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Postmenopausal Hormone Therapy Increases Risk for Venous Thromboembolic Disease

The Heart and Estrogen/progestin Replacement Study

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Background: Oral contraceptive use increases risk for venous thromboembolism, but data on the effect of postmenopausal hormone therapy are limited.

Objective: To determine the effect of therapy with estrogen plus progestin on risk for venous thromboembolic events in postmenopausal women.

Design: Randomized, double-blind, placebo-controlled trial.

Setting: 20 clinical centers in the United States.

Participants: 2763 postmenopausal women younger than 80 years of age (mean age, 67 years) who had coronary heart disease but no previous venous thromboembolism and had not had a hysterectomy.

Intervention: Conjugated equine estrogens, 0.625 mg, plus medroxyprogesterone acetate, 2.5 mg, in one tablet ($n = 1380$) or placebo that was identical in appearance ($n = 1383$).

Measurements: Documented deep venous thrombosis or pulmonary embolism.

Results: During an average of 4.1 years of follow-up, 34 women in the hormone therapy group and 13 in the placebo group experienced venous thromboembolic events (relative hazard, 2.7 [95% CI, 1.4 to 5.0] [$P = 0.003$]; excess risk, 3.9 per 1000 woman-years [CI, 1.4 to 6.4 per 1000 woman-years]; number needed to treat for harm, 256 [CI, 157 to 692]). In multivariate analysis, the risk for venous thromboembolism was increased among women who had lower-extremity fractures (relative hazard, 18.1 [CI, 5.4 to 60.4]) or cancer (relative hazard, 3.9 [CI, 1.6 to 9.4]) and for 90 days after inpatient surgery (relative hazard, 4.9 [CI, 2.4 to 9.8]) or nonsurgical hospitalization (relative hazard, 5.7 [CI, 3.0 to 10.8]). Risk was decreased with aspirin (relative hazard, 0.5 [CI, 0.2 to 0.8]) or statin use (relative hazard, 0.5 [CI, 0.2 to 0.9]).

Conclusions: Postmenopausal therapy with estrogen plus progestin increases risk for venous thromboembolism in women with coronary heart disease. This risk should be

considered when the risks and benefits of therapy are being weighed.

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Venous thromboembolism, including thrombosis of the deep veins of the legs and embolism to the pulmonary arteries, is a serious and potentially fatal event. Venous thromboembolism is uncommon in the general population, occurring in about 1 to 4 per 1000 adults annually (1, 2). However, the risk is increased in persons with previous venous thromboembolism (3), recent surgical procedures (4, 5), immobilization, fracture of a lower extremity (4, 6, 7), cancer (4, 6, 7), and inherited coagulation disorders (8, 9).

Use of oral contraceptive pills increases risk for venous thromboembolism (1, 2). This increased risk is thought to be due to estrogen and to be dose related (3, 4). The biological potency of the estrogens generally used in postmenopausal hormone therapy is about one-fourth to one-fifth that of the estrogens in modern oral contraceptives. Until recently, there has been little evidence that low-dose estrogen therapy is associated with increased risk for venous thromboembolism (5–8). Recent observational studies have suggested that postmenopausal hormone therapy causes a twofold to fourfold increase in risk for idiopathic deep venous thrombosis and pulmonary embolism (9–13). However, these findings may be biased if women taking estrogen are more likely to be evaluated for nonspecific symptoms suggestive of venous thromboembolism.

The Heart and Estrogen/progestin Replacement Study (HERS) was a randomized, blinded, placebo-controlled trial of the effect of daily conjugated equine estrogen, 0.625 mg, plus medroxyprogester-

one acetate, 2.5 mg, on the rate of new coronary events in 2763 postmenopausal women with established coronary heart disease (14). One of the specified secondary outcomes of this trial was venous thromboembolism.

An increased risk for venous thromboembolism among women assigned to hormone therapy was noted by the HERS Data and Safety Monitoring Board. The Board instructed the HERS investigators to inform participants and the scientific community of this risk and to institute measures to reduce risk. At a mean follow-up of 3.3 years, the HERS investigators notified participants to discontinue study medication in situations associated with increased risk for venous thromboembolism, such as surgery, hospitalization, fracture, and cancer, and published a letter noting the increased risk (15). This report presents the full analysis of the findings.

