

Long-Term Hormone Therapy— A Cochrane Summary

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Clinicians who prescribe hormone therapy need to consider the long-term effects on a number of health outcomes in their patients.

Most women experience menopause (the last menstrual period) between ages 40 and 58. Apart from cessation of periods, the most common symptoms are hot flushes, night sweats, vaginal dryness, and sleep disturbance.¹ Hormone therapy (HT) is the most effective treatment for symptoms. A Cochrane review of randomized trials showed a 75% reduction in flushes (18 fewer per week) with hormones compared with a 50% reduction with placebo.² This article summarizes the 2008 updated Cochrane review on the effects of long-term HT for perimenopausal and postmenopausal women on mortality, cardiovascular outcomes, cancer, gallbladder disease, cognition, fractures, and quality of life.³

METHODS

The database search followed the usual Cochrane methodology. Assessed were randomized double-blind trials of HT, delivered by either oral, transdermal, subcutaneous, or transnasal route, versus placebo, of at least 1-year duration. Various types and regimens of hormones were used; the estrogens in the studies included estradiol, estradiol valerate, and conjugated equine estrogens. Nineteen trials involving 41,904 women were included; the largest of these was the Women's Health Initiative (WHI)

study. The mean or median age in each study ranged from 48 to 72. Nine of the studies enrolled relatively healthy women, but the others included women with established medical conditions or a history of cancer. The review was generally unable to combine results from individual trials, either because they used different types of hormones or had different trial populations. All of the statistically significant findings came from the 2 biggest trials: the 1998 WHI study and the 1998 Heart and Estrogen/Progestin Replacement Study (HERS).

OUTCOMES

Death

The Cochrane review did not find any statistically significant difference between HT and placebo use for death from any cause, including coronary heart disease, stroke, or any cancer. When the WHI study was halted in 2002, after a mean of 5.6 years, women were asked to stop the study medication, and one year later only 4% of women were using hormones not related to the study.⁴

Since this Cochrane review was published, there has been ongoing postintervention surveillance in the WHI study. After 2.4 years of additional follow-up, a 15% greater mortality was found for women who had been assigned to combined HT compared to placebo. This increase in mortality was due to a higher number of deaths from non-small cell lung cancer (hazard ratio [HR], 1.87; confidence interval [CI], 1.22-2.88), thought to be due to the stimulation of growth by combined HT on already established cancers.⁵ There was no increase found for the use of estrogen alone.⁶ At a further total mean follow-up of 11 years, deaths from breast cancer for those women who had been assigned combined HT were now also increased compared to those assigned placebo (HR, 1.96; CI, 1.00-4.04).⁷

FOCUS POINT

Pooled data from 2 studies showed an increased risk of stroke (ischemic, rather than hemorrhagic) at 3 years with combined HT over placebo.

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Myocardial Infarction

Pooled data from 3 studies showed an increased risk for myocardial infarction at 1 year (relative risk [RR], 1.89; CI, 1.15-3.10) and at 3 years (RR, 1.45; CI, 1.07-1.98) for combined HT (estrogen plus progestogen) use. No other trials found any difference, and at 5 years of use, the WHI study found no difference between groups. There was no increase with estrogen only.

Stroke

Pooled data from 2 studies showed an increased risk of stroke (ischemic, rather than hemorrhagic) at 3 years with combined HT over placebo (RR, 1.46; CI, 1.02-2.09). There was no increase in risk for transient ischemic attack. At 7 years' follow-up, the estrogen-only arm of the WHI also showed an increased risk of ischemic stroke (RR, 1.35; CI, 1.08-1.70), which became apparent after 4 years of use.

Venous Thromboembolism

An increased risk for venous thromboembolism (VTE) with combined HT was found in pooled data from 2 studies (RR, 4.28 at 1 year; CI, 2.49-7.34). Risk was highest in the first 2 years of use, with a statistically significant time trend for diminishing risk. WHI data showed an increased risk for estrogen alone over placebo (RR, 2.22 at 2 years; CI, 1.12-4.39). An increased risk for VTE with hormone use was also found for women with previous cardiovascular disease, with factor V Leiden mutation, and with previous VTE, compared to women without these conditions.

Breast Cancer

The estrogen-only arm of WHI found a decrease in breast cancer with hormone use. This decrease became statistically significant when pooled with the data from the Women's International Study of Long Duration Oestrogen After Menopause study.⁸ In WHI, for women using estrogen only compared to placebo, there was an increase in repeat mammograms for "recommended short-interval follow-ups," and a review of breast biopsies reported an increased incidence of benign proliferative disease.⁹

An increase in breast cancer diagnosis was found in the WHI study after combined HT use for 5 years or longer (RR, 1.26; CI, 1.02-

1.56), and the breast cancers were at a more advanced stage than those in the placebo arm. For combined HT, breast cancer rates were initially lower, the suggestion being that combined HT may stimulate breast cancer growth but delay diagnosis, possibly by hindering mammographic detection.

Endometrial Cancer

No study showed an increase in risk for endometrial cancer with combined HT. Endometrial cancer is a well-documented adverse effect of unopposed estrogen, and in those studies where estrogen only was used, in women with a uterus, close monitoring showed that they were more likely to develop atypical endometrial hyperplasia.

