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Estrogens and Cardiovascular Disease Risk Revisited: the Women's Health Initiative

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Abstract

Purpose of Review—In 2002 and 2004, the Women's Health Initiative (WHI) found no evidence that hormone therapy (HT) with estrogen or estrogen with progestin (E+P) protected against cardiovascular disease (CVD). Since then, further analyses have been performed. This review summarizes current analyses on the effects of HT on CVD and CVD risk factors.

Recent Findings—The negative effects of HT vary by type of CVD event. Estrogen alone and E+P show consistent effects on CVD, but E+P has more impact on coronary heart disease (CHD) and venous thromboembolism (VTE). Women of all ethnicities, including those who are obese, have diabetes, or are taking daily aspirin or statins remain at risk for adverse effects from HT. While younger women or more recently menopausal women taking HT may be at relatively lower risk for CHD and myocardial infarction, they remain at risk for stroke, VTE, and peripheral artery disease. Adverse effects are enhanced in older women with menopausal symptoms. While HT lowers low-density lipoprotein cholesterol (LDL-C) and Lipoprotein (a) and raises high-density lipoprotein cholesterol, it has adverse effects on triglyceride, lipoprotein composition, and inflammatory and hemostatic markers. Baseline metabolic syndrome and high LDL-C increase the CHD risk with HT. Analyses of discontinuation data in the estrogen-alone and E+P trials suggest that the adverse effects of HT on CVD are reversible.

Summary—Recent analyses do not justify postmenopausal HT for CVD prevention. Further research on the role of HT-induced changes in CVD risk factors along with genetic studies may increase understanding and aid in developing safer therapies for menopausal symptoms.

Keywords

Cardiovascular disease; hormone therapy; CVD risk factors; Women's Health Initiative

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INTRODUCTION

Although cardiovascular disease (CVD) occurs less frequently in younger women than in younger men, lifetime risk for CVD is high in women, and it is the leading cause of death in women [1]. Because of the relatively lower rates of CVD in younger women and the favorable effects of hormone therapy (HT) on low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), attention was focused on the possible use of postmenopausal HT as a strategy to prevent CVD [2] in older women. On the basis of reports from observational studies [3], HT became viewed as a way to prevent CVD, as well as many chronic diseases of aging, including osteoporosis and dementia, in women. In 2001, 40% of postmenopausal women in the United States were using HT, even though no conclusive trial data were available to evaluate the risks and benefits [4] of such therapy. Doubts about HT began with results of secondary prevention trials that showed no benefit and some early increase in coronary heart disease (CHD) risk in women with established CVD [5, 6, 7]. The Women's Health Initiative (WHI) HT trials were designed to determine the benefits and risks of HT taken for chronic disease prevention by predominantly healthy postmenopausal women [8]. The primary outcome was CHD, but secondary outcomes included stroke, venous thromboembolism (VTE), cancer, and osteoporosis. Data also were collected to evaluate heart failure, electrocardiographic abnormalities, and CVD risk factors. After the initial results of the two hormone trials were published [9,10], other analyses were performed to explore further the effects of HT on CVD and its risk factors. This review summarizes the primary and secondary analyses on the effects of HT on CHD, stroke, VTE, peripheral artery disease (PAD), and heart failure in postmenopausal women.

Do actions of HT differ for different aspects of CVD?

The WHI trial of combined estrogen plus progestin (E+P) involved 16,608 women with intact uteri; the trial of estrogen alone was conducted in 10,739 women with prior hysterectomy; details of the methods have been published [8]. Both trials showed adverse effects on multiple aspects of CVD (Table 1). E+P was associated with a 13% increased risk of all CVD events over 5.6 years, and estrogen alone was associated with an 11% increase over 7.1-years. Variation was seen in the effects of these HT regimens on subclasses of CVD. The strongest effects in the trials of both estrogen and E+P were seen on rates of pulmonary embolism, deep vein thrombosis (DVT), and stroke; the effect on stroke was observed in ischemic but not hemorrhagic stroke subtypes. Number of interventions (coronary artery bypass graft/percutaneous coronary revascularization) showed no apparent effect from HT.

Does combined HT have different outcomes than estrogen alone?