Methods

Participants in HERS were postmenopausal women younger than 80 years of age who had coronary disease (myocardial infarction, coronary artery bypass surgery, percutaneous coronary revascularization, or angiographic evidence of at least 50% narrowing of one or more major coronary arteries) and had not had a hysterectomy. Women were excluded if their coronary event occurred within 6 months of randomization; they had used hormone therapy within 3 months of randomization; they had a history or baseline findings suggestive of venous thromboembolism, breast cancer, or endometrial cancer; or they had uncontrolled hypertension, diabetes, or other life-threatening diseases (16). The protocol was approved by the institutional review board at each of the 20 HERS clinical centers, and all participants provided written informed consent.

Participants were randomly assigned to take one tablet daily of conjugated equine estrogen, 0.625 mg, plus medroxyprogesterone acetate, 2.5 mg, or placebo that was identical in appearance. Randomization was stratified by clinical center and performed in blocks of 4. To prevent unblinding of clinical center staff, HERS participants reported breast discomfort and vaginal bleeding directly to gynecology staff, who were located separately from the clinical center staff, did not communicate with clinical center personnel about breast or gynecologic problems, and did not participate in ascertainment of outcomes.

Follow-up visits to the clinical centers occurred at 4-month intervals. Coronary events (nonfatal myocardial infarction and coronary death) were the primary outcome of the trial (14). At each visit, clinic staff asked participants if they had been told by a

physician that they had a blood clot in the legs or lungs. Women were also asked whether they had been hospitalized, and records were reviewed to determine whether venous thromboembolism had occurred. Women were not routinely asked about symptoms of venous thrombosis, such as lower-extremity edema.

Diagnosis of deep venous thrombosis required documentation of thrombosis of the popliteal or more proximal veins of the legs by venography, impedance plethysmography, or sonography. Pulmonary embolism required documentation by a nuclear lung scan that suggested a high probability of pulmonary embolism (segmental or larger perfusion defect with ventilation mismatch) or by pulmonary angiography that revealed a constant intraluminal filling defect on multiple films. Suspected venous thromboembolism was adjudicated independently and without knowledge of treatment assignment by two physicians at the HERS Coordinating Center, located at the University of California, San Francisco; disagreements were resolved by consensus. Persons who analyzed data were also blinded to participants' treatment status.

Data were collected on events that occurred during the trial that might be predictors of venous thromboembolism, including fractures, nonfatal myocardial infarction, congestive heart failure, stroke, and transient ischemic attack (16). Venous thromboembolism was classified as idiopathic in women who did not have concomitant cancer, nonfatal myocardial infarction, congestive heart failure, or stroke and did not have a fracture, inpatient surgery, or hospitalization in the 3 months before the venous thromboembolic event.

In the primary analysis, an unadjusted Cox proportional hazards model for time to first event was used to compare the rate of venous thromboembolism among women assigned to hormone therapy with the rate among women assigned to placebo. The primary analysis was intention-to-treat; participants were categorized according to treatment assignment regardless of compliance. Participants who were lost to follow-up (33 women in the hormone therapy group and 36 in the placebo group) were censored at the last date at which they were known to be alive without venous thromboembolism; vital status was known for all women at the end of the trial. We also performed an as-treated analysis, in which inclusion in the risk sets was limited to women in both treatment groups whose average compliance with therapy during the trial (measured by pill count) was at least 80%. Relative hazards were also estimated by year since randomization (women with events in earlier years were censored), and continuous trend in the log relative hazard was examined in a companion model. We repeated the

