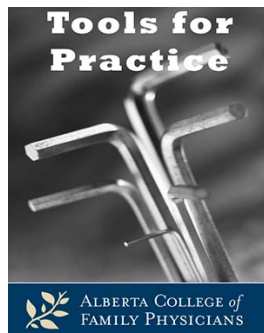


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**Evidence Updated: New Cochrane review**  
**Bottom Line: No change**  
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## **Hormone Therapy: Does Timing Make a Difference?**

**Clinical Question: Is there evidence that starting combination oral hormone therapy (HT) closer to menopause result in reduced risk of harm or even possible benefit?**

**Bottom Line: Evidence supporting the timing hypothesis of HT is not convincing. There is no consistent evidence of benefit with HT beyond symptomatic relief. Smaller but real risks are likely present even in those close to menopause.**

### **Evidence:**

- Randomized Controlled Trial (RCT):<sup>1</sup> 1006 women (mean age 52) randomized to HT or nothing x ten years.
  - Statistically significant reduction in composite outcome (death, hospitalization for heart failure, and myocardial infarction) in HT users.
    - Hazard Ratio (HR) 0.48 (0.26-0.87).
    - Limitations: Secondary analysis of an osteoporosis study with this outcome defined post-hoc; open-label design; included estrogen-only group; low event rate.
- Women's Health Initiative (WHI) subgroup analysis:<sup>2</sup>
  - Combination HT within ten years of menopause had non-statistically significant:
    - Reduced coronary heart disease (CHD): HR 0.88 (0.54-1.43).
    - Increased stroke: HR 1.58 (0.81-3.05).
    - Overall more harms than benefits (global index): HR 1.09 (0.87-1.37).
  - Limitations: Subgroup analysis; >130 statistical tests, only two statistically significant (six-seven expected by chance alone).
- Second subgroup analysis of WHI<sup>3</sup> (>300 comparisons) reported increased breast cancer if HT started <five years after menopause versus >five years (p=0.03).
- Cochrane review of 19 RCTs (40,410 patients):<sup>4</sup>
  - Subgroup analysis showed decreased mortality and CHD in HT users <ten years post-menopause, but not >ten years.

- No evidence that risk of stroke or venous thromboembolism (VTE) lower if HT started <ten years of menopause
- Limitations: Risk reductions driven by above RCT<sup>1</sup> and estrogen-only group of WHI (hysterectomy patients), which is not likely generalizable to patients without hysterectomy
- Older systematic review of 30 RCTs found similar effects on mortality for age <60 versus >60.5

**Context:**

- HT is effective for vasomotor and some urogenital symptoms in post-menopausal women.<sup>6</sup>
- Another Cochrane review<sup>7</sup> of 23 RCTs (42,830 patients, mean >60 years) reported small statistically significant increased risk for cardiovascular events, VTE, stroke, and breast cancer with HT.

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