
Postmenopausal hormone therapy and atherosclerotic disease

Several lines of evidence suggest that estrogen is an important determinant of cardiovascular risk in women. Epidemiologic data document low rates of coronary heart disease (CHD) in premenopausal women, a narrowing of the gender gap in CHD mortality after menopause, and elevated risk of CHD among young women with bilateral oophorectomy not treated with estrogen. Nearly all of the more than 30 observational studies of exogenous estrogen replacement therapy have indicated a reduced risk of CHD among women receiving estrogen therapy. In a meta-analysis comparing estrogen users and nonusers, the estimated reduction of CHD among users was 44%. In angiographic studies, women taking estrogen were less likely to have coronary artery stenosis. Estrogen is known to affect a wide range of physiologic processes that may have an impact on CHD risk. Use of oral estrogen has favorable effects on serum lipid profiles; it increases high-density lipoprotein cholesterol levels by 10% to 15% and decreases low-density lipoprotein cholesterol levels by a similar magnitude. Other proposed mechanisms include inhibition of endothelial hyperplasia, reduced arterial impedance, enhanced production of prostacyclin, increased insulin sensitivity, and inhibition of oxidation of low-density lipoprotein. Nevertheless, the role of hormone replacement therapy in preventing clinical atherosclerotic events in women remains inconclusive because of the absence of randomized trial data. The benefit-to-risk ratio must be reliably assessed, because estrogen has complex actions, including postulated benefits (CHD, osteoporosis, and menopausal symptoms) and postulated risks (endometrial cancer, breast cancer, and gallstones). Furthermore, the addition of a progestin, which is commonly given to protect the endometrium, may attenuate the lipid benefits of estrogen; the benefit-to-risk ratio of such a combined regimen is even less certain. The Women's Health Initiative, a recently launched large-scale randomized trial of estrogen, estrogen-progestin, and placebo, as well as other ongoing randomized trials, will provide invaluable information to aid postmenopausal women in making the complex decision about whether to take hormone replacement therapy. (AM HEART J 1994;128:1337-43.)

JoAnn E. Manson, MD, DrPH *Boston, Mass.*

Coronary heart disease (CHD) remains the leading cause of death in postmenopausal women; at least one third of all deaths in women in the United States are attributable to CHD. Because CHD has predominated as a cause of death in postmenopausal women, the benefit-to-risk ratio of hormone replacement therapy (HRT) will be strongly influenced by the effect of these hormones on cardiovascular events.

This article reviews the literature on the relationship of noncontraceptive hormone therapy to atherosclerotic disease, including proposed biologic mechanisms.

Evidence from several sources suggests that estrogen is an important determinant of cardiovascular risk in women. Epidemiologic data document low rates of CHD in premenopausal women, a narrowing of the gender gap in CHD mortality after menopause,¹ and elevated risk of CHD among young women with bilateral oophorectomy not treated with estrogen.² In addition, mounting data suggest that women who use estrogen replacement therapy after menopause have lower rates of CHD.^{3,4} The importance of understanding the effects of HRT on biologic processes and on quality of life is underscored by the fact that currently, in most developed countries, at least one third of a woman's life is spent in the postmenopausal period.

From the Division of Preventive Medicine and the Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School.

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Reprint requests: JoAnn E. Manson, MD, DrPH, Brigham and Women's Hospital, 900 Commonwealth Avenue East, Boston, MA 02215.