Table 1. Baseline Characteristics of HERS Participants*

Characteristic	Patients Who Received Estrogen plus Progestin (n = 1380)	Patients Who Received Placebo (n = 1383)	P Value
Age, y	67 ± 7	67 ± 7	>0.2
White, %	88	90	0.14
Current smoker, %	13	13	>0.2
Median drinks per week (interquartile range), n	0 (0–0.58)	0 (0–0.58)	>0.2
Diabetes, %	19	18	>0.2
Systolic blood pressure, mm Hg	135 ± 19	135 ± 19	>0.2
LDL cholesterol level, mmol/L (mg/dL)	3.75 ± 0.96 (145 ± 37)	3.75 ± 0.98 (145 ± 38)	>0.2
HDL cholesterol level, mmol/L (mg/dL)	1.29 ± 0.34 (50 ± 13)	1.29 ± 0.34 (50 ± 13)	>0.2
Triglyceride level, mmol/L (mg/dL)	1.90 ± 0.72 (168 ± 64)	1.65 ± 0.64	>0.2
Years since menopause	18 ± 8	1.86 ± 0.72 (18 ± 8)	>0.2
Body mass index > 27 kg/m ² , %	57	55	>0.2
Exercise >3 times per week, %	39	38	>0.2
Poor or fair general health, %	24	24	>0.2
Q-wave myocardial infarction, %	17	17	>0.2
Signs of congestive heart failure, %†	10	9	>0.2
Medication use, %			
Aspirin	79	79	>0.2
Warfarin	4	4	>0.2
Statins	35	37	>0.2
Other lipid-lowering drugs	10	10	>0.2
β-Blockers	33	32	>0.2
Calcium-channel blockers	55	55	>0.2
Diuretics	28	28	>0.2

* Values expressed with a plus/minus sign are the mean ± SD. HERS = Heart in Estrogen/progestin Replacement Study; HDL = high-density lipoprotein; LDL = low-density lipoprotein. † Presence of jugular venous distention >8 cm of water, S₃ heart sound, pulmonary rales, or pitting lower-extremity edema at baseline.

main analyses separately for idiopathic and non-idiopathic venous thromboembolism.

Potential risk factors for venous thromboembolism were first examined by using univariate proportional hazards models adjusted for treatment assignment. In these models, postrandomization events and medication use were represented by time-dependent indicators, which reverted to zero 90 days after fracture, surgery, or hospitalization or when therapy was discontinued. Variables associated with venous thromboembolism for which the associated *P* value was less than 0.2 in univariate analyses were considered for inclusion in multivariate models and retained in the model if the *P* value remained less than 0.2. Statistical analyses were performed by using SAS software, version 6.12 (SAS Institute, Inc., Cary, North Carolina).

Results

The 20 HERS centers enrolled 2763 women between February 1993 and September 1994; of these, 1380 were assigned to the hormone therapy group and 1383 to the placebo group. Participants ranged in age from 44 to 79 years (mean age [±SD], 67 ± 7 years). At baseline, the treatment groups did not differ significantly (**Table 1**).

At the end of the first year, 82% of women in the hormone therapy group and 91% in the placebo group reported taking study medication; by the end of the third year, these proportions had decreased to 75% and 81%, respectively.

Cumulative incidence curves for all venous thromboembolic events (deep venous thrombosis and pulmonary embolism) are shown in the **Figure**. During 10 985 woman-years of follow-up, 47 women experienced a venous thromboembolic event: 34 in the hormone-treated group (6.2 per 1000 woman-years) and 13 in the placebo group (2.3 per 1000 woman-years) (relative hazard, 2.7 [95% CI, 1.4 to 5.0] [*P* = 0.003]; excess risk, 3.9 per 1000 woman-years [CI, 1.4 to 6.4 per 1000 woman-years]; number needed to treat for harm, 256 [CI, 157 to 692]). The relative hazard of venous thromboembolism did not differ significantly among the 20 clinical centers.

More women in the hormone therapy group than in the placebo group experienced deep venous thrombosis (25 compared with 9; relative hazard, 2.8 [CI, 1.3 to 6.0]; *P* = 0.008) and pulmonary embolism (11 compared with 4; relative hazard, 2.8 [CI, 0.9 to 8.7]; *P* = 0.08) (**Table 2**). Two women, both in the hormone therapy group, died of pulmonary embolism. The relative hazard was increased for idiopathic (relative hazard, 3.1 [CI, 0.8 to 11.3]) and nonidiopathic venous thromboembolic events (relative hazard, 2.5 [CI, 1.2 to 5.3]). The overall results were unchanged in an as-treated analysis that was limited to women who reported taking more than 80% of their assigned study medication (relative hazard, 3.2 [CI, 1.5 to 6.9]; *P* = 0.003).

