Hormone therapy (HT) is one of the most prescribed medical regimens in the United States. Before the July 2002 publication of the opposed-estrogen arm of the Women’s Health Initiative (WHI), which linked at least 3 years of HT to an elevated risk of invasive breast cancer, an estimated 38% of postmenopausal women in this country were taking HT. In 2000, this group accounted for 46 million prescriptions for conjugated equine estrogen (CEE) and 23 million prescriptions for CEE plus medroxyprogesterone acetate (MPA).

Approved indications for HT as stipulated by the US Food and Drug Administration (FDA) include the relief of menopausal symptoms and the prevention of osteoporosis. Prevention of fractures (associated with decreased bone density), vasomotor instability (hot flashes), and atro-

**ABSTRACT**

Estrogen therapy, with or without progestins, has been widely prescribed for the treatment of menopausal symptoms. However, recent randomized trials have cast doubt on the idea that postmenopausal hormone therapy (HT) can lower the risk of certain chronic diseases, including coronary heart disease. Many retrospective and observational studies of HT had suggested that it may reduce cardiovascular morbidity and mortality. Although the placebo-controlled Postmenopausal Estrogen/Progestin Interventions trial convincingly showed HT improves lipid parameters, subsequent trials failed to disclose an associated improvement in clinical outcomes. Indeed, in the secondary prevention Heart and Estrogen/Progestin Replacement Study, HT raised cardiovascular risk over the first year of therapy, although the risk elevation reversed in subsequent years. The opposed-estrogen arm of the Women’s Health Initiative also showed elevated early cardiovascular risk with HT, as well as an increased risk of thromboembolic complications. Moreover, women taking HT showed an increased rate of invasive breast cancer that became significant after 3 years. Studies suggesting HT may prevent or slow the development of dementia or Alzheimer’s disease are preliminary; randomized trials are ongoing. HT may be cautiously recommended for the short-term relief of menopausal symptoms but should be limited to 3 years or less in most cases due to an increased risk of invasive breast cancer. HT poses greater clinical risks compared with potential benefit when used longer term for the primary or secondary prevention of chronic diseases. (Adv Stud Med. 2003;3(4):205-213)
phy of the urogenital epithelium are the most common reasons HT is prescribed.

HT is not FDA-approved for the prevention of coronary heart disease (CHD) but has been prescribed for this reason during the past decade. Until 1998, much of the evidence regarding HT and CHD was observational. Recent evidence from randomized controlled trials has shown that HT does not decrease the risk of CHD.1,3

**Short-term HT for Menopausal Symptoms**

**Recent Trial Evidence and Clinical Practice**

Estrogen is effective for relieving hot flashes associated with menopause within several weeks. In the early 1990s, a randomized controlled trial, the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, examined the short-term effects of estrogen and estrogen/progestin on menopausal symptoms and lipids. In this multicenter trial, 875 healthy postmenopausal women aged 45 to 64 years were randomized to receive CEE, CEE plus cyclic MPA, CEE plus continuous daily MPA, CEE plus cyclic micronized progesterone, or placebo.4 Over a 3-year follow-up period, the 4 active therapies were associated with significant improvements in profiles of low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and fibrinogen compared with placebo. Unopposed CEE, which had the most pronounced HDL-elevating effect, was also associated with a significantly increased risk of endometrial hyperplasia.

Regarding symptoms attributed to menopause, the PEPI investigators found all of the active treatments effectively suppressed hot flashes, night sweats, and insomnia, but none significantly affected mood, depression, cognition, or sexual function.5 HT may be an acceptable treatment for postmenopausal women without contraindications whose lives are disrupted by hot flashes, night sweats, and insomnia. Even in this group, however, other management options (pharmacologic and nonpharmacologic) exist.

In a recent release of data from the WHI regarding health-related quality of life,6 the estrogen-progestin HT regimen did not lead to a clinically meaningful improvement in general health, vitality, mental health, depressive symptoms, sexual satisfaction, sleep disturbance, physical functioning, and bodily pain. The latter 3 measures showed slight statistically significant improvements, but these represented an improvement of only 1% to 4% over baseline scores. Among women 50 to 54 years of age with moderate-to-severe vasomotor symptoms at baseline, estrogen and progestin improved vasomotor symptoms and resulted in a small benefit in terms of sleep disturbance but no benefit in terms of the other quality-of-life outcomes.