Differences were observed between estrogen alone and E+P in some but not all manifestations of CVD. In addition, baseline risk factors and demographic variables differed between women with and without a uterus. Risk profiles were more adverse in women with prior hysterectomy; however, it seems unlikely that these differences in risk profiles explain the differences observed between those treated with E+P and those treated with estrogen alone. Effects on PE (98% and 35% [n.s.], respectively) and DVT (87% and 48%) were

stronger in women treated with E+P than in those treated with estrogen alone; HRs for stroke were equivalent for both regimens (HR 1.37 and 1.35, respectively). Effects of the treatment regimens on CHD (defined as myocardial infarction [MI], silent MI, or CHD death) and PAD differed; for CHD and MI, there were non-significant increases in risk with E+P and no effect with estrogen alone; for PAD, there was a non-significant increased risk with estrogen alone, but no effect with E+P (Table 1). Notably, there was an 80% increase in risk of CHD during the first year of therapy with E+P, with less increase or a decrease in risk during further follow up [11].

Do effects of HT vary by age, health status, or metabolic characteristics?

Because of the lower CVD risk observed in premenopausal women, attention has been placed on the possibility that outcomes might differ by age. Of the women in the WHI trials, 33% were ages 50–59 years, with 15% < age 55 years. Although event rates are low in this age group, the trial investigators specifically explored the potential for differences in CVD outcomes by age or by years since menopause at baseline (Table 2). A nonsignificant difference in CHD outcomes was observed with the E+P regimen for time since menopause (p for trend = 0.08) but not for age. For the estrogen-only regimen, HRs increased with increasing decade of age (p for trend = 0.02) but not with years since menopause. In contrast, HRs for stroke did not differ by age or time since menopause for estrogen or E+P. Similarly no apparent trends were observed with age for PE, DVT, or PAD. Thus, the data suggest that while younger women or women close to menopause may be at lower risk for the effects of HT on MI, they remain at risk for stroke, PE, and DVT.

One modulator of importance for older women is the presence of vasomotor symptoms [12]. Thirty-eight percent of the women in the E+P trial and 43% in the estrogen-alone trial had vasomotor symptoms at baseline. CHD risk factors tended to be worse in women with vasomotor symptoms for the categories of age and years since menopause, and presence of vasomotor symptoms at baseline appeared to influence the results for the categories of age and years since menopause. In analyses of the two trials combined, three-way interactions of severity of vasomotor symptoms with hormone effects on CHD by age ($p=0.04$) and by years since menopause ($p=0.06$) were observed. These interactions appeared to be due to the strong effects observed in women ages 70–79 years with moderate and/or severe vasomotor symptoms. The findings appeared similar for estrogen alone and E+P (12). The implications of this observation are particularly important for older patients with persistent vasomotor symptoms who are considering initiation of hormone therapy and also for women who began hormone use before the adverse effects were known and who are now resistant to withdrawal.

Detailed analyses of individual CVD endpoints for both the estrogen alone and E+P trials included exploration of whether subgroups of women might be more or less susceptible to the effects of HT. Subgroups analyzed included ethnicity, obesity, diabetes, number of CVD risk factors, and aspirin and statin use. Although power was generally limited for these analyses, no significant p values for trends across categories were observed [13, 14, 15, 16, 17, 18]. Within the limits of the currently available data, the evidence suggests that women of all ethnic groups and women who are obese; have diabetes; or are taking CVD preventive

medications, such as aspirin or statins, remain at risk for the adverse effects of HT on CVD. Similarly, prior history of CHD, stroke, or DVT did not appear to influence CVD risks from HT [13,14,15,16,17,18]. Potential unblinding due to vaginal bleeding in the E+P trial did not bias the findings for CHD [19]. However, women with metabolic syndrome were at greater risk for CHD (p for interaction = .03) [20]. Subgroup analyses also were conducted for most endpoints, stratified by levels of biomarkers or metabolic status, such as lipids, metabolic syndrome, hemostasis, or inflammatory status. These analyses generally showed no significant interactions, except for LDL-C, where the effects of both E+P and estrogen alone on CHD were greater in women with higher LDL-C (Table 3) [13,14, 21,22]. A significant interaction was also observed with baseline factor VIII levels on CHD risk, but this observation was inconsistent between the two regimens [22]. Baseline plasmin anti-plasmin complex identified women at increased risk of stroke with HT [23].

What is known about the effects of HT on CVD risk factors and possible mediators?

