Postmenopausal Hormone Replacement Therapy
and Cardiovascular Disease

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ABSTRACT

Heart disease is the leading cause of death among postmenopausal American women. Although early observational studies suggested that hormone replacement therapy (HRT) might decrease these risks, prospective, experimental studies have not supported these results. With the recent release of these data in the media, clinicians are receiving numerous questions concerning HRT. This article reviews the current evidence and provides suggestions on how to address these inquiries.

INTRODUCTION

Historically, heart disease has been viewed as a health problem of middle-aged men, and misperceptions concerning the prevalence of cardiovascular disease among women still exist. However, cardiovascular disease is a significant health problem among women. The incidence of cardiovascular disease in men and women equals after the age of 65, and the prevalence among women exceeds that of men after the age of 75. Overall, coronary heart disease (CHD) and stroke are the leading causes of death among American women, accounting for 44.6% of all deaths in women. This figure is higher than the next four causes of female deaths combined. Also, women are more likely to die within one year following a heart attack than men. Despite these facts, it has been reported that women are expressing more concern about breast cancer than about cardiovascular disease. In reality, one of every two women will die from heart disease or stroke, whereas only one of 25 will die from breast cancer.

As a result of this high incidence, researchers are looking for interventions to decrease the morbidity and mortality associated with cardiovascular disease among women. The observation that estrogen deficiency following natural or surgically induced menopause is associated with two to three times the risk of cardiovascular disease has led researchers to investigate the use of HRT in postmenopausal women for the prevention of CHD. This paper evaluates the evidence concerning the use of HRT for this indication.

MENOPAUSE AND CARDIOVASCULAR DISEASE

The relationship between menopause and cardiovascular disease has been studied in order to determine the postmenopausal physiological changes that might contribute to this disorder. Several alterations have been noted. There is evidence that levels of total cholesterol, low-density lipoprotein (LDL)-cholesterol, and triglycerides increase after menopause while high-density lipoprotein (HDL)-cholesterol levels decline. These unfavorable changes in the plasma lipoproteins increase the risk of atherosclerosis and subsequent heart disease.

It has also been discovered that non-lipoprotein effects contribute to the development of postmenopausal CHD. For instance, decreased insulin production and insulin-receptor sensitivity have been observed in postmenopausal women. The resulting disturbance of carbohydrate metabolism is a major risk factor for CHD.

Menopause is also associated with a significant increase in the central deposition of body fat, resulting in an increased waist circumference. This pattern of body fat deposition is associated with higher triglycerides, lower HDL-cholesterol, and greater insulin resistance, all of which increase CHD risk.

It has also been hypothesized that estrogen acts directly on the vascular endothelium, resulting in increased nitric oxide and prostacyclin production and subsequent vasodilation with endothelial healing. After menopause, these protective effects are lost and increased vasoconstriction, vasospasm, and angina often ensue. Other mechanisms that have been investigated but that are not as well understood include estrogen's effects on coagulation and fibrinolytic balance.

HORMONE REPLACEMENT THERAPY

The administration of HRT has been shown to counteract many of these negative effects of menopause that increase the risk of CHD. However, the combination of hormones, dosage, and route of administration can affect the outcomes (Table 1).

Although oral estrogen monotherapy has the most favorable effect on serum lipoproteins, resulting in decreased total and LDL-cholesterol and increased HDL-cholesterol levels, it can result in increased triglyceride levels. This regimen should be used only in postmenopausal women who have undergone a partial or complete hysterectomy because of the increased risk of endometrial cancer associated with unopposed estrogen ther-
apy. It is recommended that women who have an intact uterus use combined estrogen and progestin therapy either in a continuous regimen (progestin administered daily) or in a cyclic regimen (progestin administered at established intervals). The addition of a progestin increases the activity of hepatic lipases and results in decreased HDL-cholesterol concentrations. Thus, the addition of a progestin sometimes attenuates the effect of estrogen on serum HDL-cholesterol. This effect does vary among progestins, depending on the chemical structure, androgenic activity, and the dose of the progestin. The addition of a progestin can also result in a beneficial lowering of serum triglyceride concentrations. In addition to progestins, androgens (such as methyltestosterone) can be added to the HRT regimen in order to improve energy, mood, and libido. Androgens have a negative effect on serum lipoproteins and may increase total and LDL-cholesterol and decrease HDL-cholesterol, reducing the favorable effects of estrogen supplementation.

Transdermal administration of HRT results in different effects on lipoproteins because hepatic metabolism is bypassed with this modality. Estrogen monotherapy and estrogen-plus-progestin combination patches are available. This mode of delivery can bring about modest reductions in total cholesterol and LDL-cholesterol, but it neither increases HDL-cholesterol levels nor affects triglyceride levels.

