AHA Science Advisory

Hormone Replacement Therapy and Cardiovascular Disease
A Statement for Healthcare Professionals From the American Heart Association

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For more than 50 million American women, and millions of women in other countries who are over the age of 50 years, the decision whether or not to use estrogen replacement therapy (ERT) for chronic disease prevention is often a difficult one. Established benefits of treatment for menopausal symptoms and prevention of osteoporosis must be weighed against documented risks of therapy, including venous thromboembolic events (VTE), gallbladder disease, and a possible increased risk of breast cancer. Unopposed ERT is also associated with an increased risk of endometrial cancer in women with a uterus. Therefore, it is typically combined with a progestin and is referred to as hormone replacement therapy (HRT). The impact of ERT/HRT on cardiovascular disease (CVD) is of great public health importance, because CVD is the leading cause of death and a major contributor to disability in women.[1] The purpose of this advisory is to summarize the currently available data concerning potential CVD benefits and risks associated with ERT/HRT and to provide updated clinical recommendations regarding its use in the secondary and primary prevention of CVD.

Biological Basis for a Role of ERT in CVD

Mendelsohn and Karas[2] recently reviewed the physiological effects of estrogen on the cardiovascular system. Briefly, cardiovascular cells, as well as reproductive tissues, bone, liver, and brain, express both of the known estrogen receptors, estrogen receptor-α (ER-α) and estrogen receptor-β (ER-β). These receptors are important targets for endogenous estrogen, ERT, and pharmacological estrogen agonists. Estrogen–estrogen receptor complexes serve as transcription factors that promote gene expression with a wide range of vascular effects, including regulation of vasomotor tone and response to injury, that may be protective against development of atherosclerosis and ischemic diseases. Estrogen receptors in other tissues, such as the liver, may mediate both beneficial effects (eg, changes in apoprotein gene expression that improve lipid profiles) and adverse effects (eg, increases in gene expression of coagulation proteins and/or decreases in fibrinolytic proteins). Two general estrogen-mediated vascular effects are recognized. Rapid, transient vasodilation occurs within a few minutes after estrogen exposure, independently of changes in gene expression.[2] This rapid vasodilation appears to be due to the novel ER-α–mediated activation of the endothelial nitric oxide synthase enzyme, but it is of unclear physiological significance. Longer-term effects of estrogen on the vasculature, such as those related to limiting the development of atherosclerotic lesions or vascular injury, occur over hours to days after estrogen treatment and have as their hallmark alterations in vascular gene expression. Progesterone and other hormonal receptors are also expressed in the vasculature, although their role in the development of CVD is poorly defined. At present, the sum clinical impact of the genomic and nongenomic effects of ERT/HRT is uncertain. As the molecular mechanisms responsible for the effects of estrogen are further elucidated, therapies may evolve that optimize the benefits of estrogen therapy while minimizing the risks.

In addition to potentially beneficial vascular effects of ERT, well-established lipid alterations associated with oral ERT include favorable reductions in low-density lipoprotein (LDL) cholesterol and lipoprotein(a) and increases in high-density lipoprotein (HDL) cholesterol.[3,4] When ERT is combined with medroxyprogesterone acetate (MPA), there is attenuation of the beneficial HDL-raising effect. This attenuation is decreased when ERT is combined with natural progesterone.[3] Oral ERT increases triglyceride levels $\approx$20%, although the clinical significance of this has not been established.[3]

The effects of ERT/HRT on several more recently recognized risk markers for CVD have been reviewed.[5] Fibrinogen, plasma viscosity, plasminogen activator inhibitor-1, tissue plasminogen activator, insulin sensitivity, homocysteine, and markers of platelet aggregation and endothelial cell activation

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are favorably affected by estrogen therapy. Moreover, estrogen inhibits intimal hyperplasia and smooth muscle migration, promotes angiogenesis, and has antioxidant properties. However, HRT increases C-reactive protein levels, which suggests a possible proinflammatory effect.[6] Increases in factor VII, prothrombin fragments 1 and 2, and activated protein C resistance and a decrease in antithrombin III are also seen.[5] Although these effects might adversely affect the development of CVD, the clinical relevance of the impact of HRT on these markers is not known. In general, the majority of surrogate end-point data support a positive role of ERT/HRT in the prevention of CVD, although enhanced CVD risk is also biologically plausible.

Should HRT Be Used in Women With Established CVD?

