Hormone Replacement Therapy and Coronary Heart Disease

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I. INTRODUCTION

Natural menopause usually occurs between ages 45 and 55 years and is marked by a significant reduction in hormone production by the ovaries. Levels of estrogen in postmenopausal women are decreased to about one tenth of those in premenopausal women, while progesterone becomes nearly absent. Hot flashes are a common complaint and can be severe enough to disturb sleep. More seriously, life after menopause has been associated with several chronic disease states. On average, women in the United States live approximately 30 years after menopause, and these subsequent years come with an increased risk of cardiovascular disease, coronary heart disease, osteoporosis, cancer, and dementia.1

Cardiovascular disease ranks first among causes of death in women in the United States. Indeed, the yearly mortality from cardiovascular disease in women is more than twice that from all cancers.2,3 Morbidity and mortality associated with coronary heart disease differ by gender. Although women present with symptomatic coronary heart disease at a later age than men, women exhibit a higher mortality rate and a higher rate of readmission within the first 6 months after a myocardial infarction.4 Upon presentation to the hospital with a myocardial infarction, women are less likely than men to receive therapies such as thrombolytic agents, heparin, β-blockers, aspirin, or coronary angioplasty.5

Coronary heart disease is less common in premenopausal women, and its incidence starts to increase after menopause.6 Women, on average, present with symptomatic coronary heart disease about 10 years later than men (Figure 1).7 In addition, surgical menopause (ie, bilateral oophorectomy) also confers an increased risk of cardiac events, suggesting a cardioprotective effect of female hormones.8 A delay in the occurrence of menopause is associated with a decrease in the cardiovascular mortality rate for postmenopausal women,9 but the role of estrogen in coronary heart disease of the postmenopausal state remains controversial. This manual reviews important clinical trials that have shaped current recommendations regarding the use of hormone replacement therapy (HRT) in postmenopausal women. (While the Food and Drug Administration [FDA] now uses the term postmenopausal hormone therapy in place of the term hormone replacement therapy, the latter term is used in this review.)

II. HRT AND CORONARY HEART DISEASE: OBSERVATIONAL DATA AND BIOLOGIC PLAUSIBILITY

Premenopausal women seem to be protected from cardiac events, theoretically through the effects of estrogen. This plausible explanation was reinforced by data from several observational studies conducted during the 1990s that found a 35% to 50% decreased risk of developing coronary heart disease with HRT.10–13 For example, the Nurses’ Health Study enrolled more than 48,000 healthy women and concluded that individuals taking HRT had a relative risk of 0.5 of developing cardiac events.14 In addition to evidence from observational studies, there is physiologic evidence suggesting that estrogen may have potential cardiovascular risk-modifying effects. For example, several randomized, controlled trials have shown that HRT lowers serum low-density lipoprotein cholesterol (LDL-C) levels,15 lowers lipoprotein (a) levels,16 and increases high-density lipoprotein cholesterol (HDL-C) levels.17 Direct infusion of 17β-estradiol during cardiac catheterization in women with coronary atherosclerotic heart disease has been shown to increase coronary blood flow in response to acetylcholine18 and to increase brachial-artery-flow-mediated vasodilation in postmenopausal women.19 Another randomized, controlled study demonstrated that short-term transdermal estradiol therapy significantly increased exercise time to myocardial ischemia in postmenopausal women with exertional angina.20

Based on the findings from observational studies that HRT may reduce the incidence of coronary heart disease, osteoporotic fractures, and colorectal cancer, HRT quickly became one of the most commonly prescribed drug
regimens in the United States. A 1995 survey of postmenopausal women in the United States found that nearly 35% of them used HRT. In addition to minimizing hot flashes and providing protection against osteoporosis, the proposed cardioprotection of HRT and its potential prevention of dementia fueled the popularity of this drug regimen. Indeed, medical organizations such as the American College of Physicians and American College of Obstetricians and Gynecologists previously encouraged the use of HRT for cardiovascular risk reduction as well as for other potential benefits. However, data from recent clinical trials have brought the endorsement of HRT for cardioprotection into question.

