Venous Thrombosis and Conjugated Equine Estrogen in Women Without a Uterus

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Background: Postmenopausal hormone therapy has been associated with a 2- to 3-fold increased risk of venous thromboembolism (VT) (including deep vein thrombosis and pulmonary embolism) in observational studies and secondary prevention clinical trials. Clinical trial data on the effects of estrogen alone on VT are limited.

Methods: The Women's Health Initiative estrogen trial enrolled 10 739 women aged 50 to 79 years without a uterus. Participants were randomly assigned to receive conjugated equine estrogen (0.625 mg/d) or placebo.

Results: During a mean of 7.1 years, VT occurred in 111 women randomly assigned to receive estrogen (3.0 per 1000 person-years) and 86 randomly assigned to receive placebo (2.2 per 1000 person-years; hazard ratio, 1.32; 95% confidence interval, 0.99-1.75). Deep venous thrombosis was reported in 85 women randomly assigned to receive estrogen (2.3 per 1000 person-years) and 59 randomly assigned to receive placebo (1.5 per 1000 person-years; hazard ratio, 1.47; 95% confidence interval, 1.06-2.06). The VT risk was highest in the first 2 years. There were no significant interactions between estrogen use and age, body mass index, or most other VT risk factors. Comparison of Women's Health Initiative VT findings for estrogen and previous Women's Health Initiative findings for estrogen plus progestin showed that the hazard ratios for estrogen plus progestin were significantly higher than those for estrogen alone ($P=.03$), even after adjusting for VT risk factors.

Conclusion: An early increased VT risk is associated with use of estrogen, especially within the first 2 years, but this risk increase is less than that for estrogen plus progestin.

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VENOUS THROMBOEMBOLISM (VT), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common condition, occurring in about 1 adult per 1000 person-years.[1] Postmenopausal hormone therapy (HT) and selective estrogen receptor modulators such as tamoxifen citrate and raloxifene hydrochloride have been associated with a 2- to 3-fold increased risk of VT,[2,3] and HT is also reported as a risk factor for VT.[4-9]

Risk factors for VT are distinct from those for arterial disease, with an important role for procoagulant changes (eg, thrombophilia and cancer) and immobilization, whereas classic risk factors (eg, diabetes mellitus and hypertension) have no effect.[10] Study investigators report factor V Leiden G1691A with HT increases VT risk approximately 15-fold.[11,12] The largest clinical trial on VT and HT is the Women's Health Initiative (WHI) report of combined oral conjugated equine estrogen (CEE) (0.625 mg/d) and medroxyprogesterone acetate (2.5 mg/d) (E+P).[13,14] The WHI E+P trial included 16 608 women aged 50 to 79 years with a mean follow-up of 5.6 years. In this trial there was an increase in VT associated with HT.[13]

The only previously reported randomized controlled intervention trial of use of estrogen alone in women without a history of VT was the Estrogen Replacement and Atherosclerosis trial.[15] In that study, 309 women with angiographically proved coronary heart disease were randomly assigned to estrogen, E+P, or placebo. The VT events were few and not significantly different between groups ($P=.16$). Another randomized trial of estrogen therapy after VT treatment was stopped because of a high incidence of recurrent VT in women treated with estrogen.[16]

The WHI CEE trial[17] was designed to determine the incidence of a number of cardiovascular and oncological events, including VT, in postmenopausal women without a uterus who were randomized to receive CEE or placebo. The WHI CEE was terminated early because of an overall increase in risk compared with benefit, largely from an increased risk of stroke. We report the final adjudicated VT data from the WHI CEE trial and examine the risk of thrombosis as a function of subject characteristics, including genetic polymorphisms. We also compare the VT hazard ratio (HR) increases from the WHI CEE and E+P trials.

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METHODS

SUBJECTS

Details of the WHI design and methods are published elsewhere.[18,19] Using a protocol and written informed consent forms approved by each site's institutional review committees, we recruited women aged 50 to 79 years. Participants (n=10 739) were postmenopausal and without a uterus at baseline. A 3-month washout was required for postmenopausal hormone users. Exclusions primarily were related to medical conditions associated with shortened survival or safety. Women with DVT or PE history were not enrolled. Women were informed of potential VT risk by mail in July 1997 after the secondary cardiovascular prevention Heart Estrogen/progestin Replacement Study[20] reported increased VT risk with E+P.

Women were randomly assigned in double-blind fashion to receive 0.625 mg of CEE (Premarin; Wyeth-Ayerst, Philadelphia, Pa) or placebo. At baseline, blood was drawn after a minimum 10-hour fast. Samples were shipped to a repository and stored at −70°C (McKesson Bioservices, Rockville, Md).

EVENTS ASCERTAINMENT

Participants were followed up for clinical events every 6 months and had annual in-clinic visits. Discharge summaries of hospital records were reviewed locally. Diagnoses of possible VT were reviewed by trained local physician adjudicators blinded to treatment assignment.[19] The VT cases identified by local adjudicators were assessed subsequently by central physician adjudicators. Agreement between local and central adjudication was 97%. This report is based on centrally adjudicated diagnoses for VT events occurring by February 29, 2004.

Diagnosis of DVT required documentation of a treating physician's diagnosis (hospital discharge summary with a diagnosis of DVT or outpatient treatment) and positive results at Doppler or duplex ultrasonography, venography, plethysmography, or isotope scanning. Diagnosis of PE required documentation of a treating physician's diagnosis and positive results at ventilation-perfusion lung scanning, pulmonary angiography, or computed tomography or documentation of signs and symptoms suggestive of PE in the setting of documented DVT. Detailed reports were not always available; therefore, the treating physician's diagnosis often was accepted unless there were conflicting diagnoses or evidence to the contrary. Events were defined as procedure related if they occurred within 60 days after an invasive procedure.

