The Changing View of Hormone Replacement Therapy

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Among postmenopausal women, 38% use hormone replacement therapy (HRT)—the leading brand of conjugated equine estrogen is the second most prescribed drug in the United States. Although adverse effects of this therapy have been recognized, it was traditionally reasoned that HRT could be broadly recommended to postmenopausal women because coronary heart disease was their most significant health risk. Evolving vascular biologic understanding, however, suggests that HRT, in direct opposition to the existing observational study data, does not reduce coronary heart disease risk. During the summer of 2002, three important studies on HRT dramatically changed our view of this widespread treatment. These trials provide clear, new, guidelines for patients and physicians contemplating HRT therapy.
[Rev Cardiovasc Med. *2003;4(2):68–71*]

Key words: Hormone replacement therapy • Coronary heart disease • Endometrial cancer • Vasomotor stability • Urogenital atrophy • Osteoporosis

Three important studies on hormone replacement therapy (HRT), published during the summer of 2002, have dramatically changed our view of this widespread treatment. These include the Women's Health Initiative (WHI), the first large primary prevention study[1]; the longer-follow-up Heart and Estrogen/Progestin Replacement Study (HERS II), a secondary prevention study[2]; and the latest meta-analysis of observational data on HRT.[3]

A full understanding of the effects of HRT is important because 38% of postmenopausal women use this therapy—the leading brand of conjugated equine estrogen is the second most prescribed drug in the United States. Prior to the publication of the original HERS study in 1998,[4] numerous observational studies had suggested both beneficial and adverse effects of HRT. In these studies, HRT was found to reduce vasomotor instability (hot flashes), urogenital atrophy, osteoporosis and fractures, colon cancer, and, most importantly, coronary heart disease events. Adverse effects were also recognized, including stroke, thromboembolic events, breast and ovarian cancers, and cholecystitis. At the time, it was reasoned that, despite the adverse effects, HRT could be broadly recommended to postmenopausal women because coronary heart disease was their most significant health risk. In 1998, the surprising results of the original HERS study were published, covering the effects of conjugated estrogen, 0.625 mg/d, and medroxyprogesterone acetate, 2.5 mg/d, in 2762 postmenopausal women with established coronary heart disease. The study demonstrated no difference in coronary heart disease events over the trial's 4.1-year mean follow-up, but there appeared to be an early increase in coronary events followed by a later decrease. The study was thus continued for an additional 2.7 years of follow-up.

During the WHI trial, there was a statistically significant increase in breast cancer and a global disease index with the use of HRT.

At about the time of the publication of the original HERS study, the vascular biologic consequences of HRT were becoming better defined, suggesting that HRT might not be beneficial to patients with coronary heart disease.[5] It remains established that HRT has mostly beneficial effects on serum lipids, including increases in HDL cholesterol and decreases in LDL cholesterol. Triglycerides are often increased as well, but the significance of this effect has been debated because most of the increase is in the larger triglyceride-rich, nonatherogenic particles. Several short-term studies of estrogen demonstrated improvements in endothelium-mediated vasodilation, suggesting increased nitric oxide availability, which appears to be an important antiatherogenic factor. Longer-term studies, however, demonstrated no improvement in endothelial function.[6]

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At the same time, increases in some markers of inflammation, such as C-reactive protein, were reported with HRT.[7] Inflammation is also thought to be an important atherogenic factor. The findings on inflammation, coupled with the long-standing awareness that HRT also increases coagulation, made it apparent that, based on fundamental vascular biology, HRT would not reduce coronary heart disease risk. This new vascular biologic understanding was in direct opposition to the existing observational study data, as well as the fact that premenopausal women have lower risk of coronary heart disease.

HERS II Study

In July 2002, the longer follow-up (6.8 years) of the HERS study was published, covering 93% of the women in the original trial who had agreed to continuing observation.[2] For the primary end points of death from coronary heart disease and nonfatal myocardial infarction, the relative hazard ratio during the latter follow-up period (HERS II) was 1.00, that is, precisely no benefit or harm. During the entire study period, the hazard ratio was also null (0.99). Thus, the earlier suggestion that HRT would prove beneficial, if continued beyond the initial period of increased procoagulant risk, proved false. In retrospect, it appeared that the later period of seemingly reduced risk in the original HERS study was a matter of chance. Secondary end points, including bypass surgery, percutaneous coronary intervention, unstable angina, congestive heart failure, sudden death, stroke, and peripheral arterial disease, were not significantly different in the women who received HRT. Only a significant increase in nonfatal ventricular arrhythmias with HRT was observed.

WHI Study

The WHI is a trial of conjugated estrogen, 0.625 mg/d, and medroxyprogesterone acetate, 2.5 mg/d, in 16,608 healthy postmenopausal women with an intact uterus. In addition, approximately 10,000 women who had undergone a hysterectomy received estrogen alone.[1] In May 2002, after 5.2 years of follow-up,

the Data and Safety Monitoring Board of the WHI discontinued the first part of the study prematurely before the planned 8.5-year duration because there was a statistically significant increase in breast cancer and a global disease index with the use of HRT. HRT had both beneficial and adverse effects. By nominal statistical analysis, HRT increased cardiovascular disease risk through increases in coronary heart disease (coronary heart disease mortality and nonfatal myocardial infarction), stroke, and thromboembolic disease (see Table 1). After adjustment for multiple statistical testing, only thromboembolic events increased statistically and overall cardiovascular disease was borderline significant. By nominal statistical analysis, HRT decreased colorectal cancer and increased breast cancer with borderline significance. Neither of these effects was significant by adjusted statistics, and the overall effect on cancer was null. By nominal statistics, HRT decreased all fractures, including hip and vertebral fractures. These effects were not significant by adjusted analysis.

