Hormone Replacement Therapy and Risk of Cardiovascular Disease
Implications of the Results of the Women’s Health Initiative

Lewis H. Kuller

Abstract—The higher rates of coronary heart disease (CHD), stroke, and venous thrombosis among women taking estrogen and progesterone (E+P) compared with placebo in the Women’s Health Initiative clinical trial have important implications for women’s health. Previous studies in both men and women have shown that estrogen therapy lowers low-density lipoprotein cholesterol and raises high-density lipoprotein cholesterol. The changes in these lipoproteins should be associated with at least a 30% decline in CHD risk. Estrogens increased very-low-density lipoprotein (VLDL) triglyceride levels and C-reactive protein. There is evidence that estrogens increase thrombin generation and fibrinolysis. The increase in VLDL triglycerides may enhance thrombotic risk as well as higher levels of atherogenic lipoproteins, such as dense low-density lipoprotein. Genetic variations in estrogen receptors and thrombosis or fibrinolysis may also be important in risks associated with E+P therapy. The increased risk of CHD and stroke with E+P therapy may be attributable to rise in VLDL triglycerides and thrombosis. (Arterioscler Thromb Vasc Biol. 2003;23:●●●●●●.)

Key Words: coronary heart disease ■ hormones ■ estrogen ■ stroke ■ clinical trials

The recent report of the results of the Women’s Health Initiative has important implications for interpreting the etiology and prevention of cardiovascular disease among women.1 After a mean of 5.2 years of follow-up, the estrogen and progesterone (E+P) versus placebo arm of the trial was stopped because of adverse effects. A global index statistic suggested that there were greater risks than potential benefits of E+P. The likelihood of benefit of E+P, even if the study had continued for 3 to 4 more years, was extremely low. The estimated hazards ratio for coronary heart disease (CHD) was 1.29 (1.02 to 1.63 with 286 cases), for stroke was 1.41 (1.07 to 1.85 with 202 cases), and for pulmonary embolism was 2.13 (1.39 to 3.25 with 101 cases). There was also an excess risk of breast cancer and CHD was the same1 (Table 1).

The adverse effects of E+P for cardiovascular disease were present across all age groups, including women who were in the early postmenopausal age group (ie, 50 to 59 years). The increase in myocardial infarction (MI) and stroke was, primarily, for nonfatal incident events. The increase in MI began within the first year, and the increase in stroke began within the first 2 years.

The increase in CHD in the Women’s Health Initiative was similar to recent longer-time follow-up results of the Heart and Estrogen Replacement Study (HERS) in secondary prevention.2 Recent studies evaluating whether estrogen alone or E+P could reduce the progression of coronary artery stenosis or carotid intima medial wall thickness have also shown little benefit of hormone therapy3–5 (Table 1).

This increase in risk of stroke and CHD was surprising given that at the end of the first year, low-density lipoproteins (LDLs) had decreased by 12.7% in the E+P group compared with placebo and that high-density lipoproteins (HDLs) had increased by 7.3%. If one assumes an ≈2% reduction in CHD for every 1% decline in LDL cholesterol (LDLc) and an ≈2% to 3% decrease for every 1% increase in HDL, then one would have anticipated an ≈30% to 35% reduction in the incidence of CHD based only on change in lipoprotein levels.6,7 There are other mechanisms that also suggest that estrogen or E+P therapy should reduce the risk of CHD, including effects on endothelial function and increased fibrinolysis7-8 (Table 2).

The reduction in LDLc with estrogen therapy has been noted for both men and women.9 The increased risk of CHD for estrogen therapy was noted many years ago in the coronary drug project among men who had prior CHD.10 The doses of estrogen (5 or 2.5 mg) for men were much higher than for women in the Women’s Health Initiative, 0.625 mg of Premarin,11,12

In the Breast Cancer Primary Prevention Trial, Tamoxifen lowered total cholesterol by an average of 18 mg compared with placebo.13 There was no difference in the incidence of

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CHD after a mean of 47 months in women with a prior history of CHD and 49 months in women without history of CHD. There was a substantial increased risk of stroke among the women taking Tamoxifen, especially those older than age 50 years. In neither the Women’s Health Initiative nor the Breast Cancer Prevention Trial was there any evidence of a substantial increase in blood pressure on either estrogen/progesterone or Tamoxifen to account for the increased risk of stroke (Table 1).