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BIOLOGIC MECHANISMS

Lipid and lipoprotein effects. Although several biologic mechanisms have been proposed to support a role for estrogen in preventing CHD, the best-established mechanism is a favorable influence of estrogen on the lipid profile. In studies among postmenopausal women, unopposed estrogen has been demonstrated to reduce serum levels of low-density lipoprotein (LDL) cholesterol and raise high-density lipoprotein (HDL) cholesterol levels.⁵⁻⁸ Walsh et al.⁸ found that a regimen of 0.625 mg/day of oral conjugated estrogen increased HDL levels by an average of 16% and reduced LDL levels by an average of 15%; other forms of oral estrogen had generally similar effects. A review by Bush and Miller⁵ of earlier studies supported a 10% increase in HDL levels and a 4% decrease in LDL levels with this regimen. Only oral administration of estrogen (not transdermal or other nonoral routes) results in these lipid alterations, which are induced by delivery of estrogen to the liver via the portal vein. Such beneficial lipid changes could translate into large reductions in coronary risk, because a 1 mg/dl increase in HDL is estimated to decrease CHD risk by 3%, and a 1 mg/dl decline in LDL may confer a 2% risk reduction.^{9,10}

The influence of a combined estrogen and progestin HRT regimen on the lipid profile is controversial and less well studied. In current practice, a progestin is often prescribed for women with a uterus to reduce or eliminate the excess risk of endometrial cancer resulting from unopposed estrogen. Although data are limited, it appears that progestin itself may raise LDL levels and lower HDL levels,^{4,5} thus possibly attenuating the benefits of estrogens on the lipid profile. However, combined estrogen-progestin regimens appear to produce net reductions in LDL and elevations in HDL cholesterol levels, although the magnitude of these lipid alterations may be smaller than with estrogen alone. Miller et al.⁶ found that cyclical progestin added to estrogen blunted the estrogen-induced increase in HDL levels by approximately 14% to 17% but had little effect on the reduction of LDL levels. In another trial,¹¹ HDL increased by 13.7% among women who received 0.625 mg of estrogen plus placebo for 1 year but increased by only 4.3% among those given estrogen plus 5 mg of cyclic medroxyprogesterone. In a trial with 0.625 mg of estrogen and 2.5 mg of medroxyprogesterone, HDL levels increased by 8.7%.¹² The effect of progestins on lipids appears to depend on their type, dose, and pattern of use.⁴ The 17-nortestosterone progestins appear to have a more adverse effect on lipid profiles than the more commonly prescribed medroxyprogesterone.¹³

Estrogen increases plasma triglyceride levels, apparently by increasing hepatic synthesis of very low density lipoprotein (VLDL) triglycerides.^{8,14} In some¹⁵⁻¹⁷ but not all¹⁸ studies, combined estrogen and progestin therapy was not associated with elevated triglyceride levels. Although a role of progestin in increasing clearance or decreasing synthesis of VLDL and triglycerides has been proposed,^{19,20} further research is needed to document that a combined regimen does not adversely influence VLDL and triglyceride levels. Moreover, the role of VLDL and triglyceride alterations in the origin of atherosclerotic disease in women requires further elucidation.

Recent evidence suggests that estrogen, as well as combined estrogen-progestin, may favorably influence lipoprotein(a) [Lp(a)] levels.^{15,21} Lp(a), a recently identified marker for atherosclerotic disease, appears to be largely genetically determined and resistant to most forms of environmental modification.²² The findings from a randomized trial that a combined hormone regimen reduces Lp(a) levels²¹ is encouraging but requires confirmation from larger clinical trials. Furthermore, it remains uncertain whether modification of Lp(a) levels will translate into changes in the risk of atherosclerotic events. Further data on the effect of estrogen and combined estrogen-progestin on lipid and lipoprotein levels will be provided by the Postmenopausal Estrogen/Progestin Intervention Trial (PEPI). (Results of PEPI were reported at the annual meeting of the American Heart Association in November 1994 but were not available in time for inclusion in this article.)