NESTED CASE-CONTROL STUDY

A nested case-control study of biomarkers previously identified as potentially important in the relationship between E+P and VT, HT assignment, and risk of cardiovascular disease was conducted.[13] Cases of VT occurring between randomization assignment and February 28, 2001, were included. The CEE component included 64 VT cases. Control subjects were selected by matching trial (CEE or E+P), age, randomization date, baseline cardiovascular disease, and follow-up time. Additional controls selected for cases of myocardial infarction and stroke, by using these same matching criteria, were included in the analyses (357 total controls). The DNA polymorphisms for factor V Leiden (n=420), prothrombin *G20210A* (n=420), prothrombin *G19911A* (n=416), thermolabile variant of methylenetetrahydrofolate reductase (*C677T*) (n=421), coagulation factor XIII *Val34Leu* (*G100T*) (n=419), *4G/5G* polymorphism of plasminogen activator inhibitor-1 (n=415), and factor V HR2 (*A4070G*) (n=417) were analyzed by means of standard restriction fragment length polymorphism methods as previously reported.[13]

STATISTICAL ANALYSIS

Baseline risk factors were compared using χ^2 or Fisher exact tests in women who did or did not develop VT. These comparisons are not considered confounding factors in the subsequent CEE vs placebo analyses because the randomized design avoids confounding by baseline characteristics. Risk factor distributions include only women with known values for each factor. The primary randomization group comparisons used time-to-event methods (eg, log-rank tests and Cox regression) based on intention-to-treat principles. For each outcome, the time-to-event was defined for cases of VT as the number of days from randomization to the first diagnosis after randomization, determined by means of central adjudication. For women who did not have a VT event, censoring time was defined as the time from randomization to the earliest of death, unavailable for follow-up, or February 29, 2004. Primary outcomes comparisons are presented as annualized rates and HRs with 95% nominal confidence intervals (CIs). Total VT is the predefined primary end point, with secondary analyses examining associations with DVT and PE separately and with procedure- and non–procedure-related VT events separately. The designation of procedure- or non–procedure-related events was not captured initially. Data are presented only for events with known status. Cox proportional hazards models were stratified according to age, prior VT, and randomization status in the dietary modification trial. The HRs were classified according to time because randomizations were calculated separately for fewer than 2, 2 to 5, and more than 5 years after randomization. Trends with time after randomization were examined by means of incorporating time according to randomization group interaction terms in the Cox models.

Interactions between baseline characteristics and treatment arm were assessed in Cox proportional hazards models that included risk factor and treatment assignment as main effects. Women with missing data for a covariate were excluded from analyses including that covariate. Logistic regression analyses were used to relate VT odds ratios to biomarker values and CEE randomization group in the case-control substudy, with all case-control matching variables included as regression variables. Polymorphisms were included by contrasting women who were homozygous for an allele to the remainder of the sample. Interactions of biomarker values with CEE in relation to VT odds ratios were examined by means of likelihood ratio tests for departure from a multiplicative odds ratio model.

For additional analyses that combine E+P and CEE data, we used Cox proportional hazards analyses that stratify according to trial (CEE or E+P) and age. These analyses, which allow incidence rates and the HR for HT to depend on VT risk factors, are used to test for differences between CEE and E+P HR in relation to VT.

RESULTS

OVERALL AND SUBGROUP COMPARISONS

Examination of baseline characteristics revealed that the distributions of potential VT risk factors were similar in the CEE and placebo groups.[17] Almost one third of the women were aged 50 to 59 years, and 24.0% were aged 70 to 79 years. A little more than 75% were white, 15.0% were black, and 6.1% were Hispanic. Almost 80% were overweight (body mass index [BMI; calculated as weight in kilograms divided by the square of height in meters] >25), and more than 50% of those were obese (BMI ≥30). Statin use was reported by 7.6% and aspirin use by almost 19.5%. Nearly 2% of women had a history of VT.

Table 1. Baseline Characteristics of Participants According to Development of Venous Thrombosis During Follow-up*

Characteristic	No. (%) of Participants With Venous Thrombosis	
	No (n = 10 542)	Yes (n = 197)
Age at screening, y†		
50-59	3275 (31.1)	35 (17.8)
60-69	4755 (45.1)	97 (49.2)
70-79	2512 (23.8)	65 (33.0)
Race/ethnicity		
White	7923 (75.2)	159 (80.7)
Black	1588 (15.0)	29 (14.7)
Hispanic	649 (6.1)	6 (3.0)
Asian/Pacific Islander	164 (1.6)	0 (0)
American Indian/Alaskan Native	72 (0.7)	3 (1.5)
Unknown	146 (1.4)	0 (0)
Education		
High school diploma/ General Educational Development or less	3409 (32.6)	65 (33.2)
School after high school	4531 (43.4)	90 (45.9)
College degree or higher	2502 (24.0)	41 (20.9)
Body mass index‡		
<25	2183 (20.8)	23 (11.8)
25-29	3652 (34.9)	55 (28.2)
≥30	4642 (44.3)	117 (60.0)
Smoking		
Never	5329 (51.1)	99 (51.0)
Past	4000 (38.4)	75 (38.7)
Current	1093 (10.5)	20 (10.3)
Physical activity (≥5.25 metabolic equivalents per wk)	4838 (50.4)	70 (39.1)
Dietary omega 3 fatty acid intake, g		
≤0.046	2553 (25.4)	42 (22.1)
0.047-0.088	2469 (24.5)	47 (24.7)
0.089-0.152	2537 (25.2)	42 (22.1)
>0.152	2500 (24.9)	59 (31.1)
Dietary fish intake, medium serving per d		
≤0.088	2488 (24.7)	38 (20.0)
0.089-0.186	2420 (24.1)	50 (26.3)
0.187-0.329	2692 (26.8)	48 (25.3)
>0.329	2459 (24.4)	54 (28.4)
Dietary fish intake, medium serving		
<1 per mo	545 (5.4)	9 (4.7)
1 per mo to <1 per wk	3073 (30.5)	58 (30.5)
1 to <2 per wk	3198 (31.8)	57 (30.0)
2 to <5 per wk	2796 (27.8)	59 (31.1)
≥5 per wk	447 (4.4)	7 (3.7)
Diabetes mellitus (medically treated)	805 (7.6)	16 (8.2)
Treated for hypertension or blood pressure ≥140/90 mm Hg	4670 (47.6)	103 (55.4)
High cholesterol requiring medication	1437 (15.2)	23 (13.0)
Statin use	806 (7.6)	15 (7.6)
Aspirin use, ≥80 mg/d	2054 (19.5)	45 (22.8)
Prior oral contraceptive use, duration, y		
Nonuser	6498 (61.7)	136 (69.0)
<5	2369 (22.5)	36 (18.3)
5-9	895 (8.5)	18 (9.1)
≥10	773 (7.3)	7 (3.6)