### TABLE 1. Results of Clinical Trials of Hormone Therapy and Specialized Estrogen Receptor Modulators (SERMs)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>West66</td>
<td>Secondary prevention, estrogen replacement therapy after stroke</td>
<td>99 strokes or deaths in estradiol and 93 in placebo group, relative risk 1.1 (0.8–1.4)</td>
</tr>
<tr>
<td>Estrogen Replacement and Atherosclerosis (ERA)67</td>
<td>Secondary prevention, progression of coronary atherosclerosis, E + M</td>
<td>No effect of progression of coronary disease; 29 CHD events (100) in estrogen, 28 (104) in estrogen and progesterone, and 34 (105) in placebo groups</td>
</tr>
<tr>
<td>Heart and Estrogen/Progestrone Replacement Study (HERS II)2</td>
<td>Secondary prevention, Post CHD</td>
<td>290 CHD events, 36 of 1000 hormone users and 293 events, 36.8 of 1000 for placebo group, 6.8 years of follow-up</td>
</tr>
<tr>
<td>National Surgical Adjutant Breast and Bowel Project Prevention Trial (BCPT)15</td>
<td>Primary prevention, high risk for breast cancer, 13 388 women mean age 54 years, Tamoxifen vs placebo</td>
<td>49 cardiovascular events in placebo, 47 in Tamoxifen group, 24 strokes in placebo, 38 in Tamoxifen groups, risk ratio 1.59 (0.93–2.77)</td>
</tr>
<tr>
<td>Multiple Outcomes of Raloxifene (MORE)68</td>
<td>Osteoporotic postmenopausal women, Raloxifene vs placebo, women mean age 67 years</td>
<td>Raloxifene therapy did not affect cardiovascular disease, 55 CHD events in placebo (2.1%), 45 (1.8%) in 60 mg Raloxifene, 56 (2.2%) in 120 mg Raloxifene group, stroke 41 (1.6%) in placebo, 37 (1.4%) in 60 mg, 39 (1.5%) in 120 mg groups</td>
</tr>
<tr>
<td>Women’s Health Initiative Estrogen and Progesterone Arm1</td>
<td>Primary prevention (mostly), 0.625 estrogen and 2.5 mg medroxyprogesterone, mean age 63 years</td>
<td>5.2 years of follow-up, 164 (0.37%) per year CHD in E + P vs 122 (0.30%) placebo, relative risk 1.29 (1.02–1.59), stroke 127 (0.29%) E + P vs 83 (0.21%) in placebo, hazard ratio, 1.41 (1.07–1.85)</td>
</tr>
<tr>
<td>Estrogen and Prevention of Atherosclerosis69</td>
<td>Primary prevention, estrogen only, change in carotid intima medial wall thickness, mean age 62 years</td>
<td>Increase carotid intima medial wall thickness 0.0036 for placebo vs 2.0017 estrogen, P = 0.05</td>
</tr>
<tr>
<td>International Breast Cancer Intervention Study (IBIS-I)70</td>
<td>Women at high risk of breast cancer, Tamoxifen vs placebo, mean age 51 years, 50-month follow-up</td>
<td>63 cardiovascular events in placebo and 73 in Tamoxifen (P = 0.44), 17 stroke in placebo and 16 in Tamoxifen groups</td>
</tr>
</tbody>
</table>

### TABLE 2. Comparison of Changes in Lipoprotein, Clotting Factors and Inflammation for Various Hormone Therapies

<table>
<thead>
<tr>
<th>Trial</th>
<th>Estrogen CEE + MPA(Cyclical)</th>
<th>CEE + MPA(Continuous)</th>
<th>CEE + MP(Cyclical)</th>
<th>Tamoxifen</th>
<th>Raloxifene</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDLC</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>HDLC</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>NC↑</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>NC↓</td>
</tr>
<tr>
<td>Lipoprotein A</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
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</tr>
<tr>
<td>Fibrinogen</td>
<td>↓</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>↓</td>
</tr>
<tr>
<td>CRP</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>NC</td>
</tr>
<tr>
<td>E selectin</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>IL-6</td>
<td>NC↑</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>↓</td>
</tr>
<tr>
<td>TNFα</td>
<td>↓</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>↓</td>
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<tr>
<td>Factor VII</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
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<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>NC</td>
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<tr>
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<td>ND</td>
<td>ND</td>
<td>↓</td>
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<tr>
<td>Protein C</td>
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<td>ND</td>
<td>NC</td>
<td>ND</td>
</tr>
<tr>
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<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
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<tr>
<td>Fibrino-peptide A</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>NC</td>
</tr>
<tr>
<td>PAI-1</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>D-dimer</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>TPA antigen</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

↓ indicates increase; ↑, decrease; NC, no change; ND, no data.
The most consistent adverse effect of estrogen or E+P therapy is the increase in triglyceride levels. In the Women’s Health Initiative, there was a 6.9% increase in triglyceride levels on E+P compared with placebo, consistent with previous studies. Clinical studies using Tamoxifen have also shown increased blood triglyceride levels compared with placebo.1,13 The rise in triglycerides may also result in an overestimate of the decrease in LDLc based on the Friedwald equation for estimate LDLc levels (Table 2).