Table 2 shows relative hazards for venous thromboembolism by year since randomization. The number of episodes of pulmonary embolism was small, but a statistically significant decrease in relative hazard was seen over time (*P* = 0.05 for test of contin-

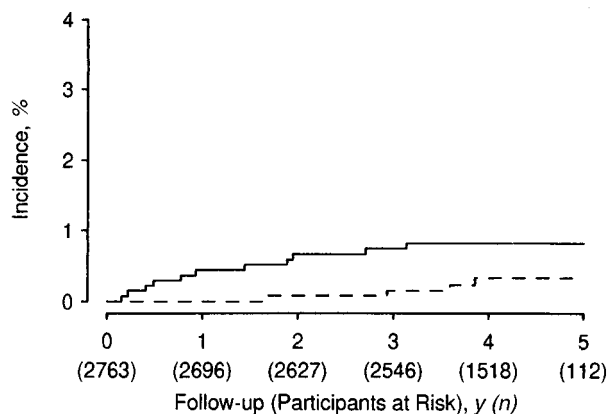
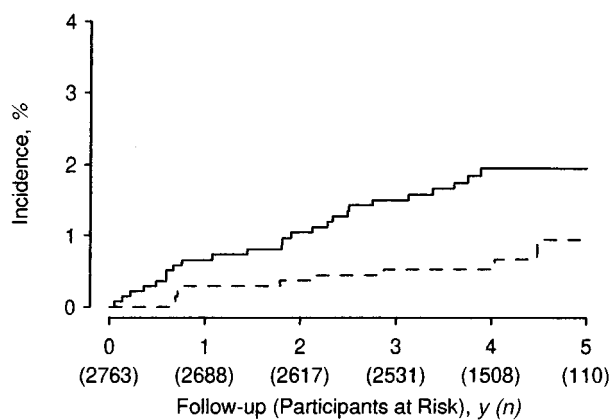
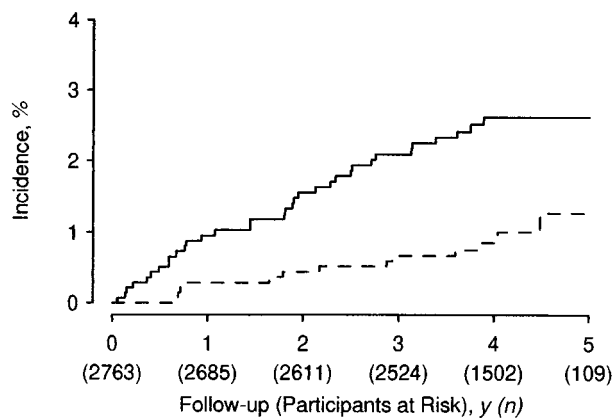


Figure. Kaplan-Meier estimates of the cumulative incidence of venous thromboembolic events (top), deep venous thrombosis (middle), and pulmonary embolism (bottom). The solid line represents the cumulative incidence of events among women assigned to hormone therapy, and the dashed line represents the cumulative incidence among women assigned to placebo. The number of women observed at each year of follow-up who remained free of an event is given in parentheses. Median follow-up was 4.1 years.

uous trend in relative hazard). There was no trend to decreasing relative hazard over time for deep venous thrombosis.

We evaluated multiple baseline characteristics of HERS participants and events that occurred during follow-up to determine predictors of venous thromboembolism. In univariate analyses, each of the variables in **Table 3** was associated with risk for venous thromboembolism ($P < 0.2$). In a multivariate model including these variables (**Table 3**), the only baseline characteristic that was independently predictive of venous thromboembolism was age older than 52 years at last menstrual period (relative hazard, 3.6 [CI, 2.0 to 6.4]; $P < 0.001$). After adjustment for other predictors, assignment to hormone therapy remained a significant predictor of venous thromboembolism (relative hazard, 2.7 [CI, 1.4 to 5.1]; $P = 0.003$).

Risk for venous thromboembolism was increased among women who had lower-extremity fractures (relative hazard, 18.1 [CI, 5.4 to 60.4]) or developed cancer (relative hazard, 3.9 [CI, 1.6 to 9.4]) and in the first 90 days after inpatient surgery (relative hazard, 4.9 [CI, 2.4 to 9.8]) and nonsurgical hospitalization (relative hazard, 5.7 [CI, 3.0 to 10.8]).