**Options for Short-term Symptomatic Relief**

Several options are available for women seeking relief from symptoms attributed to menopause (Table 1).

- Estrogen replacement with or without a progestin remains the standard treatment for the short-term relief of menopausal symptoms, with a demonstrated effectiveness of about 85% for hot flashes, night sweats, and insomnia. The symptoms improve within

### Table 1. Short-Term Effectiveness of Selected Treatments for Vasomotor Symptoms

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Effectiveness (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen</td>
<td>85</td>
</tr>
<tr>
<td>Megestrol acetate</td>
<td>85</td>
</tr>
<tr>
<td>Progestin cream</td>
<td>75</td>
</tr>
<tr>
<td>SSRIs and other neurotransmitters</td>
<td>50–70</td>
</tr>
<tr>
<td>Provera</td>
<td>50</td>
</tr>
<tr>
<td>Soy</td>
<td>50</td>
</tr>
<tr>
<td>Placebo</td>
<td>35</td>
</tr>
</tbody>
</table>

SSRIs = selective serotonin reuptake inhibitors.

Data from Rebar et al; Lograndi et al; Leonetti et al; Elkind-Hirsch; Berendsen.10

### Table 2. Contraindications to Estrogen Therapy in Postmenopausal Women

<table>
<thead>
<tr>
<th>Absolute Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Unexplained vaginal bleeding</td>
</tr>
<tr>
<td>Active or chronic liver disease</td>
</tr>
<tr>
<td>Cancer of the breast or endometrium</td>
</tr>
<tr>
<td>Recent vascular thrombosis</td>
</tr>
<tr>
<td>History of estrogen-related vascular thrombosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Relative Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertriglyceridemia</td>
</tr>
<tr>
<td>History of thromboembolic disease</td>
</tr>
<tr>
<td>Family history of breast cancer</td>
</tr>
<tr>
<td>Gallbladder disease</td>
</tr>
<tr>
<td>Migraine headaches</td>
</tr>
</tbody>
</table>

Absolute Contraindications

- Pregnancy
- Unexplained vaginal bleeding
- Active or chronic liver disease
- Cancer of the breast or endometrium
- Recent vascular thrombosis
- History of estrogen-related vascular thrombosis

Relative Contraindications

- Hypertriglyceridemia
- History of thromboembolic disease
- Family history of breast cancer
- Gallbladder disease
- Migraine headaches
EARLY EVIDENCE FOR CARDIOVASCULAR PROTECTION: HT for menopausal symptoms is controversial. Proponents of the idea noted that heart disease was rare in premenopausal women and that estrogen produced favorable changes in the lipoprotein profile. Meanwhile, skeptics observed that oral contraceptives increase the risk of venous thrombotic, coronary, and neurovascular events and cited the negative findings from the Coronary Drug Project. Two of the randomization arms in this trial of men with coronary disease included 5.0 mg or 2.5 mg of CEE per day (4–8 times the dosage typically given to women). These dosages of CEE were associated with significant increases in venous thrombotic events and no decreases in cardiac events.

The controversy was revisited in the 1980s when 2 observational reports were published in the same journal showing opposite effects of estrogen on CHD in women. The Framingham Study showed an increased risk of CHD in users of estrogen, and the Nurses Health Study showed a decreased risk of CHD in users of estrogen, The Framingham investigators found a 90% elevated risk of cardiovascular events and an excess of cerebrovascular events among women who reported using HT. The Nurses Health Study included 32,317 women who were postmenopausal and initially free of coronary artery disease. Compared with the women who had never used HT, the women who had any history of postmenopausal HT showed a 50% reduction in relative risk of coronary events (P = .007). Those reporting that they were currently taking HT showed a 70% lower relative risk (P = .001). Both findings were independent of smoking status, obesity, oral contraceptive use, or the presence of diabetes, hypertension, or elevated cholesterol levels.

