The preferred treatment for osteoporosis after menopause has for years been hormone replacement therapy (HRT). This therapy was also used because there was the belief that hormones did many wonderful things. During the past year, however, sufficient evidence has been published that has determined that the blanket use of HRT in this patient population is unacceptable. Previously, observational data had established that combination hormone therapy protected women against coronary heart disease (CHD).¹

Three pivotal studies—the Heart Estrogen/progestin Replacement Study (HERS),² the HERS II,³ and the Women's Health Initiative (WHI)⁴—have demonstrated that hormones do not protect against heart disease and in fact may increase the risk. There also may be an increase in breast cancer. Thus, the dilemma in using hormones: Do the benefits of using these drugs outweigh the risks?

The Heart Estrogen/progestin Replacement Studies
The HERS trial² was a randomized, double-blind, placebo-controlled trial that included 2763 postmenopausal women with an intact uterus and with established CHD. These women were randomly assigned to receive placebo or 0.625 mg of conjugated estrogen (CEE) plus medroxyprogesterone acetate (MPA) daily for 4.1 years. The primary outcome measure was CHD-related deaths or nonfatal myocardial infarctions (MIs).
The average age of these women was 67 years. The results showed primary CHD events (CHD-related deaths or nonfatal MIs) occurred in 172 women in the HRT group and 176 in the placebo group (P = .91). None of these differences were statistically significant at 4 years (Figure 1). The only outcomes that were statistically significant at 4 years were increased risks for venous thromboembolism (VTE) and gallbladder disease in the treatment group. There were no statistically significant increases in deaths due to cancer or any other causes.

Closer examination of the cardiac data revealed in a post hoc analysis a 52% increase in cardiovascular events in the first year of HRT versus placebo. Fewer events per year were observed toward the end of the study.

This evidence led researchers to question whether therapy continued for a longer time would confer a CHD prevention benefit. Consequently, the HERS II, an open-label, observational follow-up study was established to continue the HERS trial for another 4 years. The primary outcome measure of the HERS II was also CHD-related deaths and nonfatal MI (Figure 2). The study was stopped after 2.7 years because no benefit was reported.

The HERS II data are similar to the HERS data. In the HERS II, the total number of CHD-related deaths was 71 in the HRT-treated group compared with 58 in the group receiving placebo. In the group receiving HRT, there was a threefold increase in deep vein thrombosis (DVT), a threefold increase in pulmonary emboli, and a slight increase in gallbladder disease.

The researchers concluded after both the HERS (a total of 6.8 years when considering the length of the HERS and HERS II together) that daily use of HRT (CEE plus MPA) does not reduce the overall risk for nonfatal MI, CHD, or any other cardiovascular event.

### Women’s Health Initiative
A much larger study than HERS conducted to evaluate the effect of HRT and estrogen replacement therapy (ERT) on
various health outcomes including cardiovascular disease and fracture is the WHI, (Table). This study is the nation’s largest study of HRT.

The WHI, initiated in 1992 and planned to be completed in 2007, was designed to examine the effects of a low-calcium diet, calcium and vitamin D (Ca/D) supplementation, ERT, and HRT, as well as counseling on the risks of cardiovascular disease and cancer and the effect of osteoporosis on women’s health. Each of these arms of the study has been treated separately.

The WHI is a randomized, double-blind, placebo-controlled study with an enrollment of 16,608 women (average age, 65 years). On entering the study, all subjects had an intact uterus and no known CHD. (The latter clinical characteristic is in contrast to both HERS trials, in which all women had known CHD.)

The primary endpoints of the studies are the following:
- the HRT study, CHD;
- the Ca/D supplementation arm, hip fracture; and
- the dietary modification study, breast and colorectal cancer;

The secondary endpoints of the studies are as follows:
- the HRT study, hip and other fractures;
- the Ca/D supplementation arm, colorectal cancer, combined fractures; and
- the dietary arm, CHD.

Each arm of the study has been examined separately. The estrogen/progestin arm was abruptly stopped July 2002 after 5.2 years because a predetermined level of breast cancer was reached (but not a statistically significant increased risk). The CEE only arm of the study did not meet the cut-off point for increased risk, and it is continuing, as are the low-fat diet arm, the Ca/D supplementation arm, and the observational arm.