Elevated blood triglyceride levels are an important risk factor for both CHD and stroke, especially among women.16–19 The elevated triglycerides are associated with higher levels of dense LDLc, an important risk factor for CHD among women, and lower HDLc.19–24 The increase in triglycerides apparently is attributable to greater production of very-low-density lipoprotein (VLDL) triglycerides in the liver.20

Numerous epidemiological studies have now demonstrated that E+P therapy increases levels of C-reactive protein (CRP).25–27 Clinical epidemiological studies have consistently shown that elevated CRP is a risk factor for CHD among women. Elevated CRP has been linked to changes in complement and induces tissue factor and adhesion molecules. Tamoxifen therapy reduces levels of CRP.13 Raloxifene,28,29 another specialized estrogen receptor modulator, does not raise triglycerides or CRP, lowers LDLc, and does not increase HDLc. Clinical trials are presently evaluating whether Raloxifene therapy will reduce risk of heart attack and stroke (Tables 1 and 2).

Estrogen or E+P therapy does not, apparently, increase other inflammatory markers or cytokines.27 For example, there seems to be no increase (or, perhaps, even a decrease) in interleukin-6 and tumor necrosis factor in women taking E+P compared with placebo, and, similarly, there seems to be a decrease in fibrinogen levels. Estrogens and E+P do not seem to be proinflammatory except for the increase in CRP. The increase in CRP only with estrogen or E+P is different from that reported by studies that show the strong relationship between CRP and risk of CHD. In these latter studies, there is usually an increase; not only in CRP, but also in other measures of inflammation, suggestive of a systemic inflammatory response (Table 2).

The rise in CRP and also the higher levels of triglycerides associated with E+P are strongly related to the degree of obesity, waist circumference, presence of diabetes, and weight gain among postmenopausal women.26,30 If the increase in CRP was an important determinant of the risk of CHD or stroke after hormone replacement therapy (HRT), then a different mechanism would be required to explain the increase in stroke and lack of benefit of Tamoxifen in reducing CHD despite decline in LDLc levels, because Tamoxifen lowers CRP levels.

Martin et al41 reported that isolated human VLDL can support all of the components of the extrinsic coagulation pathway yielding physiological relevant rates of thrombin generation in a dose-dependent manner. They concluded that the intact lipoprotein structure, and not specific VLDL-associated inhibitors, accounts for the strong association between human VLDL and prothrombin generation.

The increase in coronary events (at least with E+T therapy) within the first year of therapy, the increase in the incidence of stroke in the absence of an increase in blood pressure levels, and the known substantial risk of venous thrombosis and pulmonary embolism suggest an adverse effect on thrombosis or fibrinolysis as a possible adverse cardiovascular effect of HRT.32 The benefit of both aspirin and anticoagulant therapy in reducing risk of MI and stroke is strong evidence of an important role of thrombosis in the risk of cardiovascular disease. HRT (estrogen) is associated with beneficial effects on clotting, thrombosis, and, potentially, thrombogenic effects such as decrease in antithrombin III and protein S and an increase in factor VII13,28,29,33–45 (Table 2).

In the Estrogen-Progesterone Intervention Trial (PEPI), estrogen alone and in combination with progesterone resulted in a large and sustained increase in concentrations of CRP but a decrease in soluble e-selectin and no change in either the von Willebrand factor or factor VIII. There were no differences in these effects across treatment arms by type of progesterone or cycling of the progesterone therapy25 (Table 2).