This review also included information regarding the effect of estrogen in women with previous endometrial cancer. The early discontinuation of unopposed estrogen in women with previous stage I or II endometrial cancer meant that this trial was underpowered to determine risk. However, the recurrence rates were low in both arms of the study: 1.9% for placebo and 2.3% for estrogen use over a median follow-up of 3 years.¹⁰

Ovarian Cancer

There was a trend towards an increase in ovarian cancer in the WHI combined arm. A systematic review, on mainly observational studies, suggests that both estrogen only and combined HT may be associated with an increased risk for ovarian cancer.¹¹

Cognitive Function

Results for cognitive outcomes come from the WHI studies. In the WHI Memory Study, neither combined HT nor estrogen only conferred any benefit in global cognitive function for women older than 65.

The short duration WHI Study of Cognitive Aging found, for all participants, a rise in mean scores used to measure global cognitive function, attributed to the learning effect of repeated administration of cognitive tests. However, a marked decrease in these scores occurred more frequently in the HT treatment group, reaching statistical significance for combined HT. There was a greater adverse effect in those women with the lowest baseline scores.

One small study included women with previous Alzheimer disease and found no

FOCUSPOINT

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TABLE 1. WHI Study Hazard Ratios for Various Outcomes for Women Ages 50-79¹

Outcome	Hazard Ratio (95% CI) for Estrogen and Progestogen	Hazard Ratio (95% CI) for Estrogen Only
Stroke (mainly ischemic)	1.41 (1.07-1.85)	1.39 (1.10-1.77)
Breast cancer	1.24 (1.01-1.54)	0.77 (0.59-1.01)
Deep venous thrombosis	1.95 (1.43-2.67)	1.47 (1.06-2.06)
Coronary heart disease	1.24 (1.00-1.54)	0.95 (0.70-1.16)
Dementia (women ages >65)	2.05 (1.21-3.48)	1.49 (0.83-2.66)
Gallbladder disease and procedure	1.59 (1.20-1.97)	1.67 (1.35-2.06)
Hip fracture	0.66 (0.45-0.98)	0.61 (0.41-0.91)
Total fracture	0.76 (0.69-0.85)	0.70 (0.63-0.79)
Colorectal cancer	0.63 (0.43-0.92)	1.08 (0.75-1.55)
Total mortality	0.98 (0.82-1.18)	1.04 (0.88-1.22)

Abbreviations: CI, confidence interval; WHI, Women's Health Initiative.

difference in status between estrogen use and placebo.¹² These findings are in agreement with a recent Cochrane review that found no prevention in cognitive decline in older postmenopausal women when HT was given as short-term or longer-term (up to 5 years) therapy.¹³

Gallbladder Disease

Gallbladder disease was increased for both estrogen only and combined HT in the WHI study. For one extra occurrence of gallbladder disease, 323 women would need to take estrogen only and 500 women would need to take combined HT for one year.

TABLE 2. Additional Cases/1,000 HT Users, Ages 50-59, Over a 5-Year Period¹⁸

Outcome	Combined (CI)	Estrogen Only (CI)
Breast cancer	6 (5-7)	2 (1-4)
Venous thromboembolism	7 (5-10)	2 (0-4)
Stroke	1 (1-2)	1 (1-2)

Abbreviations: CI, confidence interval; HT, hormone therapy.

Quality of Life

There was no clinically meaningful quality-of-life benefit found in the WHI, though these findings may not be applicable to women taking HT specifically for severe hot flashes that affect their quality of life.

Hip Fracture

WHI found a decreased risk of hip fracture for both estrogen alone (RR, 0.64; CI, 0.45-0.93) and combined HT (RR, 0.68; CI, 0.48-0.97). This reduction became statistically significant only after 5 years of use. This decreased fracture risk was not found in the HERS study with combined HT use. WHI also showed a decreased risk for vertebral fracture in both arms of the study, again after 5 years of use. In WHI, risks with HT still outweighed the benefit for fracture, even for those women at highest risk of fracture.¹⁴

Colorectal Cancer

The combined HT arm of WHI also found a reduced risk of colorectal cancer compared to placebo, after 5 years of use, which was offset by the finding that the cancers tended to be more advanced, with more likelihood of lymphatic or metastatic involvement.

CONCLUSION

Follow-up studies from the WHI show that the increased risk for cardiovascular disease, which includes stroke and VTE, had disappeared 3 years after HT was stopped.¹⁵ Although the increased risk for breast cancer declined soon after discontinuation of hormones, the follow-up of a total mean of 11 years still found an increase in breast cancer incidence for those women who had been assigned to combined HT (HR, 1.25; CI, 1.07-1.46), with the cancers more likely to be node-positive.⁷

Women in the WHI were older, and there has been the suggestion that if hormones are started earlier, a beneficial effect, a “window of opportunity,” would be found.¹⁶ A recent publication from WHI looked at the women who had been using hormones in the past before entry into the study. Women who had started hormones close to menopause had no benefit for coronary disease and had an adverse risk for stroke and VTE. Regarding breast cancer, those starting closer to menopause appeared to have a greater increase in risk compared with those starting later.¹⁷

In summary, this review found that both estrogen alone and combined HT increased the risk for gallbladder disease, stroke, and thromboembolism (Table 1). In addition, combined HT increased the risk for heart attack after 1 year's use and dementia in women older than 65. HT offered the benefit of reduction in fracture risk, but only after 5 years of use, when the highest risks for cardiovascular events were determined. The findings of the WHI study dominated this review. These women had a mean age of 63, and the study excluded women with severe flushes. For healthy younger women in their 50s, with debilitating flushes, the absolute risks of HT use are low (Table 2). For most women, flushes are self-limiting, and advice is now generally to use the lowest dose of hormone therapy for the shortest period for relief of symptoms.¹

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FOCUSPOINT
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