Randomized, controlled data in the past several years from both primary and secondary prevention trials have shown no decrease in rates of cardiovascular events among postmenopausal women assigned to HRT. These findings were surprising to many, given the previous observational data that suggested HRT protected women from coronary heart disease. This discrepancy illustrates the potential limitations of observational studies. In retrospect, it seems that those results were biased, with analysis correcting for socioeconomic status, coronary risk factors, and education showing no obtained benefit from HRT. It has been demonstrated that patients who are more medically compliant tend to be healthier than those who are not, producing a “compliance bias.” The study participants using HRT also were more likely to have a higher socioeconomic status and better access to health care than women who were not on HRT, leading to a potential “healthy user” bias.

III. HRT CLINICAL TRIALS

CASE VIGNETTE 1

Patient 1 is a 58-year-old postmenopausal woman who is being followed by a cardiologist for familial hyperlipidemia. She has heard that HRT is “good for the heart” and wants to know if she should be taking it. She does not have a prior history of coronary heart disease but does have diet-controlled diabetes and smokes a pack of cigarettes daily. There is no personal or family history of breast cancer.

- What evidence is there regarding use of HRT for primary prevention of coronary heart disease?

PRIMARY PREVENTION

The Women’s Health Initiative (WHI) Trial

The WHI was a landmark trial in the study of HRT and the primary prevention of cardiovascular disease.
The randomized HRT trial component of this study was designed to determine if estrogen plus progestin therapy (conjugated equine estrogen 0.625 mg/day plus medroxyprogesterone 2.5 mg/day) or estrogen alone in hysterectomized women would affect the risks of several chronic diseases, including coronary heart disease, in predominantly healthy postmenopausal women. A total of 16,608 postmenopausal women aged 50 to 79 years (average age, 63 years) were randomized to receive estrogen plus progestin or placebo. The baseline characteristics of the study participants included smokers, diabetics, and women with hypertension (11%, 4.4%, and 36%, respectively). The WHI study was designed for a follow-up of 8.5 years; however, investigators stopped the study after 5.2 years of follow-up due to an excess of adverse events. Absolute excess risks per 10,000 person-years in the treatment group were 7 more cardiac events, 8 more strokes, 8 more invasive breast cancers, and 8 more pulmonary embolisms. Absolute risk reductions were 6 fewer colorectal cancers and 5 fewer hip fractures. The total absolute excess risk of adverse events was 19 per 10,000 person-years. Although this study was stopped because the test statistic for invasive breast cancer exceeded the stopping boundary for this adverse effect with an unfavorable global risk score, there was an early increase in cardiovascular events among women in the treatment group versus the placebo group.

The WHI trial demonstrated that estrogen plus progestin replacement therapy had multiple adverse effects on cardiovascular risk factors and coronary heart disease in predominantly healthy postmenopausal women (Figure 2). First, the rate of adverse cardiovascular events (primarily nonfatal myocardial infarction) increased by 29% in the treatment group. Second, the difference in adverse cardiovascular events appeared soon after randomization (within the first year for myocardial infarction and by the second year for stroke) and persisted for the duration of the trial. The authors concluded that this trend was not likely to reverse with subsequent follow-up. Finally, there was a significant increase in stroke and venous thromboembolic events. The investigators concluded that estrogen and progestin should not be used for preventing chronic conditions in postmenopausal women.

Although the majority of WHI study participants experienced no adverse events (only 19 adverse events per 10,000 person years), total population risk remains high, and the global risk-to-benefit profile argues against the use of HRT for the purpose of preventing chronic disease states in postmenopausal women. In addition, estrogen plus progestin did not have a clinically meaningful effect on health-related quality of life. HRT also did not improve cognitive function when compared with placebo, with a small increased risk of
cognitive decline and a doubled risk of dementia.\textsuperscript{26,27} The randomized, controlled estrogen-only arm of the WHI trial for postmenopausal women who had undergone hysterectomy continues, as there was not an increase in unfavorable global risk for this group requiring early termination of the trial.

• How should patient 1 be managed?

According to the WHI trial, HRT does not reduce the risk of adverse cardiovascular events in healthy postmenopausal women. Indeed, the use of HRT in women without a prior history of cardiovascular disease resulted in a 29% increase in the rate of adverse cardiovascular events, which appeared soon after randomization and persisted for the duration of the trial (5.2 years). This patient should not be prescribed HRT for the purpose of preventing coronary heart disease. She should instead undergo traditional risk factor modifications, such as statin therapy for hyperlipidemia, blood glucose control, smoking cessation, diet, and exercise.