Previous short-term trials of HT established that HT lowers LDL-C and raises HDL-C [24]; these results had contributed to early optimism about cardioprotective effects of HT. In the two WHI trials, a 13% decrease was observed in LDL-C and a 7% increase was observed in HDL-C. Because it was expected that these changes in LDL-C and HDL-C would be associated with a 20–30% decrease in CHD, the effects of E+P and estrogen alone on other biomarkers were examined (Table 3). Several measures of lipids, lipoproteins, inflammation, and hemostasis are affected significantly by HT [22]. However, interaction tests showed no significant effects of any of the potential mediators on the effects of HT. Although HT reduces LDL-C levels, it does not reduce the LDL particle numbers – meaning that with HT the LDL particles may be smaller and more atherogenic. This result may explain the lack of improvement in CHD risk, despite lowered LDL-C. Among potential effects of mediators of HT effects on stroke, only interactions with D-dimer ($p=.03$) were observed. Hormone therapy with either regimen increased C-reactive protein (CRP) and matrix metalloproteinase-9 levels, decreased E selectin levels, and had no effect on interleukin-6 level. HT increased levels of plasmin-antiplasmin complex and decreased fibrinogen, plasminogen activator inhibitor 1 antigen, homocysteine, glucose, and insulin levels but had no effect on factor VIII, prothrombin fragment 1.2, thrombin-activatable fibrinolysis inhibitor, or von Willebrand factor levels (Table 3). Despite the inability to demonstrate significant interactions, the altered lipoprotein milieu associated with higher triglyceride, and smaller LDL and HDL particles, as well as the increased inflammatory state associated with CRP elevations, may provide partial explanations for the increase in CVD events associated with HT. Further analyses of these biomarkers and their genetic variants may ultimately provide information that could increase understanding of the mechanisms of their actions and aid in the development of safe therapies for menopausal symptoms.

Analyses of preclinical disease

There has been only one analysis of preclinical disease in WHI, measured 7.4 years after the estrogen-alone trial was initiated in a convenience sample of 1064 women, ages 50–59 years. After adjustment for risk factors, a trend was observed toward lower calcium scores in

those taking estrogen alone ($p=.03$) [25]. On the other hand, the Women's Angiographic Vitamin and Estrogen (WAVE) trial in women with established coronary disease showed that HT increased the degree of vascular occlusion [6].

What happens after HT is discontinued?

The women in the WHI HT trials have been under continuous surveillance since the two trials ended. Three years after discontinuing the E+P intervention, the increased CVD risk, including risk for stroke and VTE, was no longer observed [26]. Similar results were found in women who had followed the estrogen-alone regimen, with increased risk of CVD, including stroke and DVT, no longer observed [27].

Commentary

HT is not indicated for chronic disease prevention and should be used in younger women with or without a uterus for relief of menopausal symptoms at as low a dose as possible for short periods. This recommendation has been endorsed by the U.S. Food and Drug Administration, the American College of Obstetricians and Gynecologists, the North American Menopause Society, and the American Heart Association. Nevertheless, some suggest that HT should be recommended more broadly; these suggestions have been based on either animal or in vitro studies [28], flawed re-analyses or reviews of WHI data [29, 30], flawed meta-analyses [31], observational analyses, or smaller or uncontrolled trials [32]. The current review focuses on data from large randomized trials of the effects of HT on CVD and its risk factors. Other non-CVD endpoints were analyzed in the WHI trials [11]. Overall, risk was increased for women receiving E+P compared with estrogen alone, despite reduced risk of fractures, a reduced risk of diabetes, and a possible reduced risk of breast cancer with estrogen alone. An adverse effect of E+P, but not estrogen alone, on colorectal cancer and lung cancer mortality was observed, and both E+P and estrogen alone had adverse effects on cognitive function and dementia. Both treatments also increased incontinence, gallbladder disease, and kidney stones, and estrogen alone increased gastroesophageal reflux disease; these other endpoints also need to be considered when clinical decisions regarding HT are made.

Conclusion

In conclusion, much remains to be learned about the mechanisms of hormone action on the cardiovascular system and how external hormone therapy influences CVD. The hypothesis that estrogen started shortly after menopause will be cardioprotective during the ensuing decades after menopause cannot be tested in a definitive clinical trial. Thus, research is needed to determine why premenopausal women have less CVD than men of similar ages; whether this observation is directly attributable to estrogen in women, androgens in men, or to some other factor; and whether any actions of estrogen provide information that could lead to the design of a safe therapy to relieve menopausal symptoms.

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Key Points

- Adverse effects of HT extend to all subtypes of CVD, and there is only modest evidence of differences by age or time since menopause.
- Although many CVD risk factors are changed during HT, more research is needed to determine which changes are the key mediators of HT effects on CVD.
- Recent analyses of WHI data do not provide justification for the use of postmenopausal HT for the prevention of CVD, but support use in young symptomatic women without adverse risk factor profiles for a short period.