(continued)

Table 1. Baseline Characteristics of Participants According to Development of Venous Thrombosis During Follow-up* (cont)

Characteristic	No. (%) of Participants With Venous Thrombosis	
	No (n = 10 542)	Yes (n = 197)
Prior use of estrogen alone, duration, y		
Nonuser	5661 (53.7)	102 (51.8)
<5	2629 (24.9)	56 (28.4)
5-9	930 (8.8)	12 (6.1)
≥10	1322 (12.5)	27 (13.7)
Prior use of estrogen and progestin, duration, y		
Nonuser	10 080 (95.6)	191 (97.0)
<5	298 (2.8)	4 (2.0)
5-9	97 (0.9)	1 (0.5)
≥10	67 (0.6)	1 (0.5)
No. of pregnancies		
Never pregnant	701 (6.7)	12 (6.1)
1	610 (5.8)	11 (5.6)
2-4	5627 (53.7)	95 (48.5)
≥5	3537 (33.8)	78 (39.8)
Age at menopause, y		
<40	2079 (23.2)	48 (29.8)
40-49	4205 (46.9)	68 (42.2)
≥50	2684 (29.9)	45 (28.0)
History of venous thrombosis	165 (1.6)	6 (3.0)
History of deep vein thrombosis	144 (1.4)	5 (2.5)
History of pulmonary embolism	30 (0.3)	2 (1.0)
History of cardiovascular disease	1053 (10.1)	30 (15.4)

*Baseline characteristics were not recorded for all women.

†Mean (SD) age in those without venous thrombosis was 63.6 (7.3) and in those with venous thrombosis was 65.6 (6.6).

‡Mean (SD) body mass index (calculated as weight in kilograms divided by the square of height in meters) in the 10 477 responding participants without venous thrombosis was 30.0 (6.2) and in the 195 responding participants with venous thrombosis was 32.4 (6.7).

Table 2. Venous Thrombosis Outcomes* According to Randomization Assignment

Outcome	No. (%) of Participants		Hazard Ratio (95% Confidence Interval)†
	CEE (n = 5310)	Placebo (n = 5429)	
Mean follow-up, mo	85.0	85.4	. . .
VT	111 (0.30)	86 (0.22)	1.32 (0.99-1.75)
DVT	85 (0.23)	59 (0.15)	1.47 (1.06-2.06)
PE	52 (0.14)	39 (0.10)	1.37 (0.90-2.07)
DVT and PE‡	26 (0.07)	12 (0.03)	2.22 (1.12-4.40)
Non–procedure-related			
VT	78 (0.21)	54 (0.14)	1.47 (1.04-2.08)
DVT	64 (0.17)	37 (0.10)	1.78 (1.18-2.66)
PE	32 (0.09)	28 (0.07)	1.17 (0.71-1.95)
Procedure-related			
VT	27 (0.07)	28 (0.07)	1.00 (0.59-1.69)
DVT	18 (0.05)	20 (0.05)	0.92 (0.48-1.73)
PE	16 (0.04)	9 (0.02)	1.85 (0.82-4.18)

Abbreviations: CEE, conjugated equine estrogen; DVT, deep vein thrombosis; PE, pulmonary embolism; VT, venous thromboembolism.

*Annualized percentage.

†Hazard ratios and confidence intervals are from the Cox proportional hazards models adjusted for age, prior disease, and dietary modification trial randomization assignment status.

‡The time to event is defined as the time from randomization assignment to the later of the DVT or PE diagnoses.

Table 3. Incidence* of Venous Thrombosis According to Age and Randomization Assignment

Age at Screening, y	Deep Vein Thrombosis		Pulmonary Embolism		Venous Thromboembolism	
	No. (%) of Participants	HR (95% CI)†	No. (%) of Participants	HR (95% CI)†	No. (%) of Participants	HR (95% CI)†
50-59						
Placebo	10 (0.08)	1.00	8 (0.06)	1.00	15 (0.12)	1.00
CEE	16 (0.13)	1.64 (0.74-3.60)	12 (0.10)	1.54 (0.63-3.77)	20 (0.16)	1.37 (0.70-2.68)
60-69						
Placebo	29 (0.17)	2.17 (1.06-4.45)	17 (0.10)	1.63 (0.70-3.78)	43 (0.25)	2.16 (1.20-3.89)
CEE	39 (0.23)	3.02 (1.51-6.06)	28 (0.17)	2.80 (1.28-6.16)	54 (0.32)	2.82 (1.59-5.01)
70-79						
Placebo	20 (0.22)	2.94 (1.37-6.30)	14 (0.16)	2.67 (1.12-6.39)	28 (0.31)	2.78 (1.48-5.22)
CEE	30 (0.34)	4.54 (2.22-9.31)	12 (0.14)	2.36 (0.96-5.80)	37 (0.42)	3.77 (2.07-6.89)
P value for interaction‡	.93		.39		.99	

Abbreviations: CEE, conjugated equine estrogen; CI, confidence interval; HR, hazard ratio.
*Annualized percentage.
†From Cox proportional hazards models adjusted for prior venous thromboembolism, and dietary modification randomization assignment.
‡From a likelihood ratio test comparing Cox proportional hazards models adjusted for the main effects of randomization assignment and age with and without the interaction of randomization assignment and age.

