

WHI data confirm short-term heart disease risks of combination menopausal hormone therapy

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New analyses from the Women's Health Initiative (WHI) confirm that combination hormone therapy increases the risk of heart disease in healthy postmenopausal women. Researchers report a trend toward an increased risk of heart disease during the first two years of hormone therapy among women who began therapy within 10 years of menopause, and a more marked elevation of risk among women who began hormone therapy more than 10 years after menopause. Analyses indicate that overall a woman's risk of heart disease more than doubles within the first two years of taking combination HT.

The difference in the initial level of risk does not appear related to age, based on findings that the increased risk of heart disease was similar between women in their 50s on combination hormone therapy and women in their 60s.

The study is in the Feb. 16, 2010, *Annals of Internal Medicine*. The WHI is sponsored by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH).

"Today, most women who take hormone therapy for menopausal symptoms begin therapy shortly after menopause. Based on today's report, even these women appear to be at increased risk of heart disease for several years after starting combination hormone therapy," noted Susan B. Shurin, M.D., NHLBI acting director. "It is clearer than ever

that women who are considering postmenopausal hormone therapy for menopausal symptoms should discuss their risk of heart disease and other risks - such as [breast cancer](#), stroke, and dangerous blood clots - with their doctors before starting therapy."

Jacques E. Rossouw, M.D., chief of the NHLBI Women's Health Initiative Branch and a coauthor of the paper, added, "Although the number of recently menopausal women who would be expected to suffer a heart attack during the first years of combination hormone therapy is small, the risk is likely to be real. Our findings continue to support FDA recommendations that postmenopausal hormone therapy should not be used for the prevention of heart disease."

Combination hormone therapy includes progestin in combination with estrogen. Adding progestin is known to prevent endometrial cancer in women with a uterus. Today's findings do not apply to women who have had a hysterectomy and take estrogen-only hormone therapy. Similar analyses on the results of the clinical trial of estrogen only therapy are planned.

Researchers from the Harvard School of Public Health and the NHLBI reanalyzed data from the landmark WHI clinical trial of the effects of combination hormone therapy in 16,608 postmenopausal women with an intact uterus, ages 50 to 79 years (average age of 63) at enrollment.

In the new analyses, the researchers compared the effects of hormone therapy on heart disease risk among women who began hormone therapy within 10 years of menopause and women who began therapy more than 10 years after menopause. The researchers used models that adjusted for adherence, or the actual amount of medication that participants took during the study. They also studied the effects of hormone therapy on heart disease over time (up to eight years). In addition, they compared the findings with similar analyses of 34,575 women in the Nurses Health

Study, an observational study with an average follow-up of 9.3 years. The researchers report similar effects of hormone therapy from both studies.

In the WHI clinical trial of estrogen-plus-progestin, 8,506 participants were randomly assigned to receive a combination of estrogen (0.625 milligrams of conjugated equine estrogens per day) plus progestin (2.5 mg of medroxyprogesterone acetate), and 8,102 women were given placebo (inactive pill). The study was stopped in 2002 after an average of 5.6 years of treatment due to an increase in breast cancer in the women on hormone therapy. Compared to women on placebo, women on combination hormone therapy were also at increased risk of stroke, dangerous blood clots, and heart disease, while their risk of colorectal cancer and hip fractures was lower.

Overall, among the 8,506 women assigned to combination hormone therapy during the study, there were 188 cases of coronary heart disease (80 in the first two years), compared to 147 heart disease cases (51 in the first two years) among the 8,102 women on placebo. When adjusted for adherence, the analysis shows that women on combination hormone therapy were about 2.4 times more likely to develop heart disease in the first two years. At eight years, the women on combination hormone therapy were 69 percent more likely to develop heart disease.

The new analyses also showed:

- Women who were within 10 years of menopause had a trend toward an increased risk of heart disease, with a 29 percent higher risk at two years from the start of hormone therapy. Although the increased risk of heart disease was not statistically significant, this finding is consistent with a similar analysis of data from the larger Nurses Health Study.

- Women who started combination hormone therapy less than 10 years after menopause remained at increased risk of heart disease on average for about six years, after which those in the treatment group appeared to have a lower risk of heart disease compared to similar women who were not on combination hormone therapy. In the nurses study, the initially increased risk on combination hormone therapy changed toward lower risk of heart disease after about three years.
- In contrast, women who started hormone therapy 10 years or more after menopause were nearly 3 times more likely to develop heart disease within the first two years of treatment compared to women on placebo. These women continued to be at increased risk of heart disease throughout the 8 years of follow-up.

It is not clear why the heart disease risk appears to be higher in women who start combination hormone therapy a decade after menopause than in women who begin combination hormone therapy within 10 years after menopause. According to Sengwee Toh, Sc.D., lead author of the paper and now an instructor in the Department of Population Medicine, Harvard Medical School, "This study suggests that the risk of heart disease may depend on when women start their combination hormone therapy and how long they are on this treatment. Future investigations should consider both of these aspects."

The WHI is a major 15-year research program designed to address the most frequent causes of death, disability, and poor quality of life in postmenopausal women: cardiovascular disease, cancer, and osteoporosis. The principal findings from the two WHI hormone therapy trials, which studied 27,347 [postmenopausal women](#) on estrogen plus progestin, estrogen-alone, or placebo, found that the overall risks of long-

term use of [hormone therapy](#) outweigh the benefits. Both of these trials were stopped early because of increased health risks and failure to prevent [heart disease](#), a key question of the studies.

Provided by NIH/National Heart, Lung and Blood Institute

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