\textbf{PATIENT VIGNETTE 2}

Patient 2 is a 65-year-old woman who has been taking daily HRT for more than 10 years. She has diabetes, hypertension, and hyperlipidemia. She had a myocardial infarction at age 60 years and has had stable exertional angina. She seeks your advice about whether to continue taking HRT.

• What evidence is there regarding use of HRT for secondary prevention of coronary heart disease?

\textbf{SECONDARY PREVENTION}

\textbf{Heart and Estrogen/Progestin Replacement Study (HERS)}

HERS I was the first large randomized, controlled trial to determine if estrogen plus progestin therapy would provide protection from cardiac events in postmenopausal women with established coronary heart disease.\textsuperscript{28} This trial enrolled 2763 postmenopausal women with an intact uterus (average age, 66.7 years) who were randomized to receive placebo or HRT (conjugated equine estrogen 0.625 mg/day plus medroxyprogesterone 2.5 mg/day). The subjects were followed for 4.1 years, and several cardiovascular outcomes were assessed. Despite an improvement in lipid profile (11% decrease in LDL-C and 10% increase in HDL-C), there were no significant differences in the primary outcome of nonfatal myocardial infarction or coronary death between the placebo and treatment groups. In addition, there was a significant trend towards early cardiac events in the HRT group during the first year of treatment, followed by a decrease in risk in the subsequent years. There was a significant increase in other adverse events in the treatment group, such as venous thromboembolic events and symptomatic gall bladder disease.

The HERS I trial concluded that estrogen with progestin provided no cardioprotective benefit compared to placebo in the secondary prevention of coronary heart disease and was associated with an increased risk of cardiac events in the first year of therapy. With the initial HERS I data, the American Heart Association (AHA) recommended against initiating HRT for the secondary prevention of coronary heart disease.\textsuperscript{29} To determine if HRT conveyed a benefit on coronary heart disease outcomes over a longer duration of follow-up, 93% of the surviving HERS I cohort was followed for another 2.7 years in a subsequent observational study, HERS II.\textsuperscript{30} HERS II confirmed the original findings from HERS, concluding there is no benefit from HRT in reducing the risk of cardiovascular events in women with established coronary heart disease (\textbf{Figure 3}).

In summary, the HERS I trial did not demonstrate a significant difference between treatment groups in the incidence of cardiovascular events despite a beneficial effect on lipid profile. With longer follow-up in HERS II, it became evident that HRT did not reduce the risk of cardiovascular events in the secondary prevention of coronary heart disease in postmenopausal women. Finally, there was a strong trend toward an increase in risk for fatal stroke and thromboembolic events. Of note, the overall hazard ratios remained similar even after

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{Hormone replacement therapy is not beneficial for the secondary prevention of coronary heart disease. In the HERS II trial, there was no difference in adverse cardiac events between treatment groups in postmenopausal women with an established history of coronary heart disease. (Adapted with permission from Grady D, Herrington D, Bittner V, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up [published erratum appears in JAMA 2002;288:1064]. JAMA 2002;288:55.)}
\end{figure}
adjustment for inconsistent statin use in the 2 treatment groups.

**Estrogen Replacement and Atherosclerosis (ERA) Trial**

Other secondary prevention trials have provided no evidence that HRT reduces the risk of cardiac events. For example, the ERA trial randomized 309 postmenopausal women with angiographically confirmed coronary heart disease to receive estrogen plus progestin (conjugated equine estrogen 0.625 mg/day plus medroxyprogesterone 2.5 mg/day), estrogen only, or placebo.\(^\text{31}\) As with the WHI and HERS trials, hormone therapy increased HDL-C and triglyceride levels while decreasing LDL-C levels. After a follow-up period of 3.2 years, repeat coronary angiography showed no differences in the progression or regression of atherosclerosis between the placebo and treatment groups, despite the beneficial effects of HRT on lipoprotein levels. These results provided angiographic confirmation of the clinical outcomes seen in the original HERS study. HRT did not offer protection from coronary atherosclerosis in postmenopausal women with established coronary heart disease.