The Heart and Estrogen/progestin Replacement Study (HERS) was specifically designed to test the hypothesis that treatment with conjugated equine estrogen (CEE) 0.625 mg/d plus MPA 2.5 mg/d would reduce the combined incidence of nonfatal myocardial infarction (MI) and coronary heart disease (CHD) death compared with placebo in women with prior history of MI, coronary revascularization, or angiographic evidence of CHD.[7] This was the first large-scale randomized clinical-outcome trial of HRT for prevention of CHD in postmenopausal women. After an average of 4.1 years of follow-up, there was no difference in the primary outcome of nonfatal MI and coronary death between the hormone and placebo arms. A post hoc time-trend analysis revealed a significant 52% increase in cardiovascular events (42.5/1000 person-years versus 28.0/1000 person-years) in the first year in the HRT group compared with placebo, with a nonsignificant trend toward fewer events in the treatment arm compared with placebo in later years (23.0/1000 person-years versus 34.4/1000 person-years).

Numerous explanations have been proposed for the overall null effect of HRT in HERS. These include inadequate duration of follow-up, adverse effects of MPA, bidirectional effects of estrogen (early risk and late benefit), a population of women too old to benefit from therapy (average age was 66.7 years), a preparation of HRT that was not ideal, chance, or that HRT is ineffective in preventing recurrent cardiovascular events in women with established disease.[8] A long-term follow-up of the HERS cohort may provide additional information about the role of HRT in secondary prevention.

The Estrogen Replacement and Atherosclerosis (ERA) Trial, the first randomized angiographic end-point trial to test the effect of ERT and HRT on the progression of atherosclerosis in postmenopausal women with documented coronary stenosis, showed no benefit of CEE 0.625 mg/d combined with MPA 2.5 mg/d on angiographic progression of disease, lending support to the HERS findings.[9] The ERA Trial also included an estrogen-only arm that showed no angiographic benefit compared with placebo, which suggests that the null result of HRT was not due to adverse effects of MPA. The generalizability of these findings has been questioned because of the relevance of angiographic end points, the drug regimen, the older age of the participants (mean of 65.8 years), and the length of time since menopause before

Ongoing Studies of HRT and CHD

Angiographic End-Point Trials
- Estrogen and Bypass Graft Atherosclerosis Regression Trial (EAGER)
- Women's Lipid Lowering Heart Atherosclerosis Trial (WELLHART)
- Women's Atherosclerosis Vitamin/Estrogen Trial (WAVE)

Primary prevention
- Women's Health Initiative (WHI)
- Women's International Study of long Duration Oestrogen after Menopause (WISDOM)

Secondary prevention
- HERS Follow-up Study
- EStrogen in the Prevention of ReInfarction Trial (ESPRIT)

ERT/HRT was instituted (mean of 23.1 years).[10] Although previous observational studies using angiographic end points showed a consistent inverse association between ERT/HRT use and the extent of coronary atherosclerosis, these studies were not prospective and randomized in design.[11] The discordance between these findings and the ERA results could be due to differences in populations, drug regimens, duration of therapy, extent of CHD, levels of cholesterol, and other preventive care. Alternatively, nonrandomized studies may have overestimated a benefit of HRT due to a "healthy-user" effect in women who receive such therapy. Ongoing prospective angiographic studies (Table) will provide additional data regarding the effect of HRT on the progression of coronary disease. Recently, a single-center trial of postmenopausal women with increased intimal-medial thickness showed that 48 weeks of treatment with 17-β estradiol (with or without gestodene) had no effect on the progression of carotid intimal-medial thickness despite significant beneficial effects on LDL cholesterol and fibrinogen.[12]

These data suggest no overall cardiovascular benefit and a possible early increased risk of CVD events when HRT is initiated in women with documented atherosclerosis. Several limitations inherent in the conduct and analysis of clinical trials affect the interpretation of these results. Examples include the relatively short duration of treatment, nonadherence with study medication (more women discontinued HRT than placebo in HERS, but the data were analyzed by intention to treat), and the fact that the results may not be generalizable to different HRT formulations or populations that differ from the study participants. Follow-up data from HERS are awaited to assess any potential for a longer-term effect of HRT in secondary prevention of CHD.

It has been suggested that the results of completed secondary prevention trials may not be applicable to younger women; however, it is less common for cardiovascular events to occur before women are in their 60s. Also, it is possible that ERT/HRT regimens other than those tested, such as lower doses of ERT, different preparations of estrogen or progestin, or different routes of delivery, might be beneficial for secondary prevention of CHD. Lastly, it has been hypothesized that if women were given HRT early after menopause, it might be possible to prevent the development of CHD more easily than to prevent its progression once established.

Unfortunately, no controlled data are available that address the timing of initiation of therapy on rates of CVD.

Should HRT Be Used for Primary Prevention of CHD?

Results are not yet available from ongoing large-scale controlled trials of ERT/HRT for primary prevention. Therefore, the quality of data available to guide decisions regarding HRT use for primary prevention is less than that available for secondary prevention. The majority of observational epidemiological studies that examined the role of ERT/HRT in women without established CHD have consistently demonstrated a lower incidence of CHD events among users versus nonusers. A recent meta-analysis showed an approximate 35% reduction in CHD events among users of ERT alone, with similar results observed for HRT.[13] The consistency of the data and the magnitude of benefit observed in these studies lend support to a role of HRT in the primary prevention of CHD; however, bias cannot be ruled out.

