Cardiovascular disease is the leading cause of death in the United States today. Fully 52% of women will die of cardiovascular disease, far exceeding the percentage who will die of all cancers combined, and far in excess of the 4% who will die of breast cancer. It has been known since the initial findings of the Framingham Study, however, that women have a 20-year advantage over men in the occurrence of their first coronary event.

The causes underlying this observed delay in women are not known. Hormonal differences are an obvious starting point, and menopause—the loss of estrogen—provides a potential mechanism for explaining the two-decade delay. This theory, the estrogen hypothesis, holds that estrogen conveys a protective effect against the development of cardiovascular disease, which is then lost on menopause.

A number of studies have examined the biological plausibility of this hypothesis using surrogate cardiovascular end points. In one study of healthy postmenopausal women, two doses of conjugated equine estrogens (0.625 mg/d and 1.25 mg/d) were compared with placebo in their effect on various laboratory values. Estrogen was associated with reductions in low-density lipoprotein cholesterol (LDL-C) levels, and increases in high-density lipoprotein cholesterol (HDL-C) and triglyceride levels (Figure). Reductions in LDL-C and increases in HDL-C should be beneficial, although increases in triglyceride concentrations could be harmful. Similar studies have found other potential benefits of estrogen therapy in surrogate markers of cardiovascular disease. These studies provided some plausibility to the estrogen hypothesis.

Data from observational studies of hormone use also suggested a protective effect against cardiovascular disease. Analysis of relative risks from a number of studies indicate a lower incidence of heart disease in women receiving hormone therapy, with few exceptions. Again, it is important to be cognizant of the various biases inherent in such studies and the limited conclusions that can be drawn from them.

Clinical trials
Large-scale clinical trials of hormone therapy are few. Smaller clinical trials such as the Estrogen Replacement and Arteriosclerosis (ERA) trial evaluated conjugated equine estrogens (CEE) and medroxyprogesterone acetate (MPA), and the Women’s Estrogen for Stroke Trial (WEST) evaluated 17-β-estradiol. These studies examined the use of these various hormone replacement preparations in women who had a history of cardiovascular disease. Both reported results opposite to the investigators’ expectations: there was no apparent benefit of hormone treatment on coronary artery stenosis or recurrence of stroke.

The top two trials published in 2002 are the Heart and Estrogen/Progestin Replacement Study follow-up (HERS II) and the Women’s Health Initiative (WHI) hormone replacement trial. The HERS was a much larger randomized, placebo-controlled trial. It had two groups; one received estrogen, 0.625 mg/d, plus progestin, 2.5 mg/d, and the other received placebo. Hormone treatment had no effect on the primary end point, nonfatal or fatal myocardial infarction, relative hazard [RH], 0.99, or was there a difference in total mortality (RH, 1.08). For the first time, however, there was evidence of increased rates of coronary events early in the HRT users (RH, 1.52 at 1 year after randomization). In addition, several other events were increased with hormone treatment, including an increase in the relative risk of stroke (RH, 1.13, not significant [NS]), an increase in the risk of breast cancer (RH, 1.30, NS), and significant increases in gallbladder disease (RH, 1.38) and venous thromboembolism (RH, 2.89). A continuation of this trial—the HERS III—was halted after approximately 2.5 years, as the results were not different from those in the initial trial.

One consideration when looking at the HERS is the patient population: women with preexisting cardiovascular disease. It is possible that the disease in these women had progressed too far for estrogen to convey any benefit. The Women’s Health Initiative hormone replacement trial was designed to answer the question of primary prevention: could hormone therapy help prevent the development of cardiovascular disease in healthy postmenopausal women?

The WHI trial of estrogen plus progestin versus placebo was funded by the National Heart, Lung, and Blood Institute. Dr Walsh is the director of the Menopause Clinic at Brigham and Women’s Hospital and an assistant professor of obstetrics and gynecology and reproductive medicine at Harvard Medical School, Boston, Mass.

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Institute of the National Institutes of Health (NIH). It was intended to be conducted over 8 years to determine the possible major benefits and risks of hormone replacement in healthy postmenopausal women. On July 9, 2002, the NIH halted the trial after a mean follow-up of 5.2 years because the risks outweighed the benefits. Small but significant risks were found for invasive breast cancer (8 more per 10,000 person-years), coronary heart disease (7 more events per 10,000 person-years), stroke (8 more per 10,000 person-years), and pulmonary embolism (8 more per 10,000 person-years). Benefits associated with the use of the estrogen and progestin combination were lower risks for hip fractures (5 fewer per 10,000 person-years) and colorectal cancer (6 fewer per 10,000 person years). The results of the WHI hormone replacement trial failed to support the combined use of estrogen and progestin as an intervention for primary prevention of coronary heart disease.

Current and future work
One possible explanation of why HRT appears to increase the incidence of cardiovascular disease arises from the recent profusion of work on the role of inflammation in cardiovascular disease. Current thinking holds that inflammation is the primary lesion in this disease, allowing the penetration of cholesterol into the vessel wall, formation of the fatty streak, and subsequent development of atheroma. C-reactive protein (CRP) is a marker of inflammation and can be used to assess the degree of inflammation and arteriosclerosis. An intriguing study by Ridker et al examined CRP in healthy postmenopausal women. The findings showed that CRP was an independent predictor for future cardiac events and, in addition, was the best predictor of these events, more powerful than LDL-C, HDL-C, triglycerides, or other classic cardiac measures.