Women who had myocardial infarction had a 2.1-fold higher risk for venous thromboembolism over the entire course of follow-up, but during the first 90 days after infarction, risk was increased more than fivefold (relative hazard, 5.9 [CI, 2.3 to 15.3]; $P < 0.001$). A nonsignificant increased risk for venous thromboembolism after stroke or transient ischemic attack was found (relative hazard, 2.0 [CI, 0.8 to 5.3]); this increased risk was not more marked in the first 90 days after stroke. Warfarin use was not associated with lower risk for venous thromboembolism, but the small number of women using warfarin and the fact that they were likely to be at high risk for venous thromboembolism limited our ability to detect a protective effect. The risk for venous thromboembolism was 50% lower in women who reported using aspirin during the trial than in those who did not (relative hazard, 0.5 [CI, 0.2 to 0.8]). Use of statins but not other lipid-lowering drugs also reduced the risk for venous thromboembolism by 50% (relative hazard, 0.5 [CI, 0.2 to 0.9]). No differences were seen in the relative hazard associated with hormone therapy in women with and those without other risk factors for venous thromboembolism.

Discussion

The HERS is the first large randomized trial to examine the effect of postmenopausal hormone therapy on risk for venous thromboembolism. Treatment was blinded and venous thromboembolic events were documented by accepted diagnostic tests. Women assigned to hormone therapy had a

threefold increase in risk for thromboembolic events compared with those assigned to placebo. Although the number of events was small, the relative risk seemed to be similar for both idiopathic and non-idiopathic venous thromboembolism: that is, among women with and those without other risk factors for venous thromboembolism.

The findings of HERS are consistent with those of five recent observational studies that reported a twofold to fourfold increased risk for idiopathic venous thromboembolism in postmenopausal women taking oral estrogen or estrogen plus progestin compared with nonusers (9–13). All five studies included only women without known risk factors for venous thromboembolism, and the outcome was limited to idiopathic thromboembolic events. Women with a history of venous thromboembolism were excluded from HERS, but HERS participants were older than women in the observational studies and all had coronary heart disease. In addition, both idiopathic and nonidiopathic thromboembolic events were included in the outcome in HERS. Although the relative hazards from the observational studies and the HERS trial are similar, these differences in the populations studied and the definition of outcome resulted in a rate of thromboembolism among HERS participants (2.3 per 1000) that was 10-fold higher than the rates in the observational studies. The results of observational studies may have exaggerated the risk for venous thrombosis due to hormone use if physicians have a higher suspicion of thrombosis among hormone therapy users. This potential bias should have been eliminated in HERS to the extent that blinding was successful.

Given the design of the trial, we cannot determine whether the increased risk for venous thromboembolism observed in HERS participants taking oral hormone therapy was due to the estrogen component, the progestin component, or both. However, in observational studies, risk for venous thromboembolism was increased similarly in women using unopposed estrogen and in those using estrogen plus a progestin (9, 12). On the basis of these findings and evidence from studies of oral contraceptive pills (1, 2), the estrogen component of hormone therapy is most likely responsible for the observed increased risk. Other estrogen-like drugs, including tamoxifen and raloxifene, have also been shown in randomized trials (17, 18) to increase risk for venous thromboembolism.

Oral estrogen therapy is associated with high hormone concentrations in the liver. This “first-pass” effect may alter hepatic production or metabolism of coagulation factors, but no clear mechanism has been identified. Compared with nonusers, women who take postmenopausal estrogen have higher serum levels of factor VII (19–21) and protein C (20), differences that could be thrombogenic.

Although the number of pulmonary emboli that occurred during the trial was small, the relative hazard seemed to decrease over time. The increased risk for pulmonary embolism in the first 1 to 2 years of treatment, followed by a decrease in risk, is similar to the pattern seen for the primary outcome of HERS, coronary heart disease (14), and to the increased risk for venous thromboembolism seen during the first year of treatment in observational studies (10, 13). This pattern might be explained by a