In a clinical trial of HRT, 45 healthy postmenopausal women aged 45 to 64 years were assigned randomly to 1 of 3 groups, cyclical, oral, or transdermal estradiol (both combined with a progesterone), or to no hormonal therapy. Hemostatic variables were assessed at baseline and after 6 months. Oral, but not transdermal, estradiol significantly increased the mean values of prothrombin-activation peptide (F1 and F2) and decreased levels of antithrombin compared with no treatments. Oral estrogen therapy was associated with significant increase in both mean tissue plasminogen-activator concentration and plasminogen-activator inhibitor activity and a significant rise in global fibrinolytic capacity compared with the 2 other groups, ie, transdermal estradiol or placebo. There were no significant changes in fibrinogen, factor VII, von Willebrand factor, protein C, fibrin D-dimer, and plasminogen levels between the 3 groups45 (Table 2).

In a small study of 111 women from one center participating in the Breast Cancer Prevention Trial, Cushman et al38 also reported that Tamoxifen reduced antithrombin and protein S but not protein C or APC resistance. The decline in antithrombin III is similar to that for estrogen or E+P therapy.

Genetic variation of clotting and thrombosis may identify women at higher risk of CHD or stroke after hormone therapy.46–49 Factor V Leiden mutations have been associated with a substantial increase in the risk of venous thrombosis among women undergoing HRT but have not been associated with a similar increase in the risk of arterial vascular disease in postmenopausal women.46 A genetic variant of prothrombin (factor II) is associated with a risk of both venous thrombosis and CHD. Rosendaal et al47 reported that among women 18 to 44 years of age, the mutation was associated with an ~4-fold increased risk of MI. The relative risk was high when another major cardiovascular risk factor was also present, such as smoking or metabolic risk factors. Five percent of women with MI carry the factor II mutation compared with 1.6% of the controls. Psaty et al50 evaluated 232 postmenopausal women aged 30
to 79 years who had a first MI between 1995 and 1998. Controls were a stratified sample of 723 postmenopausal women without an MI matched to cases by age, calendar year, and hypertension status. A prothrombin mutation was association with a 4-fold increased risk of MI among hypertensive hormone users but not nonhypertensive hormone users. Hormone users (6 cases and 2 controls) who were also hypertensive and had the prothrombin mutation had an estimated 10-fold (2.15 to 55.2) increased risk of myocardial infarction. There was no association, however, between the prothrombin mutation and risk of MI among hormone users who were not hypertensive. There was no association of Leiden V mutation and MI among either hypertensive or nonhypertensive hormone users.

Thrombosis, resulting in clinical cardiovascular events, usually occurs in the context of significant atherosclerotic disease in the coronary arteries. In secondary prevention trials, such as HERS, most of the women have extensive coronary atherosclerosis based on previous history of MI, angina, etc. In the primary prevention trial, such as the Women’s Health Initiative, the extent of CAD (ie, at entry to the study) was unknown. Many women, especially in the younger age groups (ie, 50 to 59 years), probably have very little coronary atherosclerosis.12,51 There is a strong association between the amount of coronary atherosclerosis, as measured by coronary calcium, and the risk of a heart attack among postmenopausal women.52 The progression of coronary atherosclerosis, as measured by increased coronary calcium, is primarily determined by the extent of coronary calcium at the initial entry point.53 Women with minimal coronary atherosclerosis at entry to the study will have a very slow progression of atherosclerosis and are at very low risk of a heart attack. It is likely that with only a 5- to 6-year follow-up, most of the clinical events (MI and angina) occurred among a small number of women who had fairly extensive coronary atherosclerosis at entry to the study but no clinical history of cardiovascular disease or stroke.

There are at least 3 reasons to explain the lack of benefit of the lowered LDLc with HRT. First, recent studies have clearly shown the more dense LDL is atherogenic, especially for women. Major risk factors for elevated small LDL among women are all related to the metabolic syndrome, especially high waist circumference and obesity. Increase in VLDL triglycerides is the primary precursor of small LDL. The increase in VLDL triglycerides would result in more small LDL. Therefore, much of the decrease in LDLc among women undergoing HRT with increased blood triglyceride levels may be in the large nonatherogenic LDL particles. The increase in VLDL triglycerides may, therefore, be a primary determinant of risk of both thrombosis and of elevation of atherogenic lipoproteins and progression of CAD.54 There is little data on the distribution of lipoprotein changes after E+P therapy and, especially, the interrelationship between host factors (such as estrogen receptor polymorphisms), genetic variations in metabolism of estrogen, progesterone, and polymorphisms related to lipoprotein metabolism. There is an urgent need to evaluate the specific changes in the distribution of lipoprotein particle size and composition among hormone users and relationship to clinical events, progression of atherosclerosis, and thrombosis.