Table 4. Incidence* of Venous Thrombosis According to Body Mass Index and Randomization Assignment

Body Mass Index†	Deep Vein Thrombosis		Pulmonary Embolism		Venous Thromboembolism	
	No. (%) of Participants	HR (95% CI)‡	No. (%) of Participants	HR (95% CI)‡	No. (%) of Participants	HR (95% CI)‡
<25						
Placebo	6 (0.08)	1.00	2 (0.03)	1.00	8 (0.10)	1.00
CEE	11 (0.14)	1.87 (0.69-5.05)	5 (0.06)	2.61 (0.51-13.49)	15 (0.19)	1.92 (0.81-4.53)
25-29						
Placebo	18 (0.13)	1.81 (0.72-4.56)	9 (0.07)	2.71 (0.58-12.54)	25 (0.18)	1.89 (0.85-4.19)
CEE	26 (0.20)	2.72 (1.12-6.62)	14 (0.11)	4.51 (1.02-19.87)	30 (0.24)	2.32 (1.06-5.08)
≥30						
Placebo	34 (0.20)	3.02 (1.26-7.22)	27 (0.16)	7.11 (1.68-30.05)	51 (0.30)	3.39 (1.60-7.17)
CEE	48 (0.29)	4.27 (1.82-10.03)	33 (0.20)	8.49 (2.03-35.53)	66 (0.39)	4.40 (2.11-9.21)
P value for interaction§	.88		.57		.66	

Abbreviations: CEE, conjugated equine estrogen; CI, confidence interval; HR, hazard ratio.
*Annualized percentage.
†Body mass index is calculated as weight in kilograms divided by the square of height in meters.
‡From Cox proportional hazards models adjusted for age, prior venous thromboembolism, and dietary modification randomization assignment.
§From a likelihood ratio test comparing Cox proportional hazards models adjusted for the main effects of randomization assignment and body mass index with and without the interaction of randomization assignment and body mass index.

After a mean follow-up of 7.1 years, 197 women developed VT: 144 with DVT, 91 with PE, and 38 with DVT and PE (some women had >1 anomaly). Fifty-five cases of VT were procedure related. **Table 1** illustrates the baseline characteristics of women who developed VT compared with those who did not.

Venous thromboembolism occurred in 111 women (0.30% per year) in the CEE arm, compared with 86 women (0.22% per year) with placebo, with an HR of 1.32 (95% CI, 0.99-1.75) (**Table 2**). The HR for CEE is slightly greater (1.47; 95% CI, 1.06-2.06) for DVT and similar for PE (1.37; 95% CI, 0.90-2.07). Results are similar for non–procedure- and procedure-related VT. The HR for women with no prior VT was 1.34 (95% CI, 1.01-1.78) compared with an HR of 0.87 (95% CI, 0.14-5.28) for women with prior VT (data not shown); there was no significant interaction between prior VT and CEE ($P=.67$). Ten VT events in the CEE group and 8 in the placebo group were associated with cancer. The HRs for VT, DVT, and PE for women without cancer were 1.33 (95% CI, 0.98-1.79), 1.51 (95% CI, 1.06-2.15), and 1.30 (95% CI, 0.84-2.02), respectively (data not shown).

Older women had an absolute higher risk of VT, but the HR associated with CEE showed no increase according to age ($P=.99$) or for DVT ($P=.93$) or PE ($P=.39$) separately (**Table 3**). Similarly, the absolute incidence of VT is strongly related to baseline BMI (**Table 4**), but there is no suggestion of dependence of the HR for CEE on BMI for overall VT ($P=.66$), DVT ($P=.88$), or PE ($P=.57$) or for non–procedure- or procedure-related VT (data not shown). Results of additional analyses (data not shown) did not suggest a dependence of the HR for CEE on age and BMI when these factors were considered simultaneously.

There is evidence of higher CEE-related HRs among women reporting levels greater than median (5.25 metabolic activities per week) of physical activity ($P=.05$). This finding should be regarded as suggestive in view of the number of HR interactions considered in this analysis (**Table 5**). There

Table 5. Incidence* of Venous Thromboembolism According to Risk Factor Categories and Randomization Assignment

