# Hormone therapy for younger women may not increase CHD risk during 5 to 7 years of follow-up, but stroke risk was increased independent of age

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

**Clinical impact ratings:** Cardiology ★★★★★☆☆

### QUESTION

In postmenopausal women, does the effect of hormone therapy (HT) (estrogen with or without progestin) on cardiovascular disease risk vary by age or years since menopause?

### METHODS

**Design:** 2 randomized placebo-controlled trials (Women's Health Initiative [WHI] trials).
**Allocation:** {Concealed}†.*
**Blinding:** Blinded {clinicians, participants, data collectors, outcome assessors, and monitoring committee}†.*
**Follow-up period:** Mean 5.6‡ and 7.1§ years.
**Setting:** 40 U.S. clinical centers.
**Participants:** 27 347 postmenopausal women 50 to 79 years of age.
**Intervention:** Conjugated equine estrogen (CEE), 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d ($n$ = 8506), or placebo ($n$ = 8102) in women with an intact uterus; CEE ($n$ = 5310) or placebo ($n$ = 5429) in women with a hysterectomy.
**Outcomes:** Coronary heart disease (CHD) (myocardial infarction or CHD death), stroke, total mortality, and a global index.
**Participant follow-up:** 94%‡‖ (intention-to-treat analysis).

### MAIN RESULTS

Overall, HT and placebo did not differ for CHD, total mortality, and the global index; risk for stroke was higher in the HT group (hazard ratio 1.3, CI 1.1 to 1.6). The effect of HT did not vary by age for any outcome (Table). Risk for CHD with HT use increased with time since menopause (nonprespecified subgroup) and was elevated only in women in whom ≥ 20 years had passed since menopause (Table). The effect of HT on other outcomes did not vary by years since menopause (Table).

### CONCLUSIONS

In postmenopausal women, the effect of hormone therapy on cardiovascular disease risk did not vary by age. Effects on CHD changed from possibly protective to harmful with increasing time since menopause. Stroke risk was elevated regardless of years since menopause.

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*For correspondence: Dr. J.E. Rossouw, National Heart, Lung, and Blood Institute, Bethesda, MD, USA. E-mail: rossouwj@nih.gov.* ■

*See Glossary.
†**Rossouw JE, Anderson GL, Prentice RL, et al.** JAMA. 2002;288:321-33.
‡**Manson JE, Hsia J, Johnson KC, et al.** N Engl J Med. 2003;349:523-34.
§Information provided by author.
‖**Anderson GL, Limacher M, Assaf AR, et al.** JAMA. 2004;291:1701-12.

**Hazard ratios (95% CI) for hormone therapy vs placebo at mean 6 to 7 years**

| Outcomes | Age groups | | | *P* value for trend |
|---|---|---|---|---|
| | 50 to 59 y | 60 to 69 y | 70 to 79 y | |
| Coronary heart disease | 0.9 (0.7 to 1.3) | 1.0 (0.8 to 1.2) | 1.3 (1.0 to 1.6) | 0.16 |
| Stroke | 1.1 (0.7 to 1.8) | 1.5 (1.2 to 1.9) | 1.2 (0.9 to 1.6) | 0.97 |
| Total mortality | 0.7 (0.5 to 0.96) | 1.1 (0.9 to 1.3) | 1.1 (0.9 to 1.4) | 0.06 |
| Global index¶ | 1.0 (0.8 to 1.1) | 1.1 (1.0-1.2) | 1.1 (1.02 to 1.3) | 0.09 |
| | Years since menopause | | | |
| | <10 y | 10 to 19 y | ≥ 20 y | |
| CHD | 0.8 (0.5 to 1.2) | 1.1 (0.8 to 1.5) | 1.3 (1.03 to 1.6) | 0.02 |
| Stroke | 1.8 (1.05 to 3.0) | 1.2 (0.9 to 1.7) | 1.3 (1.0 to 1.6) | 0.36 |
| Total mortality | 0.8 (0.5 to 1.1) | 1.0 (0.8 to 1.2) | 1.1 (1.0 to 1.4) | 0.51 |
| Global index¶ | 1.1 (0.9 to 1.3) | 1.1 (1.0 to 1.3) | 1.1 (1.0 to 1.2) | 0.82 |

¶Coronary heart disease, stroke, pulmonary embolism, breast cancer, colorectal cancer, endometrial cancer, hip fracture, or death from other causes.

## COMMENTARY

5 years after shocking headlines following the 2002 WHI publication (1) caused a pervasive fear of HT in the collective psyche of the medical and lay communities, the WHI investigators have done a further analysis that may allay anxieties about the use of HT for distressing perimenopausal vasomotor symptoms.

The WHI trials clearly showed that no justification exists for initiation of HT in older asymptomatic women as a preventive health strategy. In this population, risks for CHD, stroke, venous thromboembolism, and breast cancer outweigh benefits for hip fracture and colorectal cancer. Less clear is the balance of risks and benefits in symptomatic perimenopausal women and in rare cases when HT is being considered for older symptomatic women. After pooling data from the 2 WHI trials, including 8832 women aged 50 to 59 years, Rossouw and colleagues concluded that, in this age group, HT did not increase risk for any outcome and total mortality was reduced, translating into 1 fewer death per 1000 women per year. In women with no history of cardiovascular disease, the hazard ratio for CHD by decade after menopause went from a low of 0.78 for < 10 years, to 1.10 for 10 to 19 years, to 1.35 for ≥ 20 years ($P$ for trend 0.02). Overall, HT users in the WHI had increased risk for stroke (estimated at 9/10 000 women-years of use), and this risk did not differ on the basis of years since menopause. Among women 50 to 59 years of age, no statistically significant increase in stroke was found.

This and other recent publications from the WHI suggest that women < 60 years of age who use HT for the first time in the menopausal transition for ≤ 5 years are *not* at increased risk for breast cancer, heart attack, or stroke. A survey conducted before the original WHI publication found that only 3% to 10% of women remained on HT for ≥ 5 years (2). It is time that the medical community returned, with confidence, to short-term use of HT for improved quality of life in perimenopausal women with vasomotor symptoms. Older symptomatic women should be screened carefully for cardiovascular disease risk factors before consideration of HT on a case-by-case basis.

*Robert L. Reid, MD*
*Queen's University*
*Kingston, Ontario, Canada*

***References***

1. **Rossouw JE, Anderson GL, Prentice RL, et al.** JAMA. 2002;288:321-33.
2. **Brett KM, Reuben CA.** Obstet Gynecol. 2003;102:1240-9.