HRT also affects another lipoprotein called lipoprotein (a) (Lp(a)), which is composed of LDL-cholesterol and apo A (plasminogen). The LDL-cholesterol portion of this molecule contributes to atherosclerosis, whereas the apo A segment is associated with thrombosis. Lp(a) may provide the link between atherosclerosis and thrombosis seen with CHD, making it an independent risk factor for this disorder. Estrogen therapy, with or without progestins, consistently produces a persistent decrease in Lp(a) concentrations.

HRT is also associated with non-lipoprotein effects. Estrogen monotherapy has a favorable effect on carbohydrate metabolism, body fat distribution, and endothelial relaxation. The consequence of adding progestins or androgens is unclear.

Another option for HRT is the selective estrogen receptor modulators (SERMs). Raloxifene (Evista®, Eli Lilly) is the primary agent in this class and is used for osteoporosis prevention. In addition to its favorable effects on bone, raloxifene has been shown to decrease LDL-cholesterol, Lp(a), and fibrinogen. However, it does not have any of the favorable effects on HDL-cholesterol or plasminogen that are observed with traditional HRT.

### THE LITERATURE

Over the years, many observational studies evaluating the effects of HRT on cardiovascular risk in postmenopausal women have reported a potential benefit. Because of the limitations of an observational study design, however, questions remain concerning whether HRT is truly beneficial in preventing CHD among postmenopausal women. As a result of the self-selection of the women enrolled in these studies, these subjects are often younger, healthier, and proactive concerning their health care. These characteristics may make the results less applicable to all postmenopausal women. In response to the lingering questions, prospective, experimental studies were designed to address these concerns (Table 2).

### Transdermal Administration

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### The PEPI Trial

The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial was an experimental study primarily designed to evaluate the effect of HRT on cardiovascular disease. This randomized, double-blind, placebo-controlled trial compared estrogen monotherapy with continuous or cyclic estrogen-plus-progestin combination therapy. Two forms of progestins were assessed, medroxyprogesterone acetate (MPA) and micronized progesterone (MP). This study confirmed that all HRT therapies increased HDL-cholesterol, with the greatest increase seen in the estrogen monotherapy treatment group. The addition of either progestin decreased this effect, but MP therapy was associated with less blunting. In addition to the effects on HDL-cholesterol, all active groups experienced a decrease in LDL-cholesterol and an increase in triglycerides. Among patients receiving HRT, treatment did not affect blood pressure or postchallenge insulin levels, and decreased fibrinogen levels were observed across all HRT groups.

The PEPI trial addressed the question of how the addition of progestins to HRT affects serum lipoproteins, blood pressure, and carbohydrate metabolism. However, the endpoints assessed in this study were intermediate outcomes. Questions concerning the effect of HRT regimens on final CHD outcomes such as acute myocardial infarction (AMI), strokes, and CHD death were not addressed.

### The HERS Trials

**HERS I**

The Heart and Estrogen/Progestin Replacement Study (HERS) was an experimental trial that primarily evaluated the effect of HRT on final CHD outcomes among postmenopausal women with established cardiovascular disease (secondary prevention). Final CHD events were defined as nonfatal AMI and CHD death. Secondary outcomes included hospitalization for coronary revascularization, resuscitated cardiac arrest, unstable angina, congestive heart failure, transient ischemic attack (TIA), stroke, or peripheral arterial disease. Postmenopausal women with established coronary artery disease under the age of 80 years (mean = 66.7 years) with an intact uterus were included.

Subjects were randomly assigned to receive continuous combined estrogen and progestin (conjugated equine estrogens [CEEs] 0.625 mg/day with MPA 2.5 mg/day) or placebo and

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**Table 1**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>Lp(a)</th>
<th>Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEEs</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↑↔↓↑</td>
</tr>
<tr>
<td>Transdermal estrogens</td>
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<td>↔</td>
<td>↓</td>
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</tr>
<tr>
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</tr>
<tr>
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<td>↑</td>
<td>↓</td>
<td>↑↔↓↔</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>↓</td>
<td>↔</td>
<td>↓</td>
<td>↔↔↓↔</td>
</tr>
</tbody>
</table>

CEEs = conjugated equine estrogens; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; Lp(a) = lipoprotein a; MP = micronized progesterone; MPA = medroxyprogesterone acetate.

were observed for 4.1 years. This regimen was most likely selected because 0.625 mg of conjugated estrogens was the most common dosage used in the Nurses’ Health Study. Because women included in the HERS trial had an intact uterus, concomitant administration of a progestin was necessary to decrease the risk of endometrial hyperplasia and cancer. Continuous combined HRT with CEEs 0.625 mg and MPA 2.5 mg daily is a very common combination.