Risk Factor Category	No. (%) of Participants: Conjugated Equine Estrogen	No. (%) of Participants: Placebo	*P* Value for Interaction†
Race/ethnicity‡			
White	90 (0.32)	69 (0.24)	.06
Black	13 (0.24)	16 (0.27)	
Hispanic	6 (0.26)	0 (0)	
Asian/Pacific Islander	2 (0.71)	1 (0.42)	
American Indian/Alaskan Native	0 (0)	0 (0)	
Unknown	0 (0)	0 (0)	
Smoking			
Never	60 (0.31)	39 (0.20)	.13
Past	42 (0.30)	33 (0.22)	
Current	7 (0.19)	13 (0.33)	
Prior use of estrogen alone			
No	54 (0.27)	48 (0.23)	.22
Yes	57 (0.33)	38 (0.21)	
Prior use of estrogen and progestin			
No	106 (0.29)	85 (0.23)	.12
Yes	5 (0.31)	1 (0.05)	
Any prior postmenopausal hormone use			
No	52 (0.27)	48 (0.25)	.13
Yes	59 (0.33)	38 (0.20)	
Prior oral contraceptive use			
No	80 (0.35)	56 (0.24)	.30
Yes	31 (0.21)	30 (0.20)	
Physical activity (≥5.25 metabolic equivalents per wk)			
No	53 (0.32)	56 (0.34)	.05
Yes	44 (0.26)	26 (0.15)	
Dietary omega 3 fatty acid intake, g			
≤0.046	27 (0.30)	15 (0.16)	.20
0.047-0.088	28 (0.32)	19 (0.21)	
0.089-0.152	22 (0.24)	20 (0.22)	
>0.152	31 (0.34)	28 (0.31)	
Dietary fish intake, medium serving per d			
≤0.186	53 (0.31)	35 (0.19)	.41
>0.186	55 (0.29)	47 (0.25)	
Dietary fish intake, medium serving			
<1 per mo	5 (0.27)	4 (0.19)	.09
1 per mo to <1 per wk	40 (0.37)	18 (0.16)	
1 to <2 per wk	25 (0.22)	32 (0.28)	
2 to <5 per wk	35 (0.35)	24 (0.23)	
≥5 per wk	3 (0.19)	4 (0.25)	
Treated for hypertension or blood pressure ≥140/90 mm Hg			
No	50 (0.28)	33 (0.18)	.15
Yes	52 (0.32)	51 (0.30)	
Aspirin use, ≥80 mg/d			
No	84 (0.28)	68 (0.22)	.47
Yes	27 (0.38)	18 (0.24)	
Statin use			
No	102 (0.29)	80 (0.22)	.64
Yes	9 (0.34)	6 (0.21)	
History of cardiovascular disease			
No	94 (0.28)	71 (0.21)	.39
Yes	15 (0.40)	15 (0.41)	

*Annualized percentage.
†From a likelihood ratio test comparing Cox proportional hazards models adjusted for the main effects of randomization assignment and the corresponding covariate with and without the interaction of randomization assignment and the covariate.
‡Model includes indicators for black and other (Hispanic, Asian/Pacific Islander, American Indian/Alaskan Native, and unknown ethnicities combined) ethnicities vs white.

is little indication that the HR for CEE depends on prior exogenous hormone use, prior cardiovascular disease history, estimated omega 3 fatty acid or fish consumption, hypertension treatment, or aspirin or statin use (Table 5).

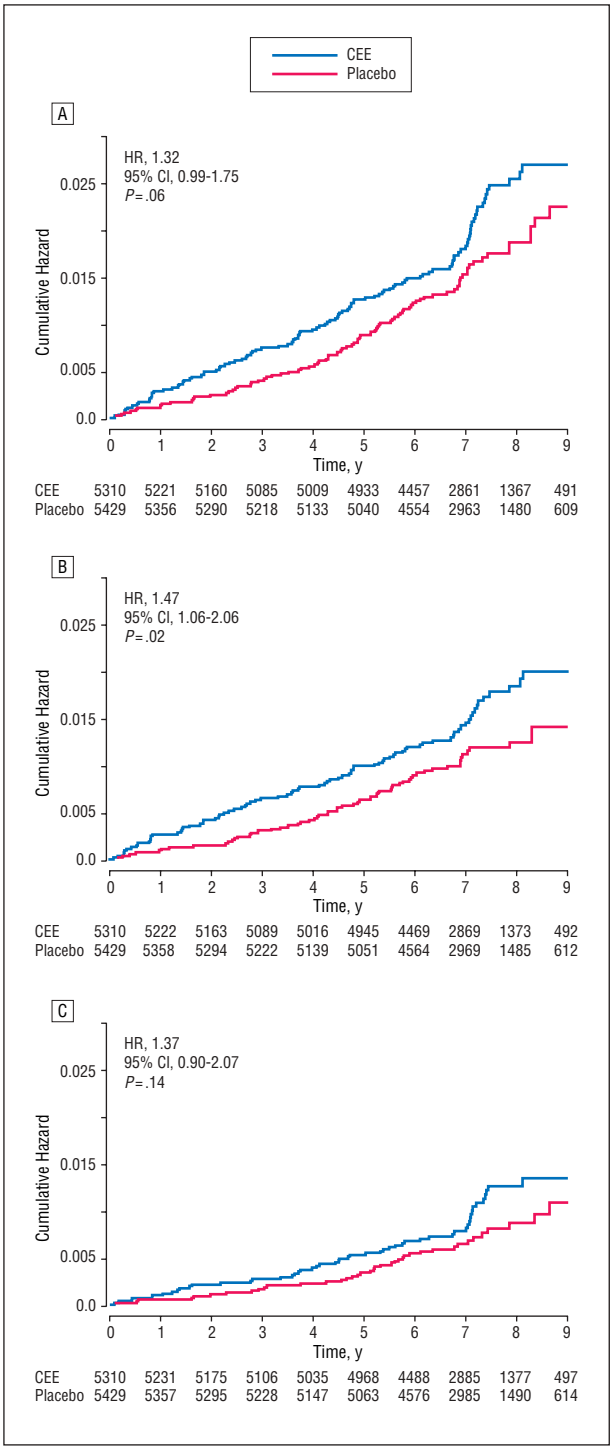

Figure. Cumulative hazards of venous thromboembolism (A), deep vein thrombosis (B), and pulmonary embolism (C) for conjugated equine estrogen (CEE) compared with those for placebo. CI indicates confidence interval; HR, hazard ratio.