**Women’s Angiographic Vitamin and Estrogen (WAVE) Trial**

Similar to HRT, the consumption of antioxidant vitamins has been linked with a reduced risk of cardiovascular disease in observational studies.\(^\text{32}\) The WAVE trial enrolled 423 postmenopausal women with angiographically demonstrated coronary artery disease, who were randomly assigned to treatment with either HRT or antioxidant vitamin supplements (vitamins E and C), alone or in combination.\(^\text{33}\) In this 2 x 2 factorial designed study, serial coronary angiography demonstrated that neither HRT nor antioxidant vitamin supplementation had any effect on the progression or regression of coronary artery lesions. Instead, a potential for harm was suggested in both treatment groups, with an increased risk of major adverse cardiac events, such as death, nonfatal myocardial infarction, or stroke (hazard ratio, 1.9 [95% confidence interval, 0.97–3.6]).\(^\text{33}\)

**Estrogen in the Prevention of Reinfarction Trial (ESPRIT)**

In another trial designed to study the effects of unopposed estrogen in postmenopausal survivors of myocardial infarction, ESPRIT demonstrated that estrogen alone (2 mg estradiol valerate) was not effective in the secondary prevention of coronary heart disease.\(^\text{34}\) Two-year follow-up in this randomized, placebo-controlled trial that enrolled 1017 postmenopausal women revealed that the frequency of reinfarction or cardiac death did not significantly differ between treatment groups. However, there was low adherence to therapy in the estrogen treatment group and a substantial crossover number to hormone use in the control group. The randomized, controlled trial data on HRT in the primary and secondary prevention of coronary heart disease is summarized in Table 1.

- **How should patient 2 be managed?**

  According to the currently available data discussed here, HRT plays no role in the secondary prevention of coronary heart disease and may increase the risk of adverse cardiac events. This finding persists despite the favorable effects of HRT on lipid profiles and endothelial function. HRT should be discontinued from the medical regimen of this patient. The physician should maintain or institute traditional risk reduction methods, such as statin therapy to optimize lipoprotein levels, strict diabetes management, blood pressure control, and lifestyle modifications.

- **What are possible mechanisms for the increased risk for cardiac events seen in the HRT trials?**

  Both the HERS and WHI trials demonstrated that postmenopausal women had an increased risk of early cardiac events with HRT (in the first 2 to 3 years of initiating therapy) despite its beneficial effects on lipid profile. In both trials, HRT decreased LDL-C levels by approximately 11% to 12% and increased HDL-C by 7% to 10%. Based on these lipoprotein level adjustments alone, one would have predicted a significant reduction in the incidence of coronary heart disease. HRT also has been shown to have beneficial effects on endothelial function and increased fibrinolysis,\(^\text{35,36}\) which would imply a further decrease in cardiovascular risk.

  It seems that HRT affects the process of coronary heart disease by a variety of contrasting mechanisms. The recent recognition that HRT increases cardiac events suggests that HRT possesses other important biologic properties adversely affecting cardiovascular risk. Indeed, HRT has been associated with increased levels of triglycerides and prothrombic effects,\(^\text{15}\) and oral estrogen has been associated with increased levels of the inflammatory marker C-reactive protein (CRP).\(^\text{37,38}\) Elevated triglycerides are an established risk factor for coronary heart disease,\(^\text{39}\) and may increase risk more in women than men.\(^\text{40}\) Elevated CRP levels have been consistently associated with an increased risk for cardiac events in women, indicating that inflammation plays an important role in the pathogenesis of cardiovascular disease.\(^\text{41}\) The potential prothrombotic effects of HRT
include a decrease in antithrombin levels, a decrease in protein S levels, and an increase in coagulation factor VII. The shift toward early cardiac events during the use of HRT may be a manifestation of the acute inflammatory and prothrombotic effects of estrogen. The antagonistic effects of HRT on various risk factors for coronary heart disease are summarized in Table 2.

- What issues related to HRT are undergoing further study?