The selective estrogen receptor modulator (SERM) raloxifene has received some attention recently in regard to postmenopausal health. A study of healthy postmenopausal women that compared raloxifene, estrogen plus progestin, and placebo showed no effect on CRP with raloxifene, compared with a nearly 80% increase over placebo in CRP with hormone therapy.

A large clinical trial has been done examining the effect of raloxifene on cardiovascular disease. The Multiple Outcomes of Raloxifene Evaluation (MORE) study was designed to evaluate the use of raloxifene for the prevention of osteoporotic fractures as its primary outcome; however, investigators tracked various other parameters, including risk factors for cardiac and cerebrovascular events. Among all participants in the study, there was essentially no difference between treatment groups in cardiovascular events (RH, 0.9; NS). However, analysis of a subgroup of women who were at high risk for heart disease showed a significant 40% reduction in the risk of cardiovascular events in the group receiving raloxifene.11 A trial specifically designed to evaluate raloxifene in women at increased risk for heart disease is currently under way (RUTH), with women in their third to fifth years of the trial.

Guidelines following the Women’s Health Initiative hormone replacement trial
Until the results of the RUTH trial are available, two national medical bodies have issued guidelines following the results of the WHI hormone replacement trial: the American Heart Association (AHA) and the American College of Obstetricians and Gynecologists (ACOG). In 2001, on the basis of the HERS trial, the AHA updated its recommendations for women who have no signs of heart disease. He stated:13:

![Figure. Changes in low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride levels induced by estrogen replacement treatment (ERT). (Source: Walsh BW, Schiff I, Rosner B, Greenberg L, Ravnikar V, Sacks FM. Effects of postmenopausal estrogen replacement on the concentrations and metabolism of plasma lipoproteins. N Engl J Med. 1991;325:1196-1204.)](image-url)
We await the further results of the Women’s Health Initiative trial to assess the risks and benefits of women taking estrogen alone.

Based on current evidence, the American Heart Association advises that women do not start or continue combined HRT for the prevention of coronary heart disease.

The ACOG also stated its position regarding the WHI hormone replacement trial. First, it noted that the WHI trial is the most well-analyzed, statistically valid study of hormone therapy in healthy postmenopausal women. The ACOG also notes that modes of hormone therapy other than estrogen plus progestin could not be considered safe until so proven in clinical trials and that the WHI hormone replacement trial did not establish any duration of hormone therapy as safe.

Until ACOG releases final recommendations from its Task Force, ACOG advises the following:

1. Women who for a number of years have been on the combined estrogen/progestin therapy studied here should not panic, but discuss their individual situation with their physician. The WHI study authors took pains to emphasize that women should not be unduly alarmed. The increased risks of breast cancer applied to an entire population of women, not to increased risks for individual women—which were very small, less than a tenth of 1 percent per year. The population risks, applied over several years to millions of women, make the increased risks an important public health concern. However, as for individual women, a decision about hormone use should take into account a woman’s individual risk for specific conditions that may be harmed or benefited by hormone use.

2. With respect to women on short-term use of combination hormone therapy for relief of menopausal symptoms, the WHI authors note that although such use was not the focus of this study, it may be reasonable for women to continue use for this purpose, since the benefits are likely to outweigh the risks. Regarding a woman’s short-term use of combined estrogen/progestin therapy when indicated for relief of menopausal symptoms, ACOG continues to recommend that this be a personal, individualized decision, made after consultations between a woman and her physician and taking into account a woman’s individual benefits and risks from such use.

Addendum

Since this lecture on October 11, 2002, the Food and Drug Administration (FDA) determined that although not all combinations of estrogens and progestins were studied in the WHI trial, in the absence of comparable data:

- The risks identified in the study should be assumed to be similar for all postmenopausal hormone therapy products.
- Thus, in January 2003, the FDA approved the prescribing information for three combinations of conjugated estrogens and progestin:
  - tablets of conjugated estrogens available in four strengths (0.3 mg, 0.625 mg, 0.9 mg, 2.5 mg)16;
  - tablets of 0.625 mg of conjugated estrogens and 5.0 mg or 2.5 mg of medroxyprogesterone17; and
  - two tablet formulations given sequentially: one tablet containing 0.625 mg of conjugated estrogens taken on days 1 through 14 and a second tablet containing 0.625 mg of conjugated estrogen plus 5 mg of medroxyprogesterone acetate taken on days 15 through 28.18

These products include the boxed warning statement, “Estrogens with or without progestins should not be used for the prevention of cardiovascular disease.”15,17 The boxed warning also states that the WHI reported increased risks for heart attacks, strokes, invasive breast cancer, and blood clots in the lungs or legs. The prescribing information includes the statement “when prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk and non-estrogen medications should be carefully considered.” The pharmaceutical manufacturer issued a “Dear Health Care Professional” letter dated January 6, 2003.

References