Many observational cohort studies followed in the next decade, and most of these showed a decreased risk of CHD in users of HT. For example, the Lipid Research Clinics Program Follow-up Study of 2270 women with a baseline age of 40 to 69 years found a 58% reduction in the relative risk of death due to a cardiovascular event; risk reduction over a mean of 8.5 years was associated with the “noncontraceptive use of estrogen.” That reduction, attributed to the protective effects of elevated HDL cholesterol levels, emerged after statistical adjustments for baseline features, including preexisting cardiovascular disease.

A meta-analysis of many of these observational studies published in 1998 acknowledged that they send a consistent message that HT is an effective cardioprotective agent. Still, the authors cautioned that most of the known biases in those studies “would tend to exaggerate estrogen’s effect.” The skepticism was based on the inconclusive nature of
observational studies, not merely doubts about the risk-benefit issues. The subjects in the uncontrolled, nonrandomized observational studies were not representative of the US population of postmenopausal women. Those who choose to receive HT tend to have leaner body mass and are more likely than women who do not receive HT to be well educated, exercise, have healthier diets, and receive more frequent medical care.

**Cardiovascular Protection in Randomized Trials**

In the multicenter PEPI trial of 875 healthy postmenopausal women, one of the first randomized controlled trials of HT, the treatment assignments consisted of CEE, CEE plus cyclic MPA, CEE plus continuous daily MPA, CEE plus cyclic micronized progesterone, or placebo for 3 years. In all of the active therapies significantly elevated mean HDL cholesterol levels compared with placebo, with the most prominent increase (6 mg/dL) seen in the group that received unopposed CEE. In addition, mean LDL cholesterol levels decreased (by 15–18 mg/dL) and mean triglyceride levels increased (by 11–14 mg/dL) markedly in all active-therapy groups. Changes in systolic blood pressure and insulin levels during the trial did not vary significantly among groups. These findings, although based on prospectively defined laboratory endpoints rather than clinical outcomes, enhanced the perception that HT may reduce cardiovascular risk.

**Randomized Trials with Clinical Endpoints**

The Heart and Estrogen/Progestin Replacement Study (HERS) was the first prospective, randomized controlled trial to examine the cardiovascular effects of HT. In this secondary prevention study, 2763 postmenopausal women with established coronary artery disease and no history of hysterectomy were randomized to receive CEE plus MPA or placebo. The average age was 67 years, and all women were younger than 80 years. The average follow-up time was 4.1 years; 75% of the women remained on assigned therapy at the end of 3 years. Less than one half of women in the HERS trial were taking lipid-lowering medications, only one third were taking beta blocking agents, and 78% were taking aspirin.

Mean levels of HDL cholesterol rose, and LDL cholesterol decreased to a significant degree (by 11% and 10% respectively, \( P < .001 \) for both parameters). There were no significant differences, however, in the rates of nonfatal acute myocardial infarction (MI) or death from CHD, the primary composite endpoint, or in the rates of separate secondary endpoints that included coronary revascularization, unstable angina, congestive heart failure, and stroke.

Analysis of CHD events by follow-up time disclosed a significant risk increase by the end of the first year among women taking HT (Table 3). The short-term risk elevation did not meet the predetermined criteria for stopping the trial. Subsequently, a significant time trend in the opposite direction was observed. After an elevation the first year, CHD risk started to fall such that it became lower than in the control group by years 4 and 5.

A follow-up analysis of HERS found a significantly elevated risk (\( P = .003 \)) of venous thromboembolic events (deep venous thrombosis or pulmonary embolism) over a mean of 4 years among women taking HT. This risk was attenuated among women taking aspirin or statins.

There has been considerable speculation as to the mechanisms behind the early CHD risk elevation followed by a gradual decrease in risk. Among the most intriguing are that the initiation of HT was associated with transient changes in other biochemical systems involved in the pathogenesis of CHD events, such as those responsible for inflammation or thrombogenesis; or that events during the first year of HT may have selected a population of survivors who were more resistant to CHD.

HERS II was a continuation of HERS that showed there was no further decrease in CHD in users of HT after an additional 3 years. At a mean follow-up time of 6.8 years, adherence to HT in the actively treated groups had declined to less than 45%, showing no persisting benefit or favorable trend.