Study results showed a positive change in the serum lipoproteins among subjects receiving HRT. On average, LDL-cholesterol concentrations decreased by 14% from baseline values and HDL-cholesterol concentrations increased by 8%, both reaching statistical significance when compared with placebo. Despite these changes in serum lipoproteins, HRT showed no benefit for the prevention of cardiovascular events among women with established CHD.

Primary CHD events were similar between groups (relative hazard [RH] = .99, 95% CI, 0.80–1.22) over the four-year observation period. Further data analysis showed that the risk of a CHD event was most pronounced during the first year of HRT treatment (RH = 1.52) but decreased every year afterward (RH = 0.67 in years four and five). The number of deaths from other causes, including cancer, was similar between groups. The rate of venous thrombosis was higher in the HRT group (RH = 2.89, 95% CI, 1.50–5.58), and there was an increased incidence of gallbladder disease (RH = 1.38, 95% CI, 1.00–1.92). The incidence of breast, endometrial, or other cancers, as well as fractures, was similar between groups.

The HERS I trial had a few limitations. Physicians were allowed to initiate medications for the treatment of dyslipidemia during the study period, and more women in the placebo group received statins than did women in the HRT group. When the study was concluded, a trend showing decreased CHD risk was apparent among subjects receiving HRT for three to four years, and it was unknown whether this trend would persist. Investigators continued the trial in HERS II to address these questions.

**HERS II**

The HERS II trial was a continuation of the HERS trial. It was designed like the previous study except that, after the initial four years, the HERS II trial was not double-blinded; it was an open-label, unblinded study. Subjects were randomly assigned to receive either HRT (CEEs and MPA) or no HRT at the discretion of their personal physicians. The women were monitored for an additional 2.7 years to evaluate whether the reduced cardiovascular disease risk observed in the first four years continued or not.

### Table 2 Summary of Prospective, Experimental Trials

<table>
<thead>
<tr>
<th>Trial (Yr)</th>
<th>Interventions</th>
<th>Sample/Duration</th>
<th>Endpoints</th>
<th>Summary of Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 2,763</td>
<td>Placebo</td>
<td>4.1 yr</td>
<td>NF-AMI CHD Death</td>
<td>HRT did not reduce the rate of CHD in women with established CAD</td>
</tr>
<tr>
<td>n = 2,321</td>
<td>CEEs 0.625 mg + MPA 2.5 mg q.d.</td>
<td>2.7 yr</td>
<td>NF-AMI CHD Death</td>
<td>HRT did not reduce the rate of CHD in women with established CAD</td>
</tr>
</tbody>
</table>

**CAD** = coronary artery disease; **CEE** = conjugated equine estrogens; **CHD** = coronary heart disease; **CVA** = cerebrovascular accident (stroke); **DVT/PE** = deep vein thrombosis and pulmonary embolism; **HDL-C** = high-density lipoprotein-cholesterol; **HERS** = Heart and Estrogen/Progestin Replacement Study; **HRT** = hormone replacement therapy; **MORE** = Multiple Outcomes of Raloxifene trial; **MP** = micronized progesterone; **MPA** = medroxyprogesterone acetate; **NF-AMI** = nonfatal acute myocardial infarction; **PEPI** = Postmenopausal Estrogen/Progestin Interventions trial; **RAL** = raloxifene; **SBP** = systolic blood pressure; **SERM** = selective estrogen receptor modulator; **TIA** = transient ischemic attack; **WHI** = Women’s Health Initiative.
cultural risk that had been observed after year one in the HERS trial would be maintained with continued therapy. Most of the HERS subjects (93% of those surviving) re-enrolled for continued monitoring in the HERS II trial.24

The results of the HERS II trial demonstrated that the trend showing decreased risk did not persist with continued therapy. No difference in cardiovascular risk existed between groups observed in HERS II (RH = 1.00, 95% CI, 0.77–1.29). The combined data from both trials supported these findings (RH = 0.99, 95% CI, 0.84–1.17). During the HERS II study, the data were adjusted for potential confounders, including statin use. This did not alter the results, and no differences were found between groups (RH = 0.97, 95% CI, 0.82–1.14).24

Summary of HERS I and II

The results of the HERS and HERS II trials22,24 suggest that treatment with daily, continuous combined CEEs and MPA provides no protection from secondary cardiovascular events among women with established cardiovascular disease over a 6.8-year period. Because of the transient increase in the risk of CHD events during the first year of therapy, followed by the absence of continued benefit, initiation of CEEs 0.625 mg/day and MPA 2.5 mg each day is not recommended for the sole indication of CHD protection.24

