



EDITORIALS

Reassurance for many healthy women considering HRT

But individual assessment of risk benefit balance remains essential

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Many women remain fearful of using menopause hormone therapy because of concerns about the risk of heart attack, stroke, and breast cancer. These concerns were prompted by the two Women's Health Initiative (WHI) clinical trials that were stopped early in 2002 and 2004. In the first trial women who took conjugated equine oestrogen and medroxyprogesterone had an increased incidence of heart attacks, strokes, and breast cancer compared with those taking placebo.¹ The second trial in women with a hysterectomy found an increased incidence of stroke and venous thromboembolism in those treated with conjugated equine oestrogen compared with the placebo group but no increased risk of breast cancer.² Neither trial reported an increase in total mortality among actively treated women compared with placebo (hazard ratio 0.98 (95% confidence interval 0.82 to 1.18) for the oestrogen plus progestin trial and 1.04 (0.88 to 1.22) for the oestrogen trial).^{1,2}

The results sent shock waves through affected patient and healthcare communities. Prescriptions for hormone therapy, once the most commonly prescribed medication, plummeted more than 70% over the following years in the US.³

Now Manson and colleagues have reported all cause and cause specific mortality among WHI participants after 18 years of follow-up, comprising five to seven years of treatment during the two trials plus an additional 12 years of follow-up after the trials ended.⁴ Hormone therapy was not associated with an increase in all cause mortality (hazard ratio 0.99; 95% CI 0.94 to 1.03), cardiovascular mortality (1.00; 0.92 to 1.08), total cancer mortality (1.03; 0.95 to 1.12), or other mortality (0.95; 0.88 to 1.02) compared with placebo in the two trials.

The WHI trials were primary prevention trials in mostly white women (80%) to evaluate whether hormone therapy prevented cardiovascular and other chronic diseases. By design, they did not include women with severe vasomotor symptoms because this would reduce adherence, and only 12.5% of participants were aged 50 to 54 years of age—around the time of menopause.⁵ The average age of women starting hormone therapy was 63 years.

Several WHI analyses have evaluated the timing of hormone therapy, finding a trend to lower risk of cardiovascular disease

associated with treatment at 50-59 years, but results have been limited by low power.^{6,7} In Manson and colleagues' new, age group analyses, women treated at age 50-59 had a greater reduction in all cause mortality than women treated at 70-79 years both during treatment (hazard ratio 0.61; 0.43 to 0.87) and after 18 years' follow-up (0.87; 0.76 to 1.00). These findings are important because they align with current guidelines that support the use of hormone therapy by healthy and recently menopausal women for symptom control.¹¹

Most notable in the new analyses are differences in mortality from breast cancer between formulations. During the original trials, breast cancer risk was increased in the oestrogen plus progestin arm (1.25; 1.07 to 1.46)⁸ but not in the oestrogen only arm (0.77; 0.57 to 1.01).⁹ Ten years after the trials ended, women who took only oestrogen had a significantly lower risk of breast cancer than the placebo group (0.77; 0.62 to 0.95).¹⁰ This difference can now be extended to breast cancer mortality. After 18 years of follow-up, women originally randomised to oestrogen alone had significantly lower breast cancer mortality than women randomised to placebo (0.55; 0.33 to 0.92).⁴ Women randomised to oestrogen plus progestin, however, had a moderate but non-significant increase in risk (1.44; 0.97 to 2.15). More research is required to understand these differences between formulations, and to identify the role of medroxyprogesterone in risk of breast cancer.

How should results affect practice?

What are the implications for symptomatic women in midlife who are considering hormone therapy? The new findings are relevant to a short duration of use, five to seven years, and should reassure healthy women considering hormone therapy for bothersome menopausal symptoms such as hot flashes. But they should not replace current guidelines that continue to stress the importance of individualised risk assessment.¹¹ Use of hormone therapy for five years with oestrogen plus medroxyprogesterone increases women's risk of breast cancer, while oestrogen alone does not have the same risk and may now be associated with reduced mortality from breast cancer in the longer term. It remains the case that hormone therapy is not intended to prevent cardiovascular disease or death.¹¹

We continue to learn a tremendous amount from the WHI, which still helps to shape guidelines and treatment of menopausal symptoms. The unexpected finding that hormone therapy did not prevent cardiovascular disease allowed for much criticism of the specific dose, formulation, and route of delivery used in that trial and prompted evaluations of different doses and modes of delivery.¹²

While the new mortality analysis is not the final word from WHI, it has provided important information for women and their doctors. Future research should now focus on determining if the results for all cause and cause specific mortality hold true for different doses, formulations, and routes of delivery.

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- 1 Rossouw JE, Anderson GL, Prentice RL, et al. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;359:321-33. doi:10.1001/jama.288.3.321 pmid:12117397.
- 2 Anderson GL, Limacher M, Assaf AR, et al. Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004;359:1701-12. doi:10.1001/jama.291.14.1701 pmid:15082697.

- 3 Ettinger B, Wang SM, Leslie RS, et al. Evolution of postmenopausal hormone therapy between 2002 and 2009. *Menopause* 2012;359:610-5. doi:10.1097/gme.0b013e31823a3e5d pmid:22207318.
- 4 Manson JE, Aragaki AK, Rossouw JE, et al. WHI Investigators. Menopausal hormone therapy and long-term all-cause and cause-specific mortality: The women's health initiative randomized trials. *JAMA* 2017;359:927-38. doi:10.1001/jama.2017.11217 pmid:28898378.
- 5 Hays J, Hunt JR, Hubbell FA, et al. The Women's Health Initiative recruitment methods and results. *Ann Epidemiol* 2003;359(Suppl):S18-77. doi:10.1016/S1047-2797(03)00042-5 pmid:14575939.
- 6 Manson JE, Hsia J, Johnson KC, et al. Women's Health Initiative Investigators. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med* 2003;359:523-34. doi:10.1056/NEJMoa030808 pmid:12904517.
- 7 Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007;359:1465-77. doi:10.1001/jama.297.13.1465 pmid:17405972.
- 8 Chlebowski RT, Hendrix SL, Langer RD, et al. WHI Investigators. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative randomized trial. *JAMA* 2003;359:3243-53. doi:10.1001/jama.289.24.3243 pmid:12824205.
- 9 Stefanick ML, Anderson GL, Margolis KL, et al. WHI Investigators. Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. *JAMA* 2006;359:1647-57. doi:10.1001/jama.295.14.1647 pmid:16609086.
- 10 LaCroix AZ, Chlebowski RT, Manson JE, et al. WHI Investigators. Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: a randomized controlled trial. *JAMA* 2011;359:1305-14. doi:10.1001/jama.2011.382 pmid:21467283.
- 11 The 2017 hormone therapy position statement of the North American Menopause Society. *Menopause* 2017;359:728-53. doi:10.1097/GME.0000000000000921 pmid:28650869.
- 12 Shufelt CL, Merz CNB, Prentice RL, et al. Hormone therapy dose, formulation, route of delivery, and risk of cardiovascular events in women: findings from the Women's Health Initiative observational study. *Menopause* 2014;359:260-6. doi:10.1097/GME.0b013e31829a64f9 pmid:24045672.

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