The Estrogen Replacement for Atherosclerosis (ERA) trial was a randomized placebo-controlled trial that found that estrogen therapy had no beneficial effect on plaque diameter among women with established cardiovascular disease.

<table>
<thead>
<tr>
<th>Year of Follow-up</th>
<th>HT Group (n = 1380)</th>
<th>Control Group (n = 1383)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>57</td>
<td>38</td>
<td>.04</td>
</tr>
<tr>
<td>Year 2</td>
<td>47</td>
<td>48</td>
<td>NS</td>
</tr>
<tr>
<td>Year 3</td>
<td>35</td>
<td>41</td>
<td>NS</td>
</tr>
<tr>
<td>Years 4 and 5</td>
<td>33</td>
<td>49</td>
<td>NS</td>
</tr>
</tbody>
</table>

CHD = coronary heart disease; HERS = Heart and Estrogen/Progestin Replacement Study; NS = not significant. \( P = .009 \) for time trend. Data from Hulley et al.
**Primary Prevention of CHD**

Investigators for the WHI at 40 US centers randomized 16 608 postmenopausal women with an intact uterus, aged 50 to 79 years (mean age, 63 years), to receive the combination of CEE and MPA or placebo in 1 daily tablet, for a projected 8.5 years. This HT arm of the WHI was discontinued early, and results were published in July 2002.1

Interim analyses showed progressive elevations in the risk of cardiovascular events. In women receiving active therapy, the risk threshold was exceeded for breast cancer and for a global index of overall clinical harm. The opposed-estrogen arm of the WHI was halted after a mean follow-up of 5.2 years. (Another WHI arm, in which 10 739 postmenopausal women without a uterus were randomized to receive unopposed estrogen or placebo, is ongoing.2)

**CHD and Other Risks in the WHI**

Table 4 shows the risks and benefits of HT found in the WHI.1 Women taking active therapy had a 29% increased risk of CHD events, which consisted largely of an excess of nonfatal MIs, and a 41% increase in risk of stroke (P ≤ .05 vs placebo for both findings). The risks of these events over time remained elevated among actively treated women throughout the follow-up period (Figure 1). There was also a more-than-doubled risk of deep venous thrombosis and pulmonary embolism.

Event curves for the endpoint of invasive breast cancer show near correspondence between the 2 treatment groups until after the third year of follow-up (Figure 2), a finding that appears consistent with previous observational studies. After that point, however, the curves diverge such that the risk among actively treated women is elevated by a significant 26% by the end of the fifth year.

Active therapy was associated with apparent benefits as well. Women taking opposed estrogen had a 37% decrease in risk of colorectal cancer and a 34% decrease in the risk of hip and vertebral fracture (Table 4), all significant differences.

The WHI outcomes suggest that HT must be given to 237 women over 5.2 years in order for 1 CHD event to occur. Similarly, 225 women must be treated to cause 1 stroke, 105 women for 1 venous thromboembolic event, and 237 women for 1 case of invasive breast cancer. On the benefit side, 336 women must take HT to prevent 1 case of colon cancer, and 403 women must take HT to prevent 1 hip fracture.

Therefore, if a clinician were to prescribe HT to generally healthy postmenopausal women, 1 at a time, treatment would be associated with at least 1
serious medical condition long before any benefit was realized. The global index used in the WHI, a composite risk indicator for a range of major adverse outcomes (Table 4), indicates only 88 women would be treated before a harmful event occurred. The bottom-line message from the trial is that the risks of opposed HT as a preventive therapy in healthy postmenopausal women outweigh any likely clinical benefits.

**HT Effects on Cognition and Dementia**

Some biochemical and physiologic studies of estrogen suggest HT has effects on neurons and cognitive function. Whether estrogen could be used to prevent cognitive decline or dementia, however, is a difficult question. Many of the studies of HT and dementia to date have been observational. In 2 meta-analyses, the authors have pooled the results of the observational studies of HT and dementia.30,31 Observational studies can show associations but cannot show cause-effect relationships. Both meta-analyses have shown a decrease in dementia in users of HT, but the authors have been careful about recommending HT to prevent dementia.