Direct effects on the vasculature. HRT may confer cardioprotection through mechanisms other than inducing favorable changes in lipoproteins. Some studies have suggested that only 25% to 50% of the risk reduction observed with estrogens are attributable to lipid alterations.^{23,24} Estrogen receptors are present in the muscularis of arteries; accumulating evidence from both animal and human studies indicates that estrogen may directly affect the vasculature and improve blood flow.²⁵ Postmenopausal women treated with transdermal estradiol for 6 weeks were found to have decreased arterial impedance and reduced vascular tone in uterine arteries.²⁶ Estrogen therapy for 2.5 months was associated with improved hemodynamic parameters measured by Doppler echocardiography of the aorta, including peak flow velocity, mean acceleration, and ejection time.²⁷ In a study that used Doppler ultrasonography to measure the pulsatility index (impedance to blood flow) in the internal carotid artery, significant reductions in impedance were observed among women treated with transdermal estradiol for 9 weeks.²⁸ Other proposed

effects on the vasculature include calcium-channel antagonistic effects,²⁹ increased production of prostacyclin in the vascular endothelium,³⁰ and decreased production of thromboxane A₂ by platelets.³⁰

Effects on hemostatic factors. The influence of estrogen and a combined regimen on coagulation factors and thrombosis is controversial. In a recent observational study, current hormone users (either estrogen alone or a combined regimen) had lower levels of fibrinogen and antithrombin III than nonusers.¹⁵ Levels of factor VII and protein C were elevated in users of estrogen alone compared with levels in nonusers, but they were not altered in users of estrogen with progestin. Although an association between factor VII levels and estrogen alone has also been observed in clinical trials,³¹ the influence of hormone therapy on hemostatic factors and thrombogenesis remains unclear and requires further study.

Other mechanisms. The influence of noncontraceptive estrogens on carbohydrate metabolism is uncertain, despite evidence that oral contraceptives may adversely influence glucose tolerance. In a recent observational study, lower fasting insulin levels (suggesting increased insulin sensitivity) and glucose levels were observed among hormone users (either estrogen alone or a combined regimen) than among nonusers, after adjusting for age, body mass index, and other variables.¹⁵ Similarly, lower levels of insulin and no evidence of impairment in glucose tolerance were reported among estrogen users as compared with nonusers in another observational study.³² In a large-scale prospective study, no increase in the incidence of non-insulin-dependent diabetes mellitus was observed among estrogen users relative to nonusers.³³

Antioxidant properties of estrogen and combined estrogen-progestin regimens have been proposed,³⁴ including inhibition of the modification and uptake of LDL cholesterol into atherosclerotic lesions.³⁵ Although estrogen has been associated with reduced blood pressure in some clinical trials,³⁶ such a benefit remains inconclusive. These potential protective mechanisms require further study.

ANIMAL STUDIES

Animal studies of HRT tend to support benefits in the prevention of atherosclerotic disease. In a randomized trial of ovariectomized monkeys fed an atherogenic diet, the extent of coronary atherosclerosis among monkeys given estrogen was only half as great as in those given placebo; a combination of estrogen and progesterone produced similar protection despite the absence of beneficial effects on lipoproteins.³⁷ Female rabbits fed diets high in cholesterol

and treated with hormones had one third the aortic accumulation of cholesterol as untreated rabbits; these findings could be only partially explained by differences in cholesterol levels.³⁵

Animal studies also document beneficial effects of hormone therapy on the vasculature. Infusion of the coronary arteries of ovariectomized monkeys with acetylcholine produced arterial constriction in monkeys without estrogen replacement but no constriction (and actually minimal dilation) of the arteries in those given estrogen.³⁸ In a study of dogs, estrogen produced hyperpolarization of the coronary vascular smooth muscle membrane.³⁹

EPIDEMIOLOGIC STUDIES

Estrogen replacement therapy. The epidemiologic literature strongly supports an inverse association between estrogen use and risk of clinical coronary events. However, nearly all the available research is observational and few studies have assessed the combined estrogen-progestin regimen. Thus available data primarily address the role of oral conjugated estrogen, generally at a dose equivalent to 0.625 mg to 1.25 mg daily.