Table 2. Venous Thrombotic Events by Treatment Group and Year of Randomization

Thromboembolic Events	Patients Who Received Hormone Therapy (n = 1380)	Patients Who Received Placebo (n = 1383)	Relative Hazard (95% CI)	P Value
	<i>n</i>			
Any venous thrombosis*	34	13	2.7 (1.4–5.0)	0.003
Year 1	13	4	3.3	0.13†
Year 2	8	2	4.1	
Year 3	7	3	2.4	
Years 4 and 5	6	4	1.5	
Deep venous thrombosis‡	25	9	2.8 (1.3–6.0)	0.008
Year 1	9	4	2.3	>0.2†
Year 2	5	1	5.1	
Year 3	6	2	3.1	
Years 4 and 5	5	2	2.5	
Pulmonary embolism§	11	4	2.8 (0.9–8.7)	0.08
Year 1	6	0	–	0.05†
Year 2	3	1	3.1	
Year 3	1	1	1.0	
Years 4 and 5	1	2	0.5	
Idiopathic event	9	3	3.1 (0.8–11.3)	0.09
Nonidiopathic event	25	10	2.5 (1.2–5.3)	0.01

* In the hormone therapy group, two women experienced both deep venous thrombosis and pulmonary embolism.

† By test of continuous trend in log-relative hazard.

‡ Two women experienced more than one episode of deep venous thrombosis.

§ Two episodes of pulmonary embolism were fatal; both occurred in the hormone therapy group.

|| Events that occurred in women who did not have concomitant cancer, nonfatal myocardial infarction, congestive heart failure, or stroke or did not have fracture, surgery, or hospitalization in the 3 months before the venous thrombotic event.

Table 3. Predictors of Venous Thromboembolic Events

Characteristic or Event	Women (Events), <i>n</i> (<i>n</i>)*	Univariate Relative Hazard (95% CI)†	Multivariate Relative Hazard (95% CI)†
Baseline characteristic			
Age > 65 years	1618	1.9 (1.0–3.6)	
Age at last menstrual period > 52 years	578	3.4 (1.9–6.0)	3.6 (2.0–6.4)
Current smoker	360	1.0 (0.4–2.3)	
More than 5 alcoholic drinks per week	274	1.3 (0.6–3.2)	
Body mass index \geq 27 kg/m ²	1543	1.0 (0.5–1.7)	
Poor or fair health	665	0.8 (0.4–1.6)	
Systolic blood pressure > 140 mm Hg	976	1.5 (0.9–2.7)	
Diabetes‡	505	1.2 (0.6–2.3)	
Assignment to hormone therapy	1380	2.7 (1.4–5.0)	2.7 (1.4–5.1)
Events during follow-up			
Fracture			
Hip			
Lower extremity (nonhip)	27 (30)	37.5 (5.1–276.2)	5.6 (0.7–43.8)
Any cancer (except nonmelanoma skin cancer)	108 (110)	27.4 (8.5–88.7)	18.1 (5.4–60.4)
Inpatient surgery within 90 days	191 (197)	7.5 (3.3–17.4)	3.9 (1.6–9.4)
Nonsurgical hospitalization within 90 days	944 (1454)	14.5 (7.7–27.1)	4.9 (2.4–9.8)
Congestive heart failure	1575 (4049)	12.2 (6.9–21.8)	5.7 (3.0–10.8)
Nonfatal myocardial infarction	658 (443)§	1.7 (0.9–3.2)	
Stroke or transient ischemic attack	254 (285)	3.6 (1.5–8.7)	2.1 (0.9–5.3)
Medication use	214 (258)	4.2 (1.6–10.8)	2.0 (0.8–5.3)
Aspirin	2534	0.4 (0.2–0.6)	0.5 (0.2–0.8)
Warfarin	403	1.9 (0.7–4.7)	
Lipid-lowering medication			
Statins	1711	0.4 (0.2–0.7)	0.5 (0.2–0.9)
Other	683	0.8 (0.3–1.9)	

* Number of events that occurred before the first thromboembolic event.

† Postrandomization events and medication use were represented by time-dependent indicators, which reverted to zero 90 days after fracture, surgery, and hospitalization or when medication use was discontinued.

‡ Women who were taking oral hypoglycemic drugs or insulin.

§ Includes women who had signs of congestive heart failure at baseline.

selective effect of hormone therapy on a specific group of women at risk for thrombosis, such as those with hypercoagulable states. However, a similar time-dependent decrease in relative hazard for deep venous thrombosis was not seen. Because pulmonary embolism is generally the result of embolization from clots in the deep veins of the legs, this apparent difference in the time-dependence of the effect of hormone therapy on pulmonary embolism and deep venous thrombosis probably represents a chance finding.