In the estrogen plus progestin component of the WHI that ended early, the primary outcome measure was CHD (nonfatal MI and CHD-related death), and the primary adverse outcome was invasive breast cancer in healthy postmenopausal women.

In the HRT-treated group, CHD events increased significantly \((P=.05)\) within the first 5.2 years (Figure 3). Preliminary data from the first 2 years (found in WHI HRT update on the National Heart, Lung, and Blood Institute Web site at http://www.nhlbi.nih.gov/whi/index.html) suggest a small increase in the number of MIs, strokes, and blood clots in subjects receiving ERT or HRT versus placebo. Over time, the differences seemed to become smaller and disappear. Overall CHD events were low during the whole trial. The rate of women having CHD was increased by 29% for women taking estrogen plus progestin relative to placebo (37 vs 30 per 10,000 person-years), reaching nominal statistical significance (but not adjusted statistical significance). Most of the excess was in nonfatal MI. No significant differences were observed in CHD-related deaths or revascularization procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty).

Stroke rates were also higher in women receiving estrogen plus progestin (41% increase, 29 vs 21 per 10,000 person-years), with most of the elevation occurring in nonfatal events.

Women in the group treated with estrogen plus progestin had twofold greater rates of VTE (34 vs 16 per 10,000 person-years), as well as DVT and pulmonary embolism individually.

The total rate of cardiovascular disease, including other events requiring hospitalization, was increased by 22% in the group treated with estrogen plus progestin.

Results of the ongoing ERT arm of the study (in women who have had hysterectomies) are still being reviewed internally by the study group every 6 months. The study group has not stopped that arm of the study, so it is not known whether the benefits of ERT in women who have had hysterectomies outweigh the risks.

The HRT-treated group had a significant increase (26%, \(P = .05\)) in invasive breast cancer compared with the group receiving placebo (Figure 4). The 26% increase (38 vs 30 per 10,000 person-years) observed in the group receiving estrogen plus progestin almost reached nominal significance, and the weighted test statistic used for monitoring reached a prespecified value. However, the adjusted rate did not reach statistical significance. No statistical significance was noted for in situ breast cancer. This means that there was a number of cases of breast cancer that was prespecified before the trial began above which the risks of HRT would outweigh the benefits. The trial was stopped because this number was reached. However, it was not a statistically significant number of cases.

There was no significant change in rates of endometrial cancer (Figure 4), and the rate of colorectal cancer decreased 37% \((P = .05)\). The development of both vertebral and hip fractures was also decreased by 33.3% (Figure 5).

In summary, HRT (CEE plus MPA) does not confer any benefit in the prevention of CHD in patients with an intact uterus. Hormone replacement therapy does increase the risk of CHD after initia-

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**Table**

Estimated Hazard Ratios of Major Clinical Outcomes in the Women’s Health Initiative Study (Through April 30, 2002)*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Cases</th>
<th>Hazard Ratio (Adjusted CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease</td>
<td>286</td>
<td>1.29 (0.85–1.97)</td>
</tr>
<tr>
<td>Stroke</td>
<td>212</td>
<td>1.41 (0.86–2.31)</td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td></td>
<td>2.07 (1.14–3.74)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>101</td>
<td>2.13 (0.99–4.45)</td>
</tr>
<tr>
<td>Invasive breast cancer</td>
<td>290</td>
<td>1.26 (0.83–1.92)</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>112</td>
<td>0.63 (0.43–0.92)</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>106</td>
<td>0.66 (0.45–0.98)</td>
</tr>
</tbody>
</table>


†CI indicates confidence interval.
**Figure 3.** Cardiovascular outcomes at 5.2 years in the Women’s Health Initiative study. CEE \(\times\) MPA indicates conjugated equine estrogens (0.625 mg/d) plus medroxyprogesterone acetate (2.5 mg/d); CHD, coronary heart disease; MI, myocardial infarction. (Source: Rossouw JE, et al; Writing Group for the Women’s Health Initiative Investigators. JAMA. 2002;288:321-333.)

**Figure 4.** Cancer outcomes at 5.2 years of average follow-up in the Women’s Health Initiative study. CEE \(\times\) MPA indicates conjugated equine estrogens (0.625 mg/d) plus medroxyprogesterone acetate (2.5 mg/d). (Source: Rossouw JE, et al; Writing Group for the Women’s Health Initiative Investigators. JAMA. 2002;288:321-333.)

