

Women's Ischemic Syndrome Evaluation Current Status and Future Research Directions Report of the National Heart, Lung and Blood Institute Workshop October 2–4, 2002

Section 4 Lessons From Hormone Replacement Trials

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The WISE workshop was convened to review results from the Women's Ischemic Syndrome Evaluation (WISE) study and other studies of ischemic heart disease to examine the nature and scope of gender differences in both chronic and acute cardiac ischemia, in terms of clinical manifestations, detection, and treatment. This section addresses the current knowledge base and research needs with regard to the role of hormone replacement therapy (HRT) in women with known ischemic heart disease and women at risk for ischemic heart disease.

Pathology and Pathophysiology

Many potential benefits of ovarian hormones (in particular, estrogen) on the cardiovascular system have been identified, including antiatherogenic and vasodilator actions.¹ In animal models, conjugated equine estrogen (CEE) augments endothelium-mediated dilation and delays progression of atherosclerosis.² Estrogen acutely increases coronary blood flow in response to acetylcholine in postmenopausal women.³ The mechanism accounting for this appears to involve a rapid nongenomic but plasma membrane estrogen receptor–dependent action via cytosolic signaling systems, such as the mitogen-activated protein kinase cascade.⁴ Endogenous ovarian hormones ap-

pear to modulate peripheral vasoreactivity, as it has been shown that endothelial function varies during the menstrual cycle. Estrogen prolongs the exercise time to the onset of myocardial ischemia in postmenopausal women with coronary disease.⁵ Data on the vascular actions of progestins are scant, less clear, and more complex because the effects of the interaction with estrogen must be taken into account.

Estrogen activates coagulation pathways, as evidenced by increased factor VII antigen and activity, increased indices of thrombin generation and activity, and decreased levels of inhibitors of thrombin generation and activity.⁶ On the other hand, estrogen increases fibrinolytic activity by reducing levels and activity of plasminogen activator inhibitor-1.⁷ The net effect of oral HRT is procoagulant, as evidenced by the 2- to 3-fold increase in venous thromboembolism seen both in observational studies and in clinical trials.

C-reactive protein levels have been shown to be predictors of future coronary events, both in patients with acute coronary syndromes and in middle-aged men and women without evidence of coronary disease. Estrogen increases C-reactive protein levels,⁸ a mechanism that may contribute to the excess in adverse vascular events associated with HRT.

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Clinical Application and Evidence

Women With Known Coronary Artery Disease

In the Heart Estrogen/progestin Replacement Study (HERS), 2763 postmenopausal women with documented coronary disease were randomized to CEE 0.625 mg/d plus conjugated medroxyprogesterone acetate (MPA) 2.5 mg/d or placebo and were followed up for 4.1 years.⁹ No difference was seen for the primary end point of coronary death and nonfatal myocardial infarction (MI), but in the first year an excess of coronary events was present in the active HRT group. Extensive post hoc analyses did not identify any subgroup of HERS participants in whom HRT was clearly beneficial or harmful,¹⁰ although women with high lipoprotein(a) levels may have obtained benefit and women with lower levels harm.¹¹ Long-term follow-up of the HERS population revealed no benefit of extended therapy,¹² with an increased risk of venous thromboembolism and biliary tract surgery and statistically nonsignificant increases in breast cancer and total mortality.¹³

In the Estrogen Replacement and Atherosclerosis (ERA) trial, 309 women with coronary disease were randomized to estrogen, estrogen plus MPA, or placebo.¹⁴ Coronary arteriography was done at baseline and after a mean follow-up of 3.2 years, and progression of coronary atherosclerosis was assessed by quantitative methods. No differences were found among the 3 groups for changes in minimum lumen diameter, which was the primary end point, or for any of the other angiographic or clinical end points.

In the Women's Angiographic Vitamin and Estrogen (WAVE) trial, 423 women with coronary disease were randomized to estrogen alone for patients with a hysterectomy, estrogen plus MPA for women with an intact uterus, or to corresponding placebo.¹⁵ Women were also randomized to vitamin C and E supplements or to vitamin placebos. Coronary arteriography was done at baseline and after a mean follow-up of 2.8 years, with progression of atherosclerosis assessed by quantitative methods. The primary outcome was annualized change in minimum lumen diameter averaged for each patient, with the worst rank of coronary lesion change imputed to women who died or experienced an interim MI. For the primary outcome, the risk was increased in women assigned to active HRT.