Although epidemiological studies have the advantage of examining the effect of therapy over a longer duration of time than is typical of a randomized clinical trial, several forms of bias inherent in observational designs have been reviewed recently.[14] Women who are prescribed HRT are often healthier than nonusers (selection bias). Monitoring and treatment may be more intensive for women taking HRT (prevention bias). Adherence to taking a medication on a regular basis (even if it is a placebo) is associated with significant survival benefit (compliance bias). HRT may be stopped because of illness, leading to misclassification as a nonuser, artificially reducing the risk among women categorized as users (survivor bias). Finally, early adverse effects of HRT may not be observed if susceptible women have died and are not part of the cohort (prevalence-incidence bias).

Randomized controlled trials are designed to overcome many of these types of bias. Ongoing trials (Table) may soon provide additional data to help guide recommendations regarding the use of HRT for primary prevention of CHD. Until these studies are completed, clinicians will have to rely on evidence from basic science, epidemiology, and results from trials in secondary prevention to make recommendations regarding the use of HRT for the primary prevention of CHD. The Women's Health Initiative, which includes a large-scale randomized trial of HRT, and a similar study in Europe (WISDOM) were initiated because there was enough evidence to believe there might be a benefit of HRT in primary prevention, yet enough uncertainty that it was ethical to randomize half of the participants to placebo.[15] Similarly, there is neither a compelling reason to initiate ERT/HRT in a woman for the sole purpose of primary CHD prevention nor a compelling reason to discontinue it if she is doing well with therapy. The decision to use HRT should be based primarily on the proven benefits of ERT/HRT on other systems and on the potential risks of therapy, as well as patient preference.

Are There Adverse Cardiovascular Effects Associated With ERT/HRT?

One meta-analysis of 22 randomized trials before 1997 that compared HRT with placebo, no therapy, or vitamin/minerals in predominantly healthy postmenopausal women showed no overall cardioprotective effect of therapy.[16] There was a nonsignificant 39% increase in cardiovascular events. Although the 2.89-fold (95% CI 0.34 to 24.8) increase in the risk of VTE was not significant, it is consistent with other population-based, nonrandomized studies and with the data from HERS. Because the data were generated from small-scale studies examining various HRT preparations, and because assessment of CVD events categorized as adverse events may not have been systematic, these results have to be confirmed in larger, randomized studies.

The Coronary Drug Project, a randomized trial conducted between 1966 and 1974 in men with documented MI, compared 2 doses of estrogen (2.5 and 5.0 mg/d) versus placebo and provided an opportunity to evaluate estrogen for secondary prevention in men.[17] A reanalysis of data from the Coronary Drug Project showed a significant increase in primary CHD events at 0 to 4 months (relative hazard 1.58, 95% CI 1.04 to 2.40).[18] This early increase in risk in men paralleled a similar time frame analyzed for the HERS trial, which showed a nonsignificant 2.3-fold increased risk for HRT versus placebo (relative hazard 2.29, 95% CI 0.94 to 5.56). Both studies documented an increased risk of thromboembolic events and gallbladder disease.

To assess the risk of CVD events in women without existing CVD who were treated with HRT, the Group Health Cooperative examined the association of new use of HRT with risk of first MI in a population-based case-control study.[19] The odds ratio for MI was nonsignificant at 1.39 (95% CI 0.52 to 3.72) among new users of HRT (<6 months) compared with nonusers. A pattern of significant reduction in risk with increased time since initiation of therapy was evident. The odds ratio was 0.66 (95% CI 0.47 to 0.92) for initiation of therapy >4 years before the index date. A follow-up study revealed that among women with hypertension, the risk of MI was increased nearly 11-fold among women who were current users of HRT and had a prothrombin variant (20210 G to A) compared with a wild-type genotype.[20] This finding suggests that screening for genetic susceptibility to thrombosis in certain subgroups of women may provide enhanced assessment of the benefits and risks of HRT.

The Women's Health Initiative has informed participants that among predominantly healthy women randomized to ERT alone (CEE 0.625 mg/d) or HRT (CEE 0.625 mg/d plus MPA 2.5 mg/d), there was an early increased risk of cardiovascular events compared with women randomized to placebo.[21] In the first 2 years of the trial, there was the anticipated excess of VTE but also an excess of MI and stroke that was not expected (Jacques Rossouw, MD, personal communication, 2000). The difference between the treatment and placebo groups appeared to diminish over time, and the trial is ongoing. The absolute percentage of women who experienced any of these early CVD events was <1%.