In a meta-analysis of 10 observational studies, users of HT had a 29% lower risk of dementia.31 The study's authors noted, however, that the observational studies were heterogeneous, making it difficult to conclude that HT had an overall beneficial effect. The same group examined 4 studies of estrogen in women with Alzheimer's disease and found a possible benefit, but the studies were small, of limited length, nonrandomized, and uncontrolled. “Given the known risks of estrogen therapy,” the authors wrote, “a recommendation to treat Alzheimer's disease or any other form of dementia with HT is premature in the absence of adequate prospective, randomized trials.”

One prospective, randomized multicenter trial has suggested HT may not have a role in treating dementia. In the Alzheimer's Disease Cooperative Study, 120 women with dementia who had undergone hysterectomy were randomized in a double-blind placebo-controlled trial to unopposed CEE (0.625 mg/day or 1.25 mg/day) or to placebo. Estrogen replacement at either dosage had no effect on cognitive or functional decline over 15 months. There were 4 cases of deep venous thrombosis, however, in this time period.

**Selective Estrogen Receptor Modulators**

Selective estrogen receptor modulators (SERMs) exhibit tissue-specific estrogen agonist or antagonist activity.33 Of the 2 commercially available SERMs, tamoxifen is FDA-approved for the treatment and prevention of estrogen receptor (ER)-positive breast cancer, whereas raloxifene earned approval based on its documented ability to increase bone mineral density.34

**Tamoxifen**

Tamoxifen was originally approved for the treatment of metastatic breast cancer. However, the randomized Breast Cancer Prevention Trial led to the acceptance of tamoxifen as a preventive therapy for breast cancer.35,36 In that trial, 13 388 women 35 years of age or older with an increased risk of breast cancer were randomized to receive 20 mg daily of tamoxifen or placebo for a projected 5 years.

The study used well-described parameters for defining elevated risk, including age 60 years or older, 5-year predicted breast cancer risk of at least 1.66% according to the Gail algorithm for women younger than 60 years, or a history of in situ lobular carcinoma. The Gail algorithm is based on a logistic regression model incorporating a range of breast cancer risk parameters.37 The model emphasizes age and number of relatives with a history of breast cancer but also includes parity, age at menarche, presence of atypical hyperplasia, and other variables.

The trial was halted prematurely after the benefit of tamoxifen became apparent. Over 4 or more years, actively treated women showed a 49%
decrease in the risk of invasive breast cancer (P < .001). With the participants stratified by age, the decrease in risk was 44% among women younger than 50 years, 51% for those aged 50 to 59 years, and 55% for those 60 years or older. The decrease reached 56% for women with in situ carcinoma at baseline and 86% for those with atypical hyperplasia. Tamoxifen was associated with a 50% decrease in the risk of noninvasive breast cancer over the entire population (P < .002). Not surprisingly, as a SERM, tamoxifen prevented the development of tumors that were ER positive but had no significant effect against ER-negative disease. Approximately two thirds of breast cancers are ER positive, suggesting that tamoxifen could be of significant benefit in many women with risk factors for breast cancer.

Caution is appropriate, however. The Breast Cancer Prevention Trial also showed tamoxifen was associated with an elevated risk of endometrial cancer and venous thromboembolic events; 68% of actively treated women, but only 50% of the control group had hot flashes during the trial.

In 2002 the US Preventive Services Task Force on Breast Cancer Prevention issued guidelines for women who were considering taking tamoxifen. These guidelines noted “fair evidence for harm” in women at low-to-average risk of breast cancer; the risks of venous thromboembolism and other events outweighed the possible benefits. For women at high risk for breast cancer and at low risk for the potential adverse effects, however, there is fair evidence that a doctor-patient discussion of taking tamoxifen “improves important health outcomes.”

RALOXIFENE

In the most important study to clarify the clinical role of raloxifene, the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, a total of 7705 postmenopausal women with osteoporosis were randomized to receive either placebo or raloxifene, 60 mg or 120 mg daily for 4 years. Active therapy increased bone mineral density in vertebrae and the femoral neck by 2% to 3%, depending on location and dosage, and reduced the risk of vertebral fracture by 40%. Women who entered the study with a history of vertebral fractures received the most benefit.