Role of Progestin

The role of progestin in cardiovascular disease remains unclear. Studies of the vascular effects of different progestins have produced conflicting results. The shift toward early cardiac events during the use of HRT may be a manifestation of the acute inflammatory and prothrombotic effects of estrogen. The antagonistic effects of HRT on various risk factors for coronary heart disease are summarized in Table 2.

Table 1. Results of Randomized Controlled Trials of HRT and Coronary Heart Disease in Postmenopausal Women

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Mean Age, yr</th>
<th>Treatment</th>
<th>Follow-up, yr</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary prevention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHI24</td>
<td>16,608</td>
<td>63</td>
<td>0.625 mg CEE + 2.5 mg MPA versus placebo</td>
<td>5.2</td>
<td>MACE: HR = 1.29 (95% CI, 1.02–1.63)</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HERS28</td>
<td>2763 (HERS); 2321 (HERS II)</td>
<td>66.7</td>
<td>0.625 mg CEE + 2.5 mg MPA versus placebo</td>
<td>6.8 (4.1 HERS, followed by 2.7 HERS II)</td>
<td>MACE: HERS HR = 0.99 (95% CI, 0.81–1.22), HERS II HR = 1.00 (95% CI, 0.77–1.29), Overall HR = 0.99 (95% CI, 0.84–1.17)</td>
</tr>
<tr>
<td>ERA31</td>
<td>309</td>
<td>65.8</td>
<td>0.625 mg CEE, 0.625 mg CEE + 2.5 mg MPA, or placebo</td>
<td>3.2</td>
<td>No significant difference in progression of angiographic coronary atherosclerosis</td>
</tr>
<tr>
<td>WAVE33</td>
<td>423</td>
<td>65</td>
<td>0.625 mg CEE + 2.5 mg MPA versus placebo</td>
<td>2.8</td>
<td>Slightly greater progression of angiographic coronary atherosclerosis with HRT, MACE: HR = 1.9 (95% CI, 0.97–3.6)</td>
</tr>
<tr>
<td>ESPRIT34</td>
<td>1017</td>
<td>62.6</td>
<td>2 mg estradiol valerate versus placebo</td>
<td>2</td>
<td>MACE: RR = 0.99 (95% CI, 0.70–1.41)</td>
</tr>
</tbody>
</table>

CEE = conjugated equine estrogen; CI = confidence interval; ERA = Estrogen Replacement and Atherosclerosis; ESPRIT = Estrogen in the Prevention of Reinfarction Trial; HERS = Heart and Estrogen/progestin Replacement Study; HR = hazard ratio; MACE = major adverse cardiac events; MPA = medroxyprogesterone acetate; RR = relative risk; WAVE = Women’s Angiographic Vitamin and Estrogen; WHI = Women’s Health Initiative.

*HERS II observational study.

Estrogen Formulations

Different estrogen formulations also may modify cardiovascular risk. The majority of primary and secondary prevention trials of HRT and coronary heart disease utilized oral conjugated equine estrogen (Table 1). Theoretically, metabolism of oral estrogen could be altered by exposure to the liver following gastrointestinal absorption. In one recent study of 21 postmenopausal women, transdermal estrogen, which avoids first-pass hepatic metabolism, did not raise CRP levels compared to oral conjugated equine estrogen. Whether this lack of increase in CRP levels ultimately affects the risk of adverse cardiac events remains unknown. Another area of uncertainty is the role of oral contraceptives in cardiovascular disease. While there may have been a small increased risk of myocardial infarction with older oral
contraceptive formulations, this effect has not been seen with the newer generations of oral contraceptives that are currently used.51 There exists, however, a small increase in risk of venous thromboembolism and ischemic stroke in users of oral contraceptive agents, especially with concurrent tobacco use and hypertension.52

Selective Estrogen Receptor Modulators (SERMs)

Selective estrogen receptor modulators represent another therapeutic approach; these non-hormonal agents exhibit estrogen-like effects on bone and the cardiovascular system but not on other tissues, such as breast and endometrium.53 Tamoxifen is a SERM used for the treatment of estrogen-receptor positive breast cancer. In the Breast Cancer Primary Prevention Trial, tamoxifen compared to placebo did not alter the risk of cardiac events in women with and without a prior history of coronary heart disease (follow-up of approximately 4 years), despite the fact that tamoxifen lowered total cholesterol levels by an average of 18 mg.54 There was, however, a substantial increase in the risk of stroke among women taking tamoxifen.