Data regarding HRT and the primary prevention of stroke risk have been reviewed recently and are not conclusive.[22] The majority of studies have had neutral outcomes, including the recently analyzed HERS data, which provided no evidence that HRT has a significant effect on the overall risk for

stroke among postmenopausal women with coronary artery disease.[23] A nonsignificant increase in the risk for fatal stroke (relative hazard 1.61, 95% CI 0.97 to 3.55) was seen. A recent report from the Nurses' Health Study suggested an increased stroke risk associated with a dose of CEE of ≥0.625 mg/d (with or without progestin) but not with lower doses.[24,25] Results from the first double-blind, placebo-controlled trial among postmenopausal women with established cerebrovascular disease, the Women's Estrogen for Stroke Trial (WEST), suggested estrogen was not effective for preventing recurrent stroke or death. In addition, women randomized to estrogen had a significant increase in the risk for fatal stroke and more severe neurological impairments after stroke.[25]

In the HERS trial, the rate of VTE was increased nearly 3-fold in the HRT group compared with placebo.[26] Risk for VTE was increased 5-fold in the first 90 days after MI, even after adjustment for hospitalization. Because ERT and immobilization may be associated with hypercoagulable states, it may be prudent to discontinue HRT during hospitalization for an acute coronary event or to ensure that appropriate measures for VTE prophylaxis are used during the period of immobilization, although data are limited. No large-scale randomized trials with clinical end points have examined the short-term effect of HRT in acute coronary syndromes or after revascularization procedures. In a preliminary report using registry data, ERT use was associated with reduced in-hospital mortality after MI; however, selection bias cannot be ruled out to explain the observation.[27]

Are There Alternatives to HRT?

Selective estrogen-receptor modulators (SERMs) bind to estrogen receptors with high affinity and exhibit estrogen-agonist effects in bone and on lipoproteins and estrogen-antagonist effects on the breast and endometrium. Although SERMs have shown beneficial effects on some surrogate markers of CVD, it is not known whether this will translate into a clinical benefit. The Raloxifene Use for The Heart (RUTH) trial is currently testing the impact of the SERM raloxifene on cardiovascular end points in >10 000 women.[28]

Soy phytoestrogens have shown beneficial effects on endothelium-dependent vasodilation and the development of atherosclerosis in nonhuman primates,[29] but recent data in healthy postmenopausal women failed to show improvements in lipoprotein levels or endothelial function after 8 weeks of treatment with isoflavones (80 mg/d).[30] Clinical end-point data from well-conducted trials are not available to make recommendations concerning use of soy for prevention of CVD.

What Are Accepted Preventive Strategies for CHD in Postmenopausal Women?

The American Heart Association and the American College of Cardiology recently published recommendations for the management of CHD risk factors in women with and without existing CHD.[31] Lifestyle approaches, including smoking avoidance, proper nutrition, and regular exercise, are indicated in all women. Lipid lowering and blood pressure control with pharmacotherapy are indicated in women who do not meet target lipid or blood pressure levels with lifestyle interventions. For women with CHD, antiplatelet agents or

(when indicated) anticoagulants, β-blockers, and ACE inhibitors should also be considered unless there are contraindications to therapy. Widespread underutilization of established preventive therapies has been documented in women; these interventions should be emphasized in clinical practice. A recent survey by the American Heart Association in 1000 randomly selected women found that 90% of women wanted to discuss prevention with their doctor but 70% had not.[32] In that study, only 8% of women identified heart disease and stroke as their greatest health concern, which could impede preventive efforts. Physicians should focus on educating women about CVD risk and should uniformly apply proven CHD risk-reduction therapies with established benefits in women.

Summary Recommendations for HRT* and CVD

Secondary Prevention

- HRT should not be initiated for the secondary prevention of CVD.
- The decision to continue or stop HRT in women with CVD who have been undergoing long-term HRT should be based on established noncoronary benefits and risks and patient preference.
- If a woman develops an acute CVD event or is immobilized while undergoing HRT, it is prudent to consider discontinuance of the HRT or to consider VTE prophylaxis while she is hospitalized to minimize risk of VTE associated with immobilization. Reinstitution of HRT should be based on established noncoronary benefits and risks, as well as patient preference.

Primary Prevention

- Firm clinical recommendations for primary prevention await the results of ongoing randomized clinical trials.
- There are insufficient data to suggest that HRT should be initiated for the sole purpose of primary prevention of CVD.
- Initiation and continuation of HRT should be based on established noncoronary benefits and risks, possible coronary benefits and risks, and patient preference.

*The majority of data available to make clinical recommendations are based on standard doses of oral CEE/MPA. Evidence is insufficient to determine whether different preparations, routes of delivery, doses, or different progestins have a more favorable or more adverse effect on clinical CVD end points.

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