A meta-analysis by Stampfer et al.³ that included 30 epidemiologic studies (16 prospective, six population-based case-control, five hospital-based case-control, and three cross-sectional using angiography) yielded a relative risk of 0.56 (95% confidence interval [CI], 0.5 to 0.61) for estrogen users compared with nonusers (Fig. 1). Reduced risks among estrogen users were observed for all study designs except hospital case-control studies, which may be most susceptible to bias because of difficulties in the selection of valid controls. The summary relative risk from the angiographic studies,^{24, 40, 41} which compared women who had coronary stenosis with those who did not have coronary stenosis, suggested substantial risk reduction with estrogen use (relative risk = 0.41; 95% CI, 0.34 to 0.5).³ Prospective studies with internal controls^{1, 23, 42-53} produced a summary relative risk of 0.58 (95% CI, 0.48 to 0.69). In the large-scale Nurses' Health Study,⁵⁴ which included 48,470 postmenopausal women during 10 years of follow-up, the multivariate relative risk was 0.56 (95% CI, 0.4 to 0.8). A meta-analysis by Bush⁵⁵ produced results similar to the meta-analysis by Stampfer. A recent meta-analysis by Grady et al.⁴ (Table I) estimated a relative risk of 0.65 for those who had ever used estrogen therapy versus those who had never used estrogen therapy, and similar risk reductions were observed for fatal and nonfatal coronary disease.

Combined estrogen-progestin regimens. Data on the effect of combined estrogen-progestin therapy on

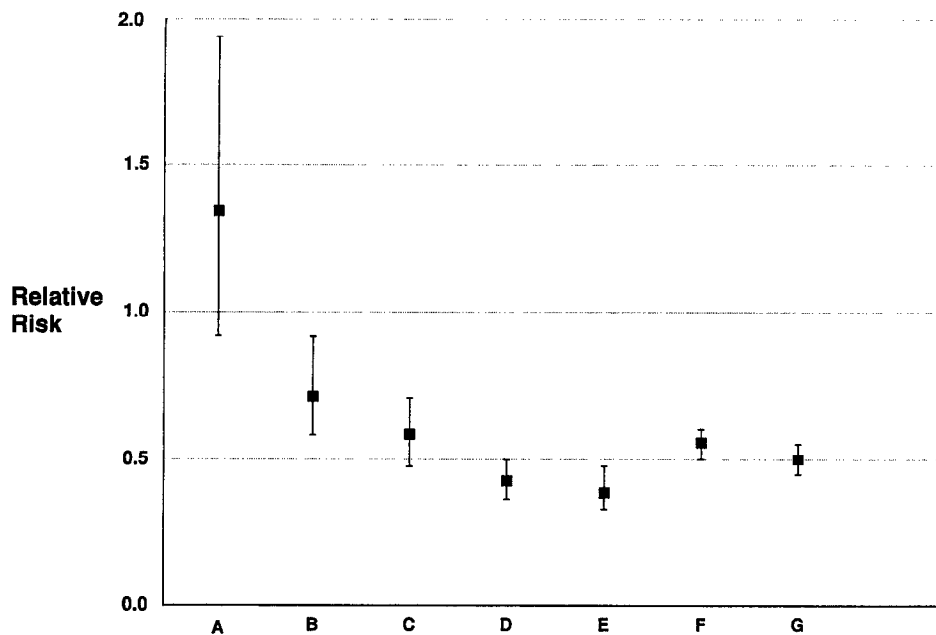


Fig. 1. Summary relative risks and 95% CI estimates for studies of estrogen use and risk of coronary disease by study design. There was significant ($p < 0.001$) heterogeneity by study design. **A**, Hospital case-control studies; **B**, population case-control studies; **C**, prospective/internal control studies; **D**, cross-sectional studies; **E**, prospective/external control studies; **F**, all studies combined; **G**, prospective internal control studies and cross-sectional studies combined. (Modified from Stampfer MJ, Colditz GA. *Prev Med* 1991;20:47-63.)