TIME TRENDS

The **Figure** shows cumulative hazard estimates for VT, DVT, and PE according to randomization group. Hazard rate increases in the CEE group occurred early in the follow-up. **Table 6** demonstrates increases in DVT and overall VT in the CEE group during the first 2 years after randomization with modest increases beyond 2 years.

Table 6. Venous Thrombosis Outcomes* According to Randomization Assignment and Time in Study

Time Since Initiation, y	Deep Vein Thrombosis, No. (%) of Participants		HR (95% CI)	Pulmonary Embolism, No. (%) of Participants		HR (95% CI)	Venous Thrombosis, No. (%) of Participants		HR (95% CI)
	CEE	Placebo		CEE	Placebo		CEE	Placebo	
<2	22 (0.21)	8 (0.07)	2.79 (1.24-6.27)	11 (0.11)	5 (0.05)	2.21 (0.77-6.36)	26 (0.25)	12 (0.11)	2.22 (1.12-4.39)
2-5	29 (0.19)	25 (0.16)	1.18 (0.69-2.01)	16 (0.11)	13 (0.08)	1.27 (0.61-2.64)	39 (0.26)	34 (0.22)	1.17 (0.74-1.85)
≥5	34 (0.29)	26 (0.21)	1.35 (0.81-2.25)	25 (0.21)	21 (0.17)	1.23 (0.69-2.19)	46 (0.39)	40 (0.33)	1.17 (0.77-1.80)
P value for time trend		.59			.71			.42	

Abbreviations: CEE, conjugated equine estrogen; CI, confidence interval; HR, hazard ratio.
*Annualized percentage.

Table 7. Association of Genetic Variants and Randomization Assignment With Odds Ratios for Venous Thrombosis*

Genetic Variant	Conjugated Equine Estrogen, No. (%) of Participants		Odds Ratio (95% Confidence Interval)	Placebo, No. (%) of Participants		Odds Ratio (95% Confidence Interval)	*P* Value for Main Effect of Variant	*P* Value for Interaction
	Cases	Controls		Cases	Controls			
Factor V Leiden								
1691 GG	33 (15.8)	176 (84.2)	1.22 (0.69-2.17)	24 (12.5)	168 (87.5)	1.00	.06	.70
1691 GA+AA	4 (36.4)	7 (63.6)	4.00 (1.07-14.97)	2 (25.0)	6 (75.0)	2.18 (0.41-11.58)		
Prothrombin								
20210 GG	35 (16.4)	179 (83.6)	1.26 (0.72-2.21)	25 (12.8)	171 (87.2)	1.00	.33	.97
20210 AG+AA	2 (33.3)	4 (66.7)	2.61 (0.42-16.11)	1 (25.0)	3 (75.0)	2.15 (0.21-21.87)		
Prothrombin								
19911 GG	7 (12.5)	49 (87.5)	0.64 (0.23-1.78)	12 (17.4)	57 (82.6)	1.00	.89	.11
19911 GA+AA	29 (18.1)	131 (81.9)	1.01 (0.47-2.13)	14 (10.7)	117 (89.3)	0.59 (0.25-1.37)		
MTHFR								
CC+CT	32 (16.0)	168 (84.0)	1.08 (0.61-1.91)	26 (14.3)	156 (85.7)	1.00	.92	.14
TT	5 (25.0)	15 (75.0)	1.72 (0.56-5.28)	1 (5.3)	18 (94.7)	0.33 (0.04-2.60)		
Factor XIII								
Val/Val + Val/Leu	34 (16.3)	175 (83.7)	1.26 (0.71-2.23)	24 (12.8)	164 (87.2)	1.00	.68	.75
Leu/Leu	2 (20.0)	8 (80.0)	1.33 (0.25-7.10)	2 (16.7)	10 (83.3)	1.54 (0.32-7.56)		
Plasminogen activator inhibitor-1								
4G/4G+4G/5G	30 (19.1)	127 (80.9)	1.36 (0.73-2.52)	21 (14.2)	127 (85.8)	1.00	.08	.57
5G/5G	6 (10.2)	53 (89.8)	0.62 (0.23-1.65)	5 (9.8)	46 (90.2)	0.69 (0.24-1.95)		
Factor V HR2								
AA	32 (16.1)	167 (83.9)	1.10 (0.62-1.97)	24 (13.9)	149 (86.1)	1.00	.68	.14
AG+GG	5 (26.3)	14 (73.7)	2.38 (0.77-7.33)	2 (7.7)	24 (92.3)	0.56 (0.12-2.57)		

Abbreviation: MTHFR, thermolabile variant of methylenetetrahydrofolate reductase.
*All analyses are from logistic regression models adjusted for age, year of randomization assignment, and prior venous thrombosis. The *P* value for the main effect is from a likelihood ratio test comparing logistic models additionally adjusted for randomization assignment, with and without the main effect of the genetic variant of interest. The *P* value for interaction is from a likelihood ratio test comparing logistic models additionally adjusted for the main effects of randomization assignment and the genetic variant with and without the interaction of randomization assignment and the genetic variant.

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Factor V Leiden G1691A mutation appears to be associated (*P*=.06) with VT risk, whereas other polymorphisms, with the possible exception of plasminogen activator inhibitor-1 (*P*=.08), are not (**Table 7**). The increased risk associated with CEE did not depend significantly (*P*=.70) on the factor V Leiden variant or on plasminogen activator inhibitor-1 (*P*=.57). **Table 8** shows the odds ratio as a function of CEE and various baseline blood lipid measures. Results show that the odds ratio associated with CEE is higher (*P*=.03) among women with relatively low high-density lipoprotein cholesterol, implying a protective effect for high-density lipoprotein cholesterol.