These two studies provided valuable information concerning the use of HRT for the prevention of postmenopausal CHD. It is important to note that these studies were not powered to detect a difference in cancer rates, fracture rates, or total mortality between the groups studied. Because the study population consisted of postmenopausal women with established CHD who were not using HRT, it did not address whether HRT would be beneficial among healthy postmenopausal women who did not have CHD.22,24

The WHI Trial

The Women’s Health Initiative (WHI) is a long-term, prospective, experimental study that addresses the use of HRT for the primary prevention of CHD among healthy, postmenopausal women. Data collection was recently suspended in the continuous combined HRT group (CEEs 0.625 mg/day with MPA 2.5 mg each day) after 5.2 years, and the results of this arm were published early; however, the estrogen monotherapy arm is still ongoing. Data were released early from the combined HRT arm because of evidence that the risks were outweighing the benefit for these subjects. This arm of the study included 16,608 postmenopausal women with an intact uterus who were between ages 50 and 79 (mean = 63.3 years). Subjects were randomly assigned to one of three groups: raloxifene 60 mg/day, 120 mg/day, or placebo. The CHD outcome measures included coronary events (i.e., AMI, unstable angina, or coronary ischemia) and cerebrovascular events (i.e., stroke or TIA).26

Results indicated no difference in CHD risks between groups for the women receiving raloxifene 60 mg/day (RR = .86, 95% CI, 0.64–1.15) or 120 mg/day (relative risk [RR] = .98, 95% CI, 0.74–1.30). However, a subset analysis indicated that among subjects with an increased risk of CHD at baseline level, CHD risk was significantly decreased with both doses of raloxifene when compared to placebo (RR = .60, 95% CI, 0.38–0.95). No increase in cardiovascular risk was detected among treatment groups at any point in time during the study.26

These results suggest that treatment with raloxifene 60 to 120 mg/day had no effect on primary prevention of CHD among postmenopausal women with osteoporosis but did show benefit in decreasing CHD among women with increased CHD risks. Because these endpoints were secondary outcomes, these results should be confirmed with an experimental study designed and powered to evaluate CHD risk as a primary outcome.26

SUMMARY

Prospective, experimental trials do not support the benefit of continuous combined HRT therapy for the primary or secondary prevention of CHD that had been suggested with earlier observational studies.

In the HERS, HERS II, and WHI trials, only one regimen of HRT was evaluated, medroxyprogesterone acetate (Prempro®, Wyeth-Ayerst), which included the progestin MPA. It is known that although it is necessary to add a progestin to a regimen in patients with an intact uterus to decrease the risk of endometrial
cancer, progestins attenuate the benefits of estrogen. In the PEPI trial, MPA was shown to offset the beneficial effects of estrogen more than the other progestin (MP) that was studied in this trial. It is not clear whether the results observed in these studies can be applied to all combined HRT therapies, including low-dose HRT regimens that include other progestins and other HRT dosage forms.

It has yet to be resolved whether estrogen monotherapy will be beneficial for the prevention of CHD among women who have had a hysterectomy and do not require progestin. This estrogen monotherapy arm of the WHI trial is still ongoing, and results should be available in three years. These data should provide more information on the benefit of estrogen monotherapy for the primary prevention of CHD. The usefulness of this regimen for the secondary prevention still needs to be evaluated.

Finally, the results of the MORE trial look promising for the CHD benefit of raloxifene among women with an established risk for CHD development, but these results require verification in future studies.

In the meantime, it is advisable not to recommend the use of continuous CEE and MPA combination therapy solely for primary or secondary prevention of CHD. Individualized patient recommendations must be made on the basis of the known benefits and the risks of HRT. The established benefits of HRT include effective control of menopausal symptoms, a decreased risk of osteoporotic fractures, and a decreased risk of colon cancer. The potential risks of HRT include a significant increase in thromboembolic disease and a possible increased risk of breast cancer. Clinicians must make individualized recommendations based on these data and patient-specific characteristics, including medical and family history.

CONCLUSION

Patient-specific characteristics and evidence-based medicine will determine who will benefit from HRT. Although there are theoretical reasons to expect decreased CHD risk with HRT, based on current evidence, HRT should not be recommended for primary and secondary CHD prevention. For women with cardiovascular risks, clinicians should focus on interventions that have proved effective to decrease CHD risks. These include smoking cessation, weight management, and exercise. Clinicians should also carefully screen for, monitor, and treat concomitant disease states known to increase CHD risks such as dyslipidemia, diabetes mellitus, and hypertension.

REFERENCES