)	1.11 (0.97–1.27)	1.12 (1.03–1.21)

\* Adapted from Heiss G, Wallace R, Anderson GL, et al. Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. *JAMA* 2008;299:1036-45.

† RR = relative risk.

‡ CI = confidence interval.

§ The apparent excess mortality during the post-intervention phase reflects an increase in deaths attributed to cancers that were not prespecified trial outcomes, particularly lung cancer. Data from 15,730 women (8,052 in the estrogen-plus-progestin group and 7,678 in the placebo group) were included in post-intervention analyses. During post-intervention follow-up, there were 33 lung cancer deaths and 101 total cancer deaths in the estrogen-plus-progestin group but only 15 lung cancer deaths and 69 total cancer deaths in the placebo group.

¶ The global index is a composite outcome representing the first event for each participant from among the following: coronary heart disease, stroke, pulmonary embolism, breast cancer, colorectal cancer, endometrial cancer, hip fracture and death.

with an indication for treatment (ie, significant vasomotor symptoms). Assignment to HT was associated with a 30% reduction in mortality among WHI participants between the ages of 50 and 59 but not among their older counterparts.<sup>11</sup> These findings do not imply that healthy, recently menopausal women should be prescribed HT for the prevention of CHD or other diseases, but rather that clinicians need not be unduly concerned about the health risks of short-term use in such women.

The WHI studied only one method of administration, dose and formulation of estrogen and progestogen, so its results are not necessarily generalizable to other hormone preparations. Indeed, there is convincing evidence from other studies that transdermal estrogen products are less likely than oral agents to precipitate venous thromboembolism<sup>12</sup> or other adverse events (eg, gallstone

formation).<sup>13</sup> Recent research also suggests that lower doses of estrogen (1/3 to 1/2 of conventional doses) may be less likely to increase the risk for stroke,<sup>14</sup> although more studies are needed to determine whether lower doses also are less likely to increase breast cancer risk. It remains unknown whether “bioidentical” estrogens and progesterone—ie, hormones with the same molecular structure as those produced by the human body—are safer than the conventional hormones tested in the WHI;<sup>15</sup> as yet, no results from large-scale trials can confirm or refute this hypothesis.

In summary, the post-intervention findings of the WHI estrogen-plus-progestin trial provide evidence against the long-term use of CEE plus MPA for chronic disease prevention, particularly in older women who are many years past the menopausal transition. However, HT remains

(continued on page 36)

single patient with severe symptoms. Go to [www.menopause.org/empres.aspx](http://www.menopause.org/empres.aspx).

**Pay Tribute to Dr. Utian and his Work**

**D**r. Wulf Utian, NAMS Founder and Executive Director, retires from NAMS at year's end. Pay tribute to his work by attending one or more of the three tribute events: the September 30 session (4:40-6:15 PM) at the San Diego Annual Meeting and two October 24 Cleveland events; a morning Consumer Education Event and a Gala "Tribute to Wulf Utian" that evening. For more, go to [www.menopause.org/WUtribute.aspx](http://www.menopause.org/WUtribute.aspx).



**ADVERTISERS' INDEX**

**Bayer HealthCare Pharmaceuticals Inc.**

Angeliq.....17-19

**Eli Lilly & Co.**

Evista .....6-10

**TO  
COME**

**North American Menopause Society, The**.....4

**Novo Nordisk Pharmaceuticals, Inc.**

Vagifem.....IBC, OBC

**Wyeth Pharmaceuticals Inc.**

Premarin.....IFC, 1-2

**Cardiovascular Corner**

*(continued from page 28)*

management of menopausal symptoms in younger women at low absolute risk for adverse cardiovascular outcomes.<sup>16</sup> ■

**JoAnn E. Manson, MD, DrPH, is Professor of Medicine and the Elizabeth F. Brigham Professor of Women's Health, Harvard Medical School; and Chief, Division of Preventive Medicine, Brigham and Women's Hospital. Shari S. Bassuk, ScD, is an Epidemiologist, Division of Preventive Medicine, Brigham and Women's Hospital, Boston, MA.**

*Dr. Manson and Dr. Bassuk report no potential conflicts related to the content of this article.*

**References**

1. Heiss G, Wallace R, Anderson GL, et al. Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. *JAMA* 2008;299:1036-45.
2. Ockene JK, Barad DH, Cochrane BB, et al. Symptom experience after discontinuing use of estrogen plus progestin. *JAMA* 2005;294:183-93.
3. US Preventive Services Task Force. Hormone therapy for the prevention of chronic conditions in postmenopausal women: recommendations from the U.S. Preventive Services Task Force. *Ann Intern Med* 2005; 142:855-60.
4. American College of Obstetricians and Gynecologists. ACOG committee opinion No. 420, November 2008: hormone therapy and heart disease. *Obstet Gynecol* 2008;112:1189-92.
5. Wathen CN, Feig DS, Feightner JW, et al. Hormone replacement ther-

apy for the primary prevention of chronic diseases: recommendation statement from the Canadian Task Force on Preventive Health Care. *CMAJ* 2004;170:1535-37.

6. Utian WH, Archer DF, Bachmann GA, et al. Estrogen and progestogen use in postmenopausal women: July 2008 position statement of The North American Menopause Society. *Menopause* 2008;15:584-602.

7. Practice Committee of the American Society for Reproductive Medicine. Estrogen and progestogen therapy in postmenopausal women. *Fertil Steril* 2008;90:S88-S102.

8. Samelson EJ, Zhang Y, Kiel DP, et al. Effect of birth cohort on risk of hip fracture: age-specific incidence rates in the Framingham Study. *Am J Public Health* 2002;92:858-62.

9. Manson JE, Bassuk SS. Invited commentary. Hormone therapy and risk of coronary heart disease: why renew the focus on the early years of menopause? *Am J Epidemiol* 2007;166:511-17.

10. Bray PF, Larson JC, Lacroix AZ, et al. Usefulness of baseline lipids and C-reactive protein in women receiving menopausal hormone therapy as predictors of treatment-related coronary events. *Am J Cardiol* 2008; 101:1599-1605.

11. Rossouw JE, Prentice RL, Manson JE, et al. Effects of postmenopausal hormone therapy on cardiovascular disease by age and years since menopause. *JAMA* 2007;297:1465-77.

12. Canonico M, Oger E, Plu-Bureau G, et al. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. *Circulation* 2007;115:840-5.

13. Liu B, Beral V, Balkwill A, et al. Gallbladder disease and use of transdermal versus oral hormone replacement therapy in postmenopausal women: prospective cohort study. *BMJ* 2008;337:a386.

14. Grodstein F, Manson JE, Stampfer MJ, Rexrode K. Postmenopausal hormone therapy and stroke: role of time since menopause and age at initiation of hormone therapy. *Arch Intern Med* 2008;168:861-6.

15. Endocrine Society. Bioidentical hormones: position statement, October 2006. Available at: [http://www.endo-society.org/advocacy/policy/upload/BH\\_Position\\_Statement\\_final\\_10\\_25\\_06\\_w\\_Header.pdf](http://www.endo-society.org/advocacy/policy/upload/BH_Position_Statement_final_10_25_06_w_Header.pdf) (Accessed July 22, 2009.)

16. Manson JE, Bassuk SS. Hot flashes, hormones & your health. New York: McGraw-Hill, 2007.