Table 1
Effects of Hormone Replacement Therapy

Event	Observational Data (Relative Risk)	Women's Health Initiative Study (Hazard Ratio)
Coronary Heart Disease	0.91 (0.67–1.33)	1.29 (1.02–1.63)
Stroke	1.12 (1.01–1.23)	1.41 (0.86–2.31)
Thromboembolic Events	2.14 (1.64–2.81)	2.11 (1.26–3.56)
Breast Cancer	1.23–1.35	1.26 (1.00–1.59)
Colon Cancer	0.80 (0.74–0.86)	0.63 (0.32–1.24)
Hip Fractures	0.76 (0.56–1.01)	0.66 (0.33–1.33)

Overall mortality was unaffected by HRT (hazard ratio, 0.98). The overall effect of HRT was assessed with a global index, which included coronary heart disease, stroke, pulmonary embolism, breast cancer, endometrial cancer, colorectal cancer, hip fracture, and death due to other causes. HRT increased the global risk (hazard ratio, 1.15) significantly by nominal analysis, but not by adjusted analysis. The message of the WHI study is that HRT over 1 year in 10,000 healthy postmenopausal women results in seven more coronary heart disease events, eight more strokes, eight more pulmonary emboli, eight more breast cancers, six fewer colorectal cancers, and five fewer hip fractures. During the 5.2 years of the trial, 10,000 women taking HRT experienced 100 additional significant events (1%) compared with placebo.

Observational Studies

As reported in previous meta-analyses of HRT, a recent meta-analysis of 43 observational studies showed that HRT was associated with a reduction in coronary heart disease risk (relative risk 0.80 for current

Main Points

- Pre-1998 studies indicated that hormone replacement therapy (HRT) reduced vasomotor instability (hot flashes), urogenital atrophy, osteoporosis and fractures, colon cancer, and, most important, adverse events from coronary heart disease.
- Adverse effects recognized in these studies included stroke, thromboembolic events, breast and ovarian cancers, and cholecystitis.
- HRT increases some markers of inflammation, such as C-reactive protein, and is also known to increase coagulation.
- In 1998, the Heart and Estrogen/Progestin Replacement Study (HERS) demonstrated no difference in adverse events from coronary heart disease associated with HRT, but in women taking conjugated estrogen and medroxyprogesterone acetate, there appeared to be an early increase in coronary events followed by a later decrease.
- In 2002, HERS II found no improvement in risk of coronary heart disease death or nonfatal myocardial infarction; it appeared that the later period of reduced risk in the original HERS study was a statistical anomaly.
- The Women's Health Initiative (WHI) stopped prematurely because of a statistically significant increase in breast cancer and a global disease index with use of HRT; thromboembolic events increased statistically.
- Overall, the 5-year effect of HRT is a 1% increase in major medical events.

users and 0.88 for users at any time, the former statistically significant) (see Table 1).[3] Coronary heart disease mortality was significantly reduced (relative risk, 0.62) in current HRT users. It is generally thought that the difference between the observational and randomized data is due to confounding effects, that is, other practices or characteristics of HRT users. Adjustment for socioeconomic factors in the current meta-analysis resulted in a 0.97 risk ratio. Thus, observational HRT studies, even with adjustment, do not predict the actual adverse effect of HRT on coronary heart disease. Other aspects of cardiovascular disease were increased in HRT users, namely stroke and thromboembolic disease.

The effects of HRT on cancer and bone fracture in the observational meta-analysis were more similar to the WHI results. Breast cancer was increased and colon cancer reduced in HRT users. Endometrial cancer was increased in HRT users, in opposition to the neutral WHI study results. In general, the meta-analysis demonstrated a reduction in fractures.

The incidence of cholecystitis in the meta-analysis increased 80% in subjects who had used HRT for less than 5 years and 150% in those who had used HRT for more than 5 years. Women with cognitive deficits had increased verbal memory, vigilance, reasoning, and motor skills, but no improvement in other areas. No effects were observed in asymptomatic women.

Stroke, thromboembolic disease, breast cancer, and cholecystitis increase with the use of HRT.

Summary

The three most recent HRT trials provide clear guidelines for women and physicians contemplating HRT therapy. HRT provides short-term relief from vasomotor instability and urogenital atrophy. Long-term treatment provides both beneficial and detrimental effects. It is important to note that HRT does not reduce coronary heart disease risk in either primary or secondary prevention situations. Coronary risk factors, such as hypercholesterolemia, should be treated by traditional approaches. Stroke, thromboembolic disease, breast cancer, and cholecystitis increase with the use of HRT. Colon cancer and bone fractures are decreased by HRT. Overall, the 5-year effect of HRT is a 1% increase in major medical events. All-cause mortality is unchanged by HRT. Finally, these studies underscore the value of randomized trials. ■

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