Treatment with raloxifene for about 40 months in the MORE trial was associated with a 75% reduction in the risk of in situ or invasive breast cancer. Again, a significant risk reduction was found to have occurred only with respect to ER-positive tumors. There was no increase in the risk of endometrial cancer with raloxifene. However, the risk of venous thromboembolic events tripled in patients taking active therapy, and hot flashes were significantly more prevalent with raloxifene (10%) versus placebo (6%).

The National Cancer Institute has launched a non-placebo-controlled randomized study of the effects of the 2 SERMs on breast cancer risk, the Study of Tamoxifen and Raloxifene (STAR). At 194 North American centers, the trial will include a projected total of 22,000 postmenopausal women with in situ lobular carcinoma or elevated breast cancer risk according to Gail criteria. The 7-year STAR trial will also compare treatment effects on the risk of CHD, osteoporosis, and endometrial cancer.

SERMS AND CARDIOVASCULAR RISK

Both tamoxifen and raloxifene produce favorable changes in lipid parameters, but these intermediate markers are not as clinically relevant as such outcomes as MI or CHD death. Breast cancer trials of tamoxifen have failed to show a cardiovascular risk benefit. A retrospective examination of the MORE trial showed, in a subgroup analysis, an association between raloxifene use and decreased CHD events. This finding should also be interpreted with caution, because the primary intention of the MORE study was not to examine CHD events. Also, the subgroup analysis was not included in the initial data analysis plans for MORE. The subgroup that did appear to have lower CHD events on raloxifene was a subset of 1035 women with elevated baseline cardiovascular risk as determined by preexisting CHD or an elevated cardiac risk score.

To examine the cardiovascular effects of raloxifene, a double-blind randomized, controlled trial, the Raloxifene Use for the Heart (RUTH) trial, will assess a wide range of CHD

<table>
<thead>
<tr>
<th>Table 5. Recommendations for Postmenopausal Hormone Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hormone therapy ([HT] estrogen alone or estrogen plus progestin) can relieve hot flashes but has risks</td>
</tr>
<tr>
<td>• Do not use HT for prevention of cardiovascular disease — risks outweigh benefits</td>
</tr>
<tr>
<td>• Discuss discontinuing HT after 1 year of therapy</td>
</tr>
<tr>
<td>• Aggressively try to stop HT after 3 years of therapy</td>
</tr>
<tr>
<td>• Selective estrogen receptor modulators should be used according to approved indications:</td>
</tr>
<tr>
<td>- Prevention or treatment of breast cancer for tamoxifen</td>
</tr>
<tr>
<td>- Prevention or treatment of osteoporosis for raloxifene</td>
</tr>
</tbody>
</table>
outcomes in 10 101 women at 187 centers in 26 countries. These women were randomized to receive raloxifene 60 mg daily or placebo. All participants have a documented history of CHD, peripheral artery disease, or multiple CHD risk factors. Women who have received HT within the past 6 months are excluded. The trial will be stopped after a total of 1670 women have experienced one of the primary CHD endpoints. The results from RUTH are not expected for at least 6 years.

**HT for Prevention: Recommendations**

HT can confer both benefit and harm in postmenopausal women (Table 5). As long-term primary or secondary preventive therapy, however, the risks of HT will usually outweigh the potential benefits. It is reasonable to discuss gradual withdrawal of HT with any postmenopausal woman currently taking this therapy. If she has been taking HT for 3 years or more (when risk of breast cancer increases), efforts to discontinue therapy should become more aggressive.

The lessons learned from our investigations of HT for cardiovascular protection should be applied to our current exploration of the risks and benefits of SERMs. However promising the wider-ranging data have been, SERMs should be used according to their FDA-approved indications: tamoxifen for the treatment and prevention of breast cancer, and raloxifene for the treatment and prevention of osteoporosis.

**REFERENCES**


women in the Walnut Creek Study. Obstet Gynecol. 1987;70:289-293.