COMPARISON OF CEE AND E+P EFFECTS ON VT

Data from the CEE and E+P trials were analyzed jointly to compare the magnitude of CEE and E+P effects on VT HRs. **Table 9** shows the HRs for CEE and E+P while allowing the VT incidence rate and the HT-related HRs to depend on VT risk factors. The CEE HR is significantly lower than the E+P HR (*P*=.02). In further analyses (data not shown), we examined the ratio of the CEE to E+P HR as a function of years after randomization. The smaller HR for CEE was most evident between 2 and 5 years after randomization, especially for non–procedure-related VT.

Table 8. Association of Blood Lipids* and Randomization Assignment With Venous Thrombosis

Blood Lipid, mg/dL	Conjugated Equine Estrogen, No. (%) of Participants		Odds Ratio (95% Confidence Interval)	Placebo, No. (%) of Participants		Odds Ratio (95% Confidence Interval)	*P* Value for Main Effect of Blood Lipid†	*P* Value for Interaction†
	Cases	Controls		Cases	Controls			
Total cholesterol								
≤208	17 (41.5)	58 (31.0)	1.79 (0.73-4.40)	9 (32.1)	55 (30.9)	1.00	<.001	.66
209-242	10 (24.4)	67 (35.8)	0.85 (0.32-2.26)	7 (25.0)	66 (37.1)	0.69 (0.24-2.00)		
>242	14 (34.1)	62 (33.2)	1.33 (0.53-3.36)	12 (42.9)	57 (32.0)	1.32 (0.51-3.43)		
LDL cholesterol								
≤126	12 (30.0)	62 (33.9)	1.80 (0.63-5.16)	6 (23.1)	57 (32.9)	1.00	.58	.78
127-155	13 (32.5)	56 (30.6)	2.12 (0.74-6.05)	9 (34.6)	60 (34.7)	1.52 (0.51-4.59)		
>155	15 (37.5)	65 (35.5)	2.09 (0.75-5.83)	11 (42.3)	56 (32.4)	1.89 (0.64-5.52)		
HDL cholesterol								
≤47	20 (50.0)	71 (38.0)	1.92 (0.78-4.71)	8 (28.6)	57 (32.2)	1.00	.33	.03
48-58	17 (42.5)	64 (34.2)	1.73 (0.69-4.38)	9 (32.1)	62 (35.0)	1.01 (0.36-2.83)		
>58	3 (7.5)	52 (27.8)	0.39 (0.10-1.56)	11 (39.3)	58 (32.8)	1.33 (0.49-3.58)		
HDL-2 subfraction cholesterol								
≤12	21 (53.8)	77 (41.2)	1.39 (0.62-3.13)	11 (39.3)	60 (34.3)	1.00	.26	.38
13-17	14 (35.9)	64 (34.2)	1.13 (0.47-2.71)	9 (32.1)	63 (36.0)	0.76 (0.29-2.00)		
>17	4 (10.3)	46 (24.6)	0.45 (0.13-1.54)	8 (28.6)	52 (29.7)	0.84 (0.31-2.27)		
HDL-3 subfraction cholesterol								
≤35	21 (53.8)	70 (37.4)	2.14 (0.91-5.05)	9 (32.1)	68 (38.9)	1.00	.57	.19
36-42	11 (28.2)	65 (34.8)	1.14 (0.44-2.98)	9 (32.1)	56 (32.0)	1.15 (0.42-3.12)		
>42	7 (17.9)	52 (27.8)	1.00 (0.35-2.90)	10 (35.7)	51 (29.1)	1.53 (0.57-4.07)		
Triglycerides								
≤109	8 (19.5)	55 (29.4)	0.86 (0.31-2.41)	9 (32.1)	53 (29.8)	1.00	.65	.34
110-168	18 (43.9)	60 (32.1)	1.73 (0.71-4.22)	8 (28.6)	65 (36.5)	0.79 (0.28-2.22)		
>168	15 (36.6)	72 (38.5)	1.23 (0.50-3.07)	11 (39.3)	60 (33.7)	1.18 (0.45-3.10)		

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein.

SI conversion factor: To convert cholesterol to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113.

*Coefficient of variation: total cholesterol, 1.3; LDL cholesterol, 2.3; HDL cholesterol, 3.5; HDL-2 subfraction cholesterol, 14.3; HDL-3 subfraction cholesterol, 4.4; triglycerides, 2.0.

†All analyses are from logistic regression models adjusted for age, year of randomization assignment, and prior venous thromboembolism. The *P* value for the main effect is from a likelihood ratio test comparing logistic models additionally adjusted for randomization assignment, with and without the main effect of the blood lipid of interest. The *P* value for interaction is from a likelihood ratio test comparing logistic models additionally adjusted for the main effects of randomization assignment and the blood lipid with and without the interaction of randomization assignment and the blood lipid.

Table 9. Hazard Ratios (95% Confidence Intervals) Comparing Disease Incidence in CEE and E+P Cohorts

Cohort	Venous Thromboembolism	Non–Procedure-Related Venous Thromboembolism	Procedure-Related Venous Thromboembolism	Deep Vein Thrombosis	Pulmonary Embolism
Unadjusted					
CEE	1.34 (1.01-1.77)	1.49 (1.05-2.11)	1.00 (0.59-1.70)	1.49 (1.07-2.08)	1.38 (0.91-2.09)
E+P	2.09 (1.59-2.74)	2.59 (1.85-3.63)	1.11 (0.63-1.93)	1.98 (1.45-2.70)	2.13 (1.45-3.12)
CEE/E+P	0.64 (0.43-0.94)	0.58 (0.36-0.94)	0.91 (0.42-1.95)	0.75 (0.48-1.18)	0.65 (0.37-1.14)
P Value	.02	.03	.80	.22	.13
Adjusted*					
CEE/E+P	0.59 (0.37-0.94)	0.59 (0.33-1.03)	0.63 (0.25-1.55)	0.67 (0.39-1.15)	0.61 (0.31-1.19)
P Value	.03	.07	.31	.14	.15

Abbreviations: CEE, conjugated equine estrogen; E+P, estrogen and progestin.