Two trials have assessed the effects of 17 β -estradiol on carotid intima-media thickness. In the Estrogen in the Prevention of Atherosclerosis Trial (EPAT), 222 postmenopausal women were randomized to 2 years of treatment with micronized 17 β -estradiol or to placebo. Among these women with elevated LDL cholesterol but no preexisting coronary disease, treatment with 17 β -estradiol reduced the rate of progression in carotid intima-media thickness.¹⁶ On the other hand, the Postmenopausal Hormone Replacement against Atherosclerosis (PHOREA) trial found no effect of 17 β -estradiol combined with either of 2 doses of a progestin on carotid intima-media thickness in a study of 321 postmenopausal women followed up for 1 year.¹⁷

The Papworth HRT and Atherosclerosis Survival Enquiry (PHASE) included 255 postmenopausal women with coronary disease randomized to transdermal 17 β -estradiol with or

without cyclic norethisterone.¹⁸ The trial was stopped early because of the likelihood that it would not show benefit. The primary end point of death, MI, or unstable angina occurred more often in the hormone group (hazard ratio 1.29; 95% CI 0.84 to 1.95).

In a small trial of postmenopausal women with unstable angina, neither CEE alone nor CEE + MPA reduced the incidence of myocardial ischemia as detected by Holter monitoring or the incidence of clinical events during 6 months of follow-up.¹⁹

Women Without Known Coronary Artery Disease

The Women's Health Initiative Estrogen + Progestin trial randomized 16 608 postmenopausal women with intact uteri to CEE 0.625 mg/d with MPA 2.5 mg/d or placebo.²⁰ The trial intervention was halted in July 2002 in accordance with the recommendation of the data safety monitoring board due to an excess of invasive breast cancer among women assigned to HRT (HR 1.26; 95% CI 1.00 to 1.59). The prespecified primary outcome was a composite of nonfatal MI and coronary death, for which an increase was observed among women assigned to HRT (HR 1.29; 95% CI 1.02 to 1.63). This risk was particularly prominent in the first year of treatment (HR 1.78), and was similar among the 97% of women without and the 3% with known coronary disease.

The Women's Health Initiative estrogen-alone trial randomized 10 739 women with prior hysterectomy to CEE or placebo. The trial is ongoing.

Selective estrogen receptor modulators are nonhormonal agents that bind with high affinity to estrogen receptors and may exhibit either estrogen-agonistic or estrogen-antagonistic effects, according to the target tissue. There are no completed clinical trials of selective estrogen receptor modulators with primary cardiovascular outcomes; however, a randomized trial with cardiovascular outcomes (Raloxifene Use for The Heart [RUTH]) in 10 101 high-risk postmenopausal women is underway.

Section 4 Recommendations

1. *Determining the cause of the early increase in cardiovascular events after initiation of HRT is identified as a research priority.* HRT therapy is effective in controlling menopausal symptoms such as hot flashes and will continue to be used for this purpose, even though it is now clearly not indicated for protection against cardiovascular events. Identification of a susceptible subset of women or of a concomitant treatment that would prevent the excess incidence of cardiovascular events would allow HRT to be used safely.
2. *Clinical trials of formulations and routes of delivery of HRT other than oral CEE with MPA are worthy of consideration.* For example, some experimental data suggest that transdermal estrogen may not induce the harmful effects of CEE and that progesterone may be safer than MPA. The use of surrogate intermediate end points for such trials is appealing; however, surrogate end points have been misleading in past HRT trials.
3. *Further research into the apparent beneficial effects of endogenous estrogen is clearly indicated.* Endogenous estrogen appears to afford cardiovascular protection to premenopausal women, and estrogen exhibits a wide

variety of cardiovascular physiological benefits. The disparity between these data and the results of clinical trials suggests that key pieces of knowledge are lacking.

4. *The message that HRT is not useful for cardiovascular protection and should not be used except for the short-term control of menopausal symptoms should be delivered to healthcare professionals and patients.* A component of this message should be that the absolute risk of a bad outcome in an early postmenopausal woman without known coronary disease already taking HRT is low.
5. *The message that HRT is not useful should be coupled with the strong message that the risk of coronary events in women with and without vascular disease can be reduced by other means.* For example, statins and angiotensin-converting enzyme inhibitors reduce coronary events in high-risk women with and without coronary disease. Diet and exercise should be the foundation of a national strategy to combat the high prevalence of obesity in postmenopausal women.

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