

Hormone Replacement Therapy: An Update

INTRODUCTION

Nearly half (43%) of all American women die of cardiovascular (CV) disease.¹ For this reason, the long-term effects of hormone replacement therapy (HRT) have been the subject of debate for decades. Although early epidemiologic data may have suggested a CV benefit for HRT users in addition to bone density preservation, the results of randomized controlled trials such as the Heart and Estrogen/Progestin Replacement Study (HERS) and the Women's Health Initiative (WHI) demonstrated different findings. The HERS (1998) was the first analysis to suggest that combined estrogen/progestin therapy does not impart cardiovascular benefit. It included postmenopausal women with established heart disease who utilized conjugated equine estrogen (CEE) and medroxyprogesterone (MPA) and found that in the first year of treatment these women were at increased risk of coronary heart disease (CHD) events. This analysis was carried out an additional 2.7 years in the HERS II trial (2002) to examine the long-term CHD effects of combined CEE+MPA. Investigators found with additional HRT treatment women with established CHD still did not have a reduced rate of CHD events. Additionally, these women were at increased risk of venous thromboembolism. This information caused the investigators to conclude, "postmenopausal HRT should not be used to reduce the risk for CHD events in women with CHD," which led to the question, "What of women without CHD?" The WHI study (2002) addressed this question and included healthy postmenopausal users of CEE and MPA. The well-publicized results of the WHI indicated that CEE+MPA users were at increased risk for CHD, as well as thromboembolic events and breast cancer. Although the CEE+MPA arm of the trial was halted, use of CEE alone was studied further and was found to have no effect on CHD incidence, but a higher incidence of stroke.

It is important to note that the mean age of participants in the HERS, HERS II, and WHI was in the mid 60s. This raises the concern that

these results may not apply to treatment begun earlier in menopause. In the WHI CEE alone arm, younger women (50-59) appeared to respond more favorably than older women in several of the outcomes. Further analysis by the investigators is ongoing. The table below lists the statistically significant outcomes of both arms of the WHI.

	CEE+ MPA	CEE alone
CHD events	7 more cases	-
Breast cancer	8 more cases	-
Strokes	8 more cases	12 more cases
PE	8 more cases	-
Hip fractures	5 fewer cases	6 fewer cases
Colorectal cancer	6 fewer cases	-

¹Risk associated in each year if 10,000 women were to take placebo and 10,000 women were to take CEE+MPA

²Risk associated in each year if 10,000 women were to take placebo and 10,000 women were to take CEE alone

This analysis found no difference in all-cause mortality.

WHI SUMMARY

1. Continuous combined CEE+MPA should not be initiated or continued for prevention of heart disease. Continuous CEE alone had no effect on CHD incidence in postmenopausal women.
2. The increased risk of breast cancer appeared after 4 years of CEE + MPA use. Women who used combined HRT before entering the study were more likely to develop breast cancer, suggesting cumulative use of HRT puts women at greater risk.
3. Continuous CEE alone may have an adverse effect on cognition in postmenopausal women age ≥ 65 years.
4. Continuous combined CEE + MPA and CEE alone both had beneficial effects in the prevention of hip fracture.
5. Continuous combined CEE + MPA had positive benefits in preventing colorectal cancer.

6. It is uncertain whether the results of this analysis apply to other estrogen/progestin combinations. These results may not apply to lower doses or different formulations of these drugs. However, clinicians should be aware of the potential for other estrogen/progestin combinations to also cause adverse effects.
7. The estrogen-only arm of the WHI stopped one year early due to an increase risk of stroke (HR 1.39 (95%CI 1.10-1.77)). Unopposed estrogen is only appropriate for women who have had a hysterectomy.
8. HRT is effective for treating menopausal symptoms and for this indication estrogen alone appears to be superior. However, even estrogen alone is not without adverse effects. The current HRT recommendation is that the lowest dose be used for the shortest duration of treatment.