Table 1

CVD outcomes in the E+P and E-alone trials

Endpoint	Estrogen + Progestin		Estrogen Alone	
	HR	95% CI	HR	95% CI
All CVD *	1.13	1.02,1.25	1.11	1.01–1.22
CHD **	1.18	0.95,1.45	0.94	0.78, 1.14
Total MI	1.24	0.98,1.56	0.97	0.79,1.21
Stroke	1.37	1.07,1.76	1.35	1.07,1.70
Pulmonary embolism	1.98	1.36,2.87	1.35	0.89,2.05
DVT	1.87	1.37,2.54	1.48	1.06,2.07
CABG/PCI	0.95	0.77,1.16	1.04	0.86,1.25
PAD	0.89	0.63–1.25	1.32	0.99,1.77
Heart failure	0.91	0.67–1.24	1.06	0.78–1.43

* HRs for All CVD reflect the time to first of any MI, CHD death, hospitalized angina, heart failure, CABG/PTCA, carotid artery disease, PVD, DVT, PE, stroke, and cardiovascular death

** CHD=MI, Silent MI or CHD death.

CABG/PTCA = coronary artery bypass graft/percutaneous coronary intervention; CHD = coronary heart disease; CVD = cardiovascular disease; DVT = deep vein thrombosis; HR = hazard ratio; MI = myocardial infarction; PAD = peripheral vascular disease; PE = pulmonary embolism.

PAD data are from References 33 and 34. HF data are from Reference 35. All other data are from Reference 11.

Table 2

Differences in Effect by Age and Years Since Menopause

Endpoint	Estrogen + Progestin		Estrogen Alone	
	Age	Years since Menopause	Age	Years since Menopause
All CVD	NO	NA	BORDERLINE *	NA
CHD	NO	BORDERLINE **	NO	NO
MI	NO	NA	YES **	YES **
Stroke	NO	NO	NO	NO
PE	NO	NO	NO	NO
DVT	NO	NO	NO	NO
PAD	NA *	NA	NA	NA
HF	NA	NA	NA	NA

CHD = coronary heart disease; CVD = cardiovascular disease; DVT = deep vein thrombosis; HF = heart failure; MI = myocardial infarction; NA=not analyzed; PAD = peripheral artery disease.

* Effect may increase with age/years since menopause, p for trend 0.05, <0.10.

** Effect increases with age/years since menopause, p for trend <0.05.

PAD data are from References 33 and 34. HF data are from Reference 35. All other data are from Reference 11.

Table 3

CVD Risk Associated with Biomarkers with HT therapy

Biomarker	Effect	P for change at 1 year	P for Interaction with baseline levels *	P for Interaction with change at 1 year **
Lipids				
LDL-C	–	<.001	.02 (CHD)	NS
LDL particle concentration	0	NS	NS	NS
HDL-C	+	<.001	NS	NS
HDL particle concentration	+	<.001	.05 (CHD)	NS
Total –C	–	<.001	NS	NS
Total –TG	+	<.001	NS	NS
27-	NA	NA	NS	NA
Hydroxycholesterol				
Lp(a)	–	<.001	NS	NS
Inflammation				
C-reactive protein	+	<.001	NS	NS
E-selectin	–	<.001	NS	NS
Interleukin 6	0	NS	NS	NS
MMP-9	+	<.001	NS	NS
Thrombosis				
D-Dimer	+	.03	NS	.03 (stroke)
Fibrinogen	–	.02	NS	NS
Factor VIII	0	NS	.04 (CHD)	NS
PAI-1 antigen	–	<.001	NS	NS
Prothrombin fragment	0	NS	NS	NS
PAP	+	<.001	.02 (stroke)	NS
TAFI	0	NS	NS	NS
APC resistance	+	<.001	NS	NS
Free TFPI	–	<.001	NS	NS
Von Willebrand factor	0	NS	NS	NS
Homocysteine	–	.01	NS	NS
Glucose	–	.002	NS	NS
Insulin	–	<.001	NS	NS

APC resistance = activated protein C resistance; free TFPI = free tissue factor protein inhibitor; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; NA=not analyzed; NS=not statistically significant; MMP-9 = matrix metalloproteinase-9; PAP = plasmin anti plasmin complex; TAFI = thrombin-activatable fibrinolysis inhibitor; TG = triglyceride.

+ = levels increased by treatment; 0 = levels not affected by treatment; – = levels decreased by treatment.

* p for interaction of baseline biomarker level with HT

p for interaction of 1 yr change in biomarker with HT

Data are from References 22 and 23.