

Postmenopausal Estrogen Replacement and Risk for Venous Thromboembolism: A Systematic Review and Meta-Analysis for the U.S. Preventive Services Task Force

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Background: Postmenopausal estrogen replacement is widely used in the United States but poses important health risks.

Purpose: To assess the risk for venous thromboembolism with postmenopausal estrogen replacement by using literature review and meta-analysis.

Data Sources: All relevant English-language studies identified in searches of the MEDLINE (1966 to December 2000), HealthSTAR (1975 to December 2000), and Cochrane Library databases, and references lists of key articles.

Study Selection: All published studies of postmenopausal estrogen replacement reporting venous thromboembolism as an outcome or adverse event.

Data Extraction: 12 studies of estrogen were identified (3 randomized, controlled trials; 8 case-control studies; and 1 cohort study). Data were extracted on participants, interventions, event rates, and confounders. Two reviewers independently rated study quality on the basis of established criteria.

Data Synthesis: A Bayesian meta-analysis was conducted. When data from all studies were pooled, current estrogen use was associated with an increased risk for venous thromboembolism (relative risk, 2.14 [95% credible interval, 1.64 to 2.81]). Estimates did not significantly change when studies were pooled according to study design, quality score, or whether participants had pre-existing coronary artery disease. The absolute rate increase was 1.5 venous thromboembolic events per 10 000 women in 1 year. Six case-control studies that reported risk according to duration of use found that risk was highest in the first year of use (relative risk, 3.49 [credible interval, 2.33 to 5.59]).

Conclusion: Postmenopausal estrogen replacement is associated with an increased risk for venous thromboembolism, and this risk may be highest in the first year of use.

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Although postmenopausal estrogen replacement is widely used (1), it poses important health risks. One risk is an increase in venous thromboembolic events. This relationship was initially established on the basis of studies of oral contraceptives (2) and was not supported by studies of postmenopausal estrogen replacement (3–5). Findings from more recent studies (6–13) indicate an increased risk. To precisely estimate the venous thromboembolic risk with postmenopausal estrogen replacement therapy, we reviewed the literature and conducted a meta-analysis of eligible studies. The most recent review of this topic did not include a meta-