**Figure 5.** Fracture outcomes at 5.2 years of average follow-up in the Women’s Health Initiative study. CEE \(\times\) MPA indicates conjugated equine estrogens (0.625 mg/d) plus medroxyprogesterone acetate (2.5 mg/d). (Source: Rossouw JE, et al; Writing Group for the Women’s Health Initiative Investigators. JAMA. 2002;288:321-333.)
tion of treatment. The WHI finding of a 41% increase in stroke is similar to the findings in the HERS trials. The development of VTE in the HERS trial was twofold and in the WHI, the increase was twofold.

The WHI is the first randomized, controlled study to confirm that HRT increases the risk of invasive breast cancer. In the past, the only available data that pointed to an increased risk were observational.

Overall, from the WHI, it is possible to conclude that among patients treated with HRT (as compared with subjects receiving placebo), 7 more CHD-related deaths, 8 more strokes, 18 more VTEs, and 8 more cases of invasive breast cancer will occur per 10,000 person-years. There will be 6 fewer colorectal cancers and 5 fewer hip fractures per 10,000 person-years.

Although the numbers may seem small, they reflect a calculation per 10,000 patient years, and when projected over the many millions of patients who take the drug, the numbers become significant. Clearly, the advantages of using HRT (including use for control of menopausal symptoms, prevention—not treatment—of osteoporosis, and prevention of colon cancer) simply do not outweigh the risks of VTE, menstrual bleeding, breast cancer, and development of cardiovascular disease associated with use of HRT.

Nonpharmacologic Management Options

Modification of Risk Factors for Osteoporosis

To manage osteoporosis in postmenopausal women without the use of HRT, the focus must shift to nonpharmacologic forms of treatment through modification of risk factors as well as other categories of agents that decrease the risk for fracture. Risk factor modification includes:

- smoking cessation,
- reduction of ethanol intake,
- prevention of fractures, and
- an exercise program.

In addition, all postmenopausal women should take 1000 mg to 1500 mg of calcium with 400 IU to 800 IU of vitamin D per day. Dual-energy x-ray absorptiometry (DXA) scanning should be done according to the International Society of Clinical Densitometry’s recommendations. All patients with risk factors who have undergone menopause after the age of 50 years should undergo DXA scanning. Risk factors include all Caucasian patients older than 50 years, female gender, sedentary lifestyle, smoking and alcohol use, and use of certain pharmacologic agents (such as thyroid hormone replacement, corticosteroids, loop diuretics [not thiazides], and anticonvulsants).

Pharmacologic Management of Osteoporosis

The National Osteoporosis Foundation (NOF) guidelines should be followed to treat patients with pharmacologic therapy. The NOF has determined that if a patient has a T-score of −1.5 or lower with a risk factor, the patient should be treated pharmacologically. All patients with a T-score of less than or equal to −2.0 should be treated, regardless of risk factors. Treatment may consist of an antiresorptive drug like the bisphosphonates or an anabolic agent like parathyroid hormone. Therapy with a proven track record in reducing fractures in the spine as well as the rest of the skeleton (nonvertebral, including hip) is crucial to preventing fractures.

Modification of Risk Factors for Cardiovascular Disease

Cardiovascular disease may also be managed by modification of risk factors, including smoking cessation, a low-fat diet, and an exercise program. Lipid levels should be optimized. Blood pressure should be strictly controlled; diabetes should also be controlled with a hemoglobin A1c goal of less than 7.0%. And, all women at risk should take a daily low dose (81 mg) of aspirin.

Comment

Prevention of osteoporosis and heart disease in postmenopausal women has been in the spotlight lately. Years ago, physicians thought hormones did everything from improving hot flashes and vaginal dryness to reducing the risk for heart disease, osteoporosis, and even wrinkles. This thinking had been based on observational data. Now that three major randomized trials show the same results, physicians have to change their thinking. They can no longer safely say that combination CEE and MPA prevents heart disease. Does this also apply to other estrogen and progestin combinations, or estrogen itself? Data that answer these questions are yet to be published. For now, the only recommended use of combination hormone therapy is for hot flashes and menopausal symptoms and for the shortest amount of time possible. If clinicians want to treat or prevent osteoporosis, they need to use other agents such as the bisphosphonates. If they want to prevent heart disease, they need to address the risk factors separately.

References