To determine how long the risk for venous thrombosis remains elevated after hormone therapy is stopped, we performed analyses focusing on events that occurred 1 week, 1 month, and 3 months after discontinuation of therapy. The relative hazard for venous thrombosis seemed to remain elevated for at least the first 30 days after discontinuation of study medication (relative hazard, 2.5 [CI, 0.6 to 9.7]), but the number of events was too small to allow us to draw firm conclusions.

Examination of risk factors for venous thromboembolism revealed several interesting findings. Risk factors that have been identified in previous observational studies (22, 23), such as age, smoking, obesity, and hypertension, were not significantly associated with venous thromboembolism after adjustment for events that occurred during follow-up (fractures, cancer, surgery, and hospitalization), but the number of venous thromboembolic events in the trial

was small and may have limited power to detect risk factors.

Older age at menopause was strongly associated with increased risk for venous thromboembolism. We examined many potential predictors, and this finding might be due to chance. If it is real, the mechanism of this association is unclear; women who undergo menopause at a later age may have higher levels of endogenous estrogen production or other hormonal differences that put them at increased risk.

Hip fracture increased risk for venous thromboembolism 6-fold, but other lower-extremity fractures increased this risk 18-fold. This difference persisted even after adjustment for use of warfarin. The higher relative hazard associated with lower-extremity fracture compared with hip fracture might be the result of chance, given the small number of venous thromboembolic events, or of the fact that early ambulation, compression devices, and physical therapy are emphasized after hip fracture but not after lower-extremity fractures. The rate of venous thromboembolism in the first 3 months after lower-extremity fracture was 23 per 100 women, suggesting that mobilization and compression devices should be encouraged after fracture and that routine anticoagulation, as instituted after hip fracture, might be of benefit.

Risk for venous thromboembolism was increased fivefold during the first 90 days after myocardial

infarction, even after adjustment for hospitalization. The reason for this increased risk is unclear. Women who have myocardial infarction may be less mobile or active for a few months after the event or may experience some persistent hypercoagulable state. The rate of venous thrombosis in the first 90 days after myocardial infarction was 10 per 100 women, even though about 80% of the participants were taking aspirin daily. This high rate of venous thromboembolism after infarction suggests that more attention should be given to mobilization after infarction and that anticoagulation should perhaps be considered, particularly in women who are otherwise at high risk.

We found reduced risk for venous thromboembolism among women taking statins but not other lipid-lowering drugs. Treatment with statins seems to decrease risk for coronary events more than would be expected on the basis of the resulting improvement in lipoprotein levels (24). Some of this beneficial effect may be due to decreased coronary arterial thrombus formation mediated by inhibitory actions on platelet deposition and aggregation or favorable effects on coagulation factors, rheology, and fibrinolysis (25, 26). These mechanisms may also decrease the risk for venous thromboembolism. To our knowledge, previous trials of lipid-lowering drugs have not reported an effect on risk for venous thromboembolism. Treatment with aspirin, which was also associated with lower risk for venous thromboembolism in our study, is known to reduce the risk for arterial thromboembolism, including myocardial infarction (27) and stroke, particularly in persons at high risk (such as those with chronic atrial fibrillation) (28). To our knowledge, no other study has evaluated the effect of long-term aspirin therapy on the risk for venous thromboembolism in women with established coronary disease.

The absolute risk for venous thromboembolic events among women in the placebo group in HERS was 2.3 per 1000 woman-years. This rate is substantially higher than that observed among younger women but is similar to rates in other populations of elderly women (22). Among women in HERS, treating 256 women for 1 year would be expected to result in one additional episode of venous thrombosis; this number needed to treat for harm is likely to be similar in other populations of elderly women. However, the number needed to treat for harm among young women is likely to be substantially higher, given the lower absolute risk for venous thrombosis. The excess risk for venous thrombosis (4.0 events per 1000 women in HERS) would be acceptable if hormone therapy provides other benefits that outweigh this risk. Clinicians should consider increased risk for venous thromboembolism when counseling women about the risks

and benefits of postmenopausal hormone therapy, and women at very high risk because of history of venous thromboembolism, cancer, lower-extremity fracture, or immobilization should avoid postmenopausal hormone therapy.

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