CHD risk are relatively sparse, because the addition of a progestin was uncommon during the time period in which most of the epidemiologic studies were conducted. Current knowledge of the effect of the dose of progestin and the specific regimen used (i.e., cyclic versus continuous) is also limited. To date, only four studies have provided data on the relationship between estrogen-progestin therapy and clinical CHD events in women.^{44, 56-58} In a small, randomized, controlled trial of 168 women,⁴⁴ those taking estrogen plus a progestin had a nonsignificantly reduced risk of CHD (relative risk = 0.3). Estrogen-progestin therapy was beneficial in one uncontrolled cohort study performed in the United Kingdom,⁵⁶ but another British study, which used a population-based case-control design, yielded null results.⁵⁷ However, compounds other than conjugated estrogen were used by a substantial number of women in both of these studies. The only controlled, prospective cohort data derive from a study of women in Sweden⁵⁸; women who took an estradiol-levonorgestrel combination of HRT had a 50% reduction in the risk of myocardial infarction (relative risk = 0.5; 95% CI, 0.28 to 0.8). In women who used estrogen alone, this risk was 0.74 (95% CI, 0.61 to 0.88). In their meta-analysis,⁴ Grady et al. estimated a range of 0.65 to 0.8 for the relative

risk of CHD associated with combined estrogen-progestin therapy (see Table I).

Stroke. Evidence concerning hormone therapy and stroke is more limited than that for CHD. In contrast to studies of estrogen therapy and CHD, where the epidemiologic evidence is strong and consistent, the evidence in relation to stroke is weak and inconsistent.⁴ Approximately 15 studies have evaluated hormone therapy and risk of stroke in women; a pooled estimate⁴ of the relative risk of stroke among estrogen users in a meta-analysis was 0.96 (95% CI, 0.82 to 1.13). In the Nurses' Health Study cohort,⁵⁴ the relative risk for stroke was 0.97 (95% CI, 0.65 to 1.45) despite a relative risk of 0.56 for CHD among estrogen users. No information is available on the effect of combined estrogen-progestin therapy on the risk of stroke. Although it is biologically plausible that hormone therapy would reduce risk of CHD but not stroke in view of the pathogenetic differences between these conditions, further research to corroborate these findings is required.

BENEFIT-TO-RISK ANALYSES

Because HRT has complex actions and affects a number of organ systems, the "bottom line" is the overall benefit-to-risk ratio and influence on quality

of life of these treatment regimens in postmenopausal women. Estrogen replacement therapy, which has been more extensively studied than combined regimens, has both postulated benefits (CHD, osteoporosis and menopausal symptoms) and postulated risks (endometrial cancer, breast cancer and gallstones). The addition of a progestin protects the endometrium but may attenuate the lipid benefits of estrogen; effects on breast cancer are at least as uncertain as for estrogen. Because of the predominance of CHD as a cause of death in postmenopausal women, the influence of these hormones on CHD risk will sway the balance in any benefit-to-risk assessment.

Several benefit-to-risk analyses have been proposed on the basis of available data.^{4, 59} Goldman and Tosteson⁵⁹ presented an analysis of current estrogen use in relation to 10-year cumulative mortality risks for women 65 to 74 years of age (Table II). Because of the postulated 40% reduction in CHD, the overall benefit-to-risk ratio strongly favored estrogen use. These analyses, however, did not address the combined estrogen-progestin regimen. A more recent benefit-to-risk analysis⁴ addressed the most plausible estimates for estrogen and a range of plausible estimates for combined estrogen-progestin (see Table I). Again, hormone therapy appeared to have a favorable benefit-to-risk ratio, predominantly because of presumed benefits in the prevention of CHD. Neither analysis accounted for effects of hormone therapy on quality of life.

Risk stratification analyses, which take into account a woman's baseline level of risk for various conditions, provide valuable information to aid the individual and her physician in making a decision about hormone therapy. Grady et al.⁴ have performed analyses of available evidence that provide estimates of the net change in life expectancy associated with hormone therapy in subgroups of women with varying risk-factor status (Table III). The investigators concluded that the optimal candidates for HRT (i.e., those likely to experience the greatest increases in life expectancy) are women with a history of heart disease or those at increased risk for CHD (estimated prolongation of life with estrogen therapy was 2.1 and 1.5 years, respectively). In contrast, women least likely to have prolongation of life are those at increased risk of breast cancer (Table III).