Raloxifene is another SERM that has been shown to reduce LDL-C levels55 and exhibit some estrogen-like vascular effects in vitro.55 Raloxifene lowers LDL-C levels and does not raise triglyceride, CRP, or HDL-C levels.53,56 The Multiple Outcomes of Raloxifene Evaluation (MORE) trial, designed to study raloxifene therapy in postmenopausal osteoporotic women, has shown that at 4 years follow-up, raloxifene significantly reduced the risk of cardiac events in a subset of women at high cardiovascular risk.57 Unlike estrogen, there was no trend toward increased early cardiac events. In an ongoing trial with a planned follow-up of at least 5 years, the Raloxifene Use For The Heart (RUTH) trial has enrolled 10,101 postmenopausal women with established coronary heart disease or multiple cardiac risk factors to study the effects of raloxifene on clinical outcomes.58

### Table 2. Opposing Effects of Hormone Replacement Therapy in Modulating Risk Factors for Coronary Heart Disease

<table>
<thead>
<tr>
<th>Beneficial effects</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase HDL-C</td>
<td>Increase triglycerides</td>
</tr>
<tr>
<td>Decrease LDL-C</td>
<td>Increase CRP</td>
</tr>
<tr>
<td>Improve endothelial function</td>
<td>Decrease antithrombin</td>
</tr>
<tr>
<td>Decrease fibrinogen</td>
<td>Decrease protein S</td>
</tr>
<tr>
<td>Decrease lipoprotein (a)</td>
<td>Increase factor VII</td>
</tr>
</tbody>
</table>

CRP = C-reactive protein; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

## IV. CURRENT ROLE OF HRT

### PATIENT VIGNETTE 3

A 50-year-old woman being followed for mitral valve prolapse presents complaining of hot flashes that often disturb her sleep. Her menstrual cycle has become irregular in the past several months. She has no other known health problems and does not smoke cigarettes. There is no family history of breast cancer or cardiovascular disease. Laboratory data reveal normal cholesterol levels. She has heard that hormone replacement therapy can relieve hot flashes and is seeking your advice about initiating treatment.

- **What are current recommendations regarding HRT therapy?**

As discussed in the previous section, several randomized, controlled secondary prevention trials and one well-designed primary prevention trial (Table 1) have demonstrated that HRT has no role in the protection from coronary heart disease, contrary to previous popular belief. In 2001, the AHA recommended against the use of long-term estrogen therapy for both primary and secondary prevention of coronary heart disease.29 The AHA reinforced these guidelines in 2002 with the results of the WHI and HERS II trials, stating “at the present time, there is no basis for adding or continuing estrogens in postmenopausal women with clinically evident coronary artery disease or cerebrovascular disease in an effort to prevent or retard progression of their underlying disease.”59 In addition, the US Preventive Services Task Force recommended against the routine use of estrogen and progestin for the prevention of chronic diseases in postmenopausal women (Table 3).60

Although it is possible that other estrogen or progestin preparations might not have the same negative cardiovascular effects as conjugated estrogen and medroxyprogesterone acetate, they should not be used for the purpose of primary or secondary prevention of cardiovascular disease until randomized, controlled trials
demonstrate otherwise. Although the net benefit of estrogen or combined estrogen-progestin replacement treatment in postmenopausal women remains uncertain, the WHI trial has established that there is an excess of health risks from estrogen-progestin therapy during the first 5 years of therapy.

With the publication of the results of the WHI trial, the FDA revised the labels for HRT in postmenopausal women.61 The new FDA warnings highlight the increased risks for cardiovascular disease and breast cancer and emphasize that these products are not approved for heart disease prevention and that HRT should only be used when the benefits clearly outweigh risks. The FDA also modified the approved indications for HRT, revising 2 of the 3 indications to include consideration of other therapies:

1. **Treatment of moderate to severe vasomotor symptoms associated with menopause.** These products should be used at the lowest effective dose for a short duration.

2. **Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause.** When these products are being prescribed solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.

