



NIH BACKGROUNDER

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Contact:
NHLBI Communications Office
(301) 496 - 4238

**Statement from Claude Lenfant, M.D., NHLBI Director,
on Preliminary Trends in the Women's Health Initiative**

Participants in the hormone replacement trial of the Women's Health Initiative (WHI) are receiving new information on preliminary study findings regarding the risks and benefits of hormone replacement therapy (HRT). This information updates what WHI investigators gave to trial participants during the informed consent process at the study's beginning, and is part of a series of updates provided to participants as new data becomes available. The update was prompted by a request from the WHI Data and Safety Monitoring Board (DSMB), an independent advisory group which reviews study performance and participant safety every 6 months.

At its most recent meeting, the DSMB judged that sufficient data had now accumulated in the first two years of the study to indicate that women in WHI who were taking hormones (estrogen and progestin or estrogen alone) had somewhat more cardiovascular events (heart attacks, strokes, and blood clots in the legs and lungs) than those taking a placebo. The actual number of women having any one of these events was small (less than 1 percent). The increases did not meet statistical criteria for stopping the trial and, therefore, may have occurred by chance. The trends diminish over time and may even go away.

Based on all available information, the DSMB voted to continue the trial. The advisory group recommended that participants be informed of the trends for cardiovascular disease and reminded that a similar association between HRT use and an early increase in cardiovascular risk had also been found in the Heart and Estrogen/Progestin Replacement Study (HERS).

This new information from WHI is considered preliminary. It does not address the larger issue of long-term benefits and risks of HRT and, therefore, it should not influence current medical practice.

When the WHI participants were originally notified about the HERS results, the relevance of this study to women enrolled in WHI was not clear. All HERS participants had heart disease at the time they enrolled, however, most WHI participants did not have heart disease at enrollment. With the identification of the initial cardiovascular trend, the DSMB wanted to ensure that WHI participants were fully informed about the new, 2-year findings from the WHI.

HERS studied estrogen combined with progestin compared to placebo in 2,763 women with a uterus. The ongoing WHI is testing estrogen combined with progestin in women with a uterus, and estrogen alone in women with a hysterectomy. The two studies showed similar early trends for cardiovascular events for women taking estrogen combined with progestin. The trend also appeared to be present in WHI women receiving estrogen alone, though it is less certain because of the smaller numbers of women in this group. WHI enrolled 16,609 women with a uterus, and 10,739 women with a hysterectomy.

Similar to the HERS findings, over time, differences in cardiovascular events between active and placebo groups in WHI appear to be reduced and may even disappear. Almost all WHI women have crossed the 2 year mark or are about to do so, therefore this information becomes available at a time when it no longer appears to be pertinent to the participants – some of whom have been in the study for 5 years. Data from other studies, including HERS and the Nurses' Health Study, suggest that benefits for heart disease may be realized later.

Recently reported results from the Estrogen Replacement and Atherosclerosis (ERA) trial indicate that after three years the coronary angiograms of women on hormones did not differ from those on placebo. Thus, hormones caused neither an improvement nor a worsening of plaque (fatty deposits) buildup in the arteries. ERA, like HERS, was a study of women with pre-established coronary heart disease. It did not have enough participants to look at clinical events. Nonetheless, ERA is consistent with HERS in finding no apparent benefit of HRT in the first few years of treatment. A large number of observational studies have suggested that long-term HRT may reduce heart disease, therefore, the

issue is not settled by HERS and ERA. ERA, HERS, and the initial findings from WHI all underscore the importance of continuing WHI as the only US study underway that can provide definitive answers about the value of hormones for primary prevention of heart disease and long term effects on bones, breast, brain function, and other health outcomes.

It is important to emphasize that the DSMB advised the National Heart, Lung, and Blood Institute (NHLBI), the lead sponsor of the study, to continue the WHI HRT trial, which it would not have done if there was currently a question about participants' safety. The DSMB will continue to review the risks and benefits of hormones at future meetings and will advise participants as needed.

The Women's Health Initiative, one of the largest prevention studies ever conducted in the United States, is focusing on strategies for preventing heart disease, breast and colorectal cancer and osteoporosis in postmenopausal women. WHI is sponsored by the NHLBI and five other components of the National Institutes of Health – the National Cancer Institute, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Institute on Aging, the Office of Disease Prevention, and the Office of Research on Women's Health.

WHI involves over 161,000 women aged 50-79 and consists of these individual studies:

- A randomized controlled clinical trial of 66,000 postmenopausal women. Individual study "arms" are examining the effect of hormone replacement therapy in preventing heart disease, the effect of a low fat dietary pattern in preventing breast or colon/rectum cancer, and the role of calcium/vitamin D supplementation in preventing osteoporotic fractures.
- An observational study of 93,000 women to identify predictors of disease.
- A study of community approaches to developing healthful behaviors.

The final results from WHI are expected in 2005.

Information about the WHI is available on the NHLBI website at

<http://www.nhlbi.nih.gov/whi/index.html>