CONCLUSIONS AND DIRECTIONS FOR FUTURE RESEARCH

At present, the evidence that HRT prevents CHD is strong but inconclusive. Evidence in support of a benefit derives primarily from epidemiologic studies

Table I. Relative risk of selected conditions for a 50-year-old white woman treated with long-term hormone replacement

Condition	Relative risk*	
	Estrogen therapy	Estrogen plus progestin
CHD	0.65	0.65-0.8
Stroke	0.96	0.96
Hip fracture	0.75	0.75
Breast cancer	1.25	1.25-2
Endometrial cancer	8.22	1

From Grady D, Rubin SM, Petitti DB, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med* 1992;117:1016-37. Reproduced with permission.

*"Best" estimates of the relative risk for developing each condition in long-term hormone users compared with nonusers.

Table II. Ten-year cumulative mortality risks for women 65 to 74 years of age

Disease	% Absolute risk	ERT % relative risk reduction/increase	ERT % absolute risk reduction/increase
CHD	6.0	↓40	↓2.40
Breast cancer	1.0	↑30	↑0.30
Hip fracture	0.6	↓60	↓0.36
Uterine cancer	0.4	↑60	↑0.24

Data from analyses by Goldman L, Tosteson ANA. *N Engl J Med* 1991;325:800-2.

ERT, Estrogen replacement therapy.

and small-scale trials of estrogen on intermediate endpoints such as lipids. Because nearly all the available epidemiologic evidence concerning hormone therapy and cardiovascular disease has been observational, bias cannot be excluded as an explanation for at least some of the CHD benefit observed. In these studies, it is the participants and their physicians who decide whether to initiate HRT. In most studies, women who use hormone therapy tend to have healthier life-style practices, fewer comorbid health conditions, and more regular contact with their physicians.^{4, 60} Despite control for many of these factors, residual confounding by these and other variables cannot be excluded in observational studies.

Conclusive evidence on the role of HRT in the prevention of cardiovascular events will emerge only from comprehensive, randomized, controlled clinical trials among postmenopausal women. The Women's Health Initiative, a recently launched large-scale, randomized trial, will assess estrogen, estrogen-progestin, and placebo in relation to risks of CHD, breast

Table III. Net change in life expectancy for a 50-year-old white woman treated with long-term hormone replacement

Variable	Life expectancy (yr)	Net change in life expectancy (yr)		
		Estrogen	E + P*	E + P†
No risk factors	82.8	+0.9	+1.0	+0.1
With hysterectomy	82.8	+1.1		
With history of CHD	76.0	+2.1	+2.2	+0.9
At risk for CHD	79.6	+1.5	+1.6	+0.6
At risk for breast cancer	82.3	+0.7	+0.8	-0.5
At risk for hip fracture	82.4	+1.0	+1.1	+0.2

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E + P, Estrogen plus progestin.

*Assuming that the addition of a progestin to the estrogen regimen does not alter any of the relative risks for disease seen with estrogen therapy, except to prevent the increased risk of endometrial cancer (relative risk for endometrial cancer estimated to be 1.0).

†Assuming that the addition of a progestin to the estrogen regimen provides only two thirds of the coronary heart disease risk reduction afforded by estrogen therapy (relative risk for coronary heart disease estimated to be 0.8) and relative risk for breast cancer in treated women is 2.0.

cancer, osteoporotic fractures, and other major endpoints, as well as quality of life. Invaluable data will also derive from other ongoing clinical trials, including the PEPI and the Heart Estrogen Replacement Study. Important questions remain to be answered about the magnitude of the apparent reduction in CHD with hormone therapy, the role of a combined estrogen-progestin regimen, the influence of hormone therapy on quality of life, and the overall benefit-to-risk ratio of hormone therapy in postmenopausal women. These randomized trials should help to answer these questions and thereby aid postmenopausal women in making the complex decision about whether or not to take HRT.

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