3. **Prevention of postmenopausal osteoporosis.** When these products are being prescribed solely for the prevention of postmenopausal osteoporosis, approved non-estrogen treatments should be carefully considered, and HRT should only be considered for women at significant risk of osteoporosis that outweighs the risks of the drug.

HRT is effective in treating the vasomotor symptoms of menopause and may be appropriate for short-term use in selected patients, except in those with a history of breast cancer, coronary heart disease, previous venous thromboembolic event, or stroke. It should be noted that the average age of the women enrolled in the WHI trial was 63 years, and that most women with vasomotor symptoms of menopause are several years younger and have a lower incidence of cardiovascular disease. The patient suffering from disruptive hot flashes without risk factors for cardiovascular disease may find symptom relief from a short course, such as 2 to 3 years, of HRT.62 The FDA recommends that “If a woman and her health-care provider decide that estrogen-containing products are appropriate, they should be used at the lowest doses for the shortest duration to reach treatment goals.”63 She should be educated in the increased risks of HRT, such as stroke, venous thromboembolism, hypertriglyceridemia, and breast cancer. If an acute cardiovascular event occurs, HRT should be discontinued and should not be resumed as a strategy for secondary prevention. Given the recent data, HRT use should be avoided in postmenopausal women with established coronary heart disease. Traditional risk-reduction measures should be employed for these patients and for those with multiple risk factors for cardiovascular disease, such as smoking cessation, optimization of lipid profile, blood pressure, exercise, and weight and diabetes control.

### Table 3. USPSTF Recommendations and Clinical Considerations on the Use of HRT for Prevention of Chronic Conditions in Postmenopausal Women

| HRT should not be routinely used for the prevention of chronic diseases in postmenopausal women. |
| Evidence is insufficient to recommend for or against the use of unopposed estrogen for the prevention of chronic conditions in postmenopausal women who have had a hysterectomy. |
| Clinicians should develop a shared decision-making approach to preventing chronic diseases in postmenopausal women. |
| The USPSTF did not consider the use of HRT for the management of menopausal symptoms. |
| The quality of evidence on the benefits and harms of HRT varies for different hormone regimens. |
| Evidence is inconclusive to determine whether phytoestrogens are effective for reducing the risk of cardiovascular disease. |

HRT = hormone replacement therapy; USPSTF = US Preventive Services Task Force.


### • How should patient 3 be managed?

Many postmenopausal women suffer from intolerable hot flashes. HRT is currently indicated by the FDA for the treatment of moderate to severe vasomotor symptoms associated with menopause in postmenopausal women without a history of coronary heart disease, stroke, venous thromboembolic events, or breast cancer. HRT may be appropriate for short-term use in selected women. She should be informed of the increased risks of using HRT, such as adverse cardiac events and stroke. HRT should be discontinued permanently should an acute cardiovascular event occur.
V. SUMMARY POINTS

Coronary heart disease is the leading cause of death in US women.
The morbidity and mortality associated with coronary heart disease is higher in women than in men.
The incidence of symptomatic coronary heart disease in women increases after menopause.
Early observational studies suggested that HRT possessed cardioprotective effects. Recent randomized, controlled data have proven otherwise.
HRT increases the rate of adverse cardiac events in healthy postmenopausal women.
HRT does not reduce the risk of cardiac events in postmenopausal women with established coronary heart disease.
HRT increases the risk of fatal stroke and thromboembolism.
Progestins may attenuate the cardiovascular effects of estrogen. Randomized, controlled trials of the cardiovascular influences of estrogen-only treatment and selective estrogen receptor modulators have not yet been completed.
The effects of different formulations and doses of estrogen on cardiovascular risk remain unknown.
In the absence of contraindications, HRT may be used for the short-term treatment of moderate to severe vasomotor symptoms.
HRT should not be used for the prevention of chronic conditions in postmenopausal women. Clinicians should develop a shared decision-making approach to preventing chronic diseases in postmenopausal women.
Therapies other than HRT should be considered for the treatment of osteoporosis and vaginal atrophy.
Traditional risk reduction strategies (smoking cessation, optimization of lipid profile, blood pressure, diet, exercise, weight and diabetes control) should be used to reduce the incidence of coronary heart disease in postmenopausal women.

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