*All analyses adjusted for age, ethnicity, body mass index, smoking history, prior hormone therapy, education, physical activity, general health, history of cardiovascular disease, family history of myocardial infarction, family history of stroke, baseline statin use, and baseline aspirin use, as well as corresponding history of venous thromboembolism, deep vein thrombosis, or pulmonary embolism.

COMMENT

Our results in healthy postmenopausal women without a uterus indicate increased risk of VT, including DVT and PE, among women treated with CEE compared with placebo. The relative increase in risk is significantly ($P = .02$) less than that shown in the WHI E+P trial.[13] The WHI CEE and E+P trial results are consistent with results from other studies of postmenopausal HT, as well as from studies of selective estrogen receptor modulators.[12,21-23]

Investigators in previous studies were inconsistent concerning the duration of VT risk increase among HT users.[7,8,16,20] In WHI, the increased risk of VT with CEE was highest in the first 2 years of therapy. In a meta-analysis

including 6 case-control studies of HT reporting first-year use,[24] the pooled relative risk for a VT event was 3.49 in the first year and 1.91 thereafter. Similarly, in the WHI E+P study, the greatest risk of VT with HT was in the first year and remained increased for at least 5 years after randomization.[13,14]

There was little evidence of an effect of CEE on procedure-related VT, as was the case for the WHI E+P trial.[13] The HRs for VT, DVT, and PE in women who developed cancer were similar to those in women who did not develop cancer, suggesting that VT increase was not attributable to differential cancer rates.

The WHI and other observational study investigators report an increased risk of VT with increasing age and obesity.[10,25,26] It is likely that the higher rate of VT in the CEE placebo group than in the E+P placebo group is attributable to the latter having a higher average age and BMI. However, no synergy was observed between these risk factors and CEE. Similar to previous findings with oral contraceptives,[27] there does not seem to be an increased risk of VT in former HT users. In observational studies, VT risk increased for oral estrogen and oral estrogen combined with progestin.[8,28] However, authors of a recent report indicated that users of esterified estrogens had a lower VT risk than did CEE users and that such risk did not differ from that in nonusers.[29]

Our results indicate that use of CEE or E+P among women with prior VT should be discouraged in the absence of ongoing anticoagulation therapy. Although there were only 171 women with previous VT, our observation of high risk of recurrence concurs with the WHI E+P trial[13] and the Estrogen in Venous Thromboembolism Trial[30] findings (1.3-year incidence of VT of 10.7% with estradiol plus norethisterone acetate compared with 2.3% with placebo[30]).

Results from neither WHI trial (CEE or E+P) indicate the use of aspirin or statins to prevent VT among women receiving HT. However, in the Heart Estrogen/progestin Replacement Study[20] of women with coronary disease, aspirin and statin use appeared to attenuate the risk of VT associated with E+P. The Pulmonary Embolism Prevention trial[31] results also indicate attenuation with aspirin use.

In a previous study, the absolute risk of VT among women taking CEE with heterozygous factor V Leiden was estimated as 2.9% per year among families affected by factor V Leiden[32] and 1.5% per year among women with coronary disease.[11] Investigators in a previous case-control study reported an interaction between the risk associated with factor V Leiden and HT.[12] In WHI CEE, there appeared to be an association of factor V Leiden to overall risk of VT, but there did not appear to be a synergistic interaction with CEE, which is similar to findings from the WHI E+P trial.[13] Prothrombin 20210A had a nonsignificant trend toward a positive association with VT risk, but the analysis may have been underpowered to show a significant difference.

The strengths of our study include the randomized double-blind design and high ascertainment of outcome events in a large group of postmenopausal women without a uterus. The baseline characteristics of these women are similar to those of other women who might consider HT. The analysis was limited by power considerations for subgroup analyses, particularly those related to the nested case-control component that included only 64 VT cases. However, apart from factor V Leiden, given the observed weak or absent associations of the genetic disorders with VT, it is unlikely that a clinically relevant interaction of these genetic factors with CEE exists. Nonadherence to study medications was observed,[17] which presumably attenuates the observed associations of CEE with VT. Therefore, our risk estimates are likely underestimates. Definitions of VT may have differed slightly between centers, but because all adjudicators were blinded to study group, this should not have affected the findings. Finally, our results apply only to CEE. Results of one report indicated that users of esterified estrogens had lower VT risk than CEE users had, and that such risk did not differ from risk in nonusers,[29] but results from another report suggested that the risk of VT with HT does not differ according to formulation.[12]

We observed a significantly lower HR for CEE than for E+P in the WHI, even after adjusting for differences in the populations to the extent possible. Although the results of these analyses suggest that the effect of CEE on VT risk may be greater among physically active women and women with relatively low high-density lipoprotein cholesterol, this finding may be attributable to chance given the number of interactions examined. However, the findings merit further study in other contexts.

Our data suggest that although the absolute incidence is relatively low, the use of CEE increases the relative risk of VT in postmenopausal women without a uterus. Women with appropriate indications, such as short-term treatment of severe menopausal symptoms, should use CEE only after careful consideration of the relative risks and benefits, especially if the women have other risk factors for VT, including previous VT, older age, obesity, and perhaps factor V Leiden.

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