QUESTIONS TO ASK

1. Should HRT be initiated in this patient?

-What are the real benefits?

HRT shows positive benefit in the prevention of hip fracture and colorectal cancer; it also is an effective treatment for the symptoms of menopause.

2. What are the risks of short term and long term therapy?

-Short-term therapy. The WHI and the HERS trials found increased risk of myocardial infarction and venous thromboembolism in the first 12 months of HRT therapy. The WHI found increased risk of stroke between 1 and 2 years of therapy. The benefits of therapy for even 2-3 years to manage the symptoms of menopause still carries risk; however, benefits may outweigh risks in individual patients.

-Long-term therapy. The HERS II and WHI found that CEE + MPA is of no value in reversing established coronary heart disease or preventing CHD in apparently healthy women. In addition, therapy longer than 4 years carries the additional risk of breast cancer.

3. Is there a safer way to attain the desired benefits?

-If the patient is being prescribed HRT solely for the prevention of cardiovascular disease, therapy should be discontinued, or not initiated.

-If prescribed for osteoporosis prevention or treatment of menopausal symptoms consider alternative therapies.

4. Should HRT discontinuation be attempted?

-It depends upon the duration of treatment and the possibility of achieving desired benefits by other means

ALTERNATIVE THERAPIES

Osteoporosis Prevention

1. Address modifiable risk factors (i.e. physical inactivity, smoking, excessive alcohol consumption, drug causes).
2. Recommend elemental calcium 1200 mg + vitamin D 400 IU daily.
3. Consider the use of non hormonal therapies such as bisphosphates [alendronate *Fosamax*®, risedronate *Actonel*®] and selective estrogen receptor modulators [raloxifene *Evista*®] for the prevention of osteoporosis in high-risk patients.

Treatment of Vasomotor Symptoms

1. Clonidine. Moderately effective for the treatment of vasomotor symptoms. Common adverse effects include orthostatic hypotension, dry mouth, constipation, and drowsiness.
2. Antidepressants. Fluoxetine *Prozac*® 20mg QD, venlafaxine *Effexor*® 12.5mg BID, paroxetine *Paxil*® 10-20mg QD, and sertraline *Zoloft*® 25-50mg QD have been shown to decrease vasomotor symptoms.
3. Lifestyle changes. Encourage lifestyle habits that will decrease vasomotor symptoms, such as sleeping in a cool room, avoiding foods that aggravate warmth, and dressing less warmly.

Treatment of Genitourinary Symptoms

1. Non-hormonal vaginal moisturizers. Simple vaginal lubricants and moisturizers are available over the counter.
2. Vaginal hormonal therapy. Estrogen creams offer local treatment of urogenital symptoms with less risk of systemic hormonal effects. Since these agents can have a systemic effect, progestin therapy may be required.

Prevention and treatment of cardiovascular disease

1. Address lifestyle behaviors (i.e. smoking cessation, regular exercise, maintenance of appropriate weight).
2. Prevent and control elevated blood pressure.
3. Prevent and control elevated cholesterol.
4. Manage diabetes.

TAPERING METHODS

Tapering these agents can take several months.

1. Lowering the dose. Gradually decrease the patient's dose of HRT. The lower dose can be used for several weeks. If lower doses produce menopausal symptoms, the dose should not again be adjusted until the patient is tolerating the current dose.
2. Decreasing the frequency. Gradually decrease the number of days each week the patient takes HRT. Again, if symptoms return, dosage adjustment should not be performed until the patient tolerates the current dose of HRT.
3. Combination method. Additionally, you can lower the dose and decrease the frequency of HRT concurrently.
4. Patch. This is any easy way of decreasing the weekly estrogen content of the patient's HRT. Each week small amounts of the patch can be cut off, so that lesser amounts are applied. It is important to note that not all patches can be cut, and the manufacturer has not tested this form of dosing. The following patches are probably suitable for cutting: Climara®, Fempatch®, and Vivelle®.

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