Second, the 12% decrease in LDLc may not be very effective in modifying the progression of atherosclerosis. The levels of LDL increase substantially during the perimenopausal to postmenopausal period. The E+P therapy does not result in a substantial enough decrease of LDL to return the levels in most women to their premenopausal or perimenopausal levels.

Statins, on the other hand, have a much greater effect on LDLc, including the dense LDL, and apparently do result in returning the LDLc to premenopausal or perimenopausal levels.55 Statin therapy reduces risk of CHD among women.56–58 It is possible that over this short 5- to 6-year period, the change in LDLc is not that effective in reducing the rate of progression or characteristics of the atherosclerotic plaque. The Community Primary Prevention Trial (CPPT) reduced LDLc by 11% and CHD deaths and nonfatal MI by 19% with cholestyramine in men.59 The greatest difference in CHD incidence between treatment and placebo groups was for participants with a positive exercise test, especially for CHD deaths, suggesting that benefit may have been primarily for men with more extensive coronary artery disease at entry to the study. The drug therapy did not increase triglyceride levels.

Third, the higher levels of VLDL triglycerides on hormone therapy may increase the risk of thrombosis, heart attack, and stroke, especially among asymptomatic women with preexisting atherosclerotic disease.60 The primary prevention trial model of the Women’s Health Initiative is not the same approach as primate models of coronary atherosclerosis prevention by estrogen or E+P therapy.61,62 The traditional animal models of efficacy of estrogen or E+P generally include an initial high fat/high cholesterol diet and then a comparison of E+P versus a placebo over time. These models evaluate the development and early progression of atherosclerosis rather than the effects of the E+P on progression of established atherosclerotic plaques, especially over a fairly long-term period. This model has also demonstrated that medroxyprogesterone apparently reduces the benefit of estrogens on the prevention of atherosclerosis.63 It is still possible that treatment with estrogen or E+P starting earlier during the perimenopause among women with little coronary atherosclerosis would slow or prevent progression of coronary atherosclerosis and reduce long-term risk of clinical disease. It is also possible that any benefit of hormone therapy could be limited to a subset of women that have a better lipid response or less effect on thrombosis attributable to genetic variations in estrogen receptors or metabolism.64,65

The estrogen arm of the Women’s Health Initiative is continuing and remains a double-blind trial. It is still possible that the adverse effects of hormone therapy will be limited to the combination of estrogen and medroxyprogesterone. The best hypothesis at the present time to explain the increased risk of cardiovascular disease among estrogen-progesterone users is that elevation of VLDL triglycerides and thrombosis, secondary to E+P therapy, may be the key determinant in the apparent increased risk or lack of benefit of cardiovascular disease with E+P therapy.
The higher VLDL triglyceride levels will be related to obesity or increased waist circumference, weight gain, insulin resistance, and the metabolic syndrome. Genetic polymorphisms of prothrombin and, perhaps, of other determinants of thrombosis or fibrinolysis may additionally contribute to the increased risk. Postmenopausal women who have moderate to extensive coronary atherosclerosis are likely at highest risk of increased thrombosis and clinical cardiovascular events, including both MI and stroke.

The women who have an increase in triglyceride levels are likely to also have some increase in dense LDL, or at least little change in their dense LDL, on E+P therapy compared with placebo. This increase in levels of dense LDL may additionally contribute to the progression of atherosclerotic disease.

Whether lower doses of estrogen and, possibly, different types of progesterone or testosterone with the estrogen may, ultimately, prove to be more beneficial than the combination of E+P used in the Women’s Health Initiative will need to be determined in clinical trials. Presently, there is no evidence that any dose of estrogen or different progesterone will have a more favorable outcome than has been reported in the Women’s Health Initiative.

There is an important opportunity to determine the cause or mechanism of the increased CVD risk for women on E+P therapy. The risk-benefit of E+P (for most postmenopausal women) seems to be higher risk than benefit. Until we have clearly demonstrated benefit versus risk in clinical trials, all E+P therapy should be considered suspect for increasing cardiovascular risk (ie, MI, stroke, and venous thromboembolism) and, therefore, should be used very cautiously (if at all) for long-term preventive therapies among postmenopausal women. The research focus should be on understanding mechanisms and improving outcome and not just switching to a different type of estrogen or progesterone without proven benefit. [66–70 cited in Table 1]

References

27. Cushman M. Effects of hormone replacement therapy and estrogen receptor modulators on markers of inflammation and coagulation. Am J Cardiol. 2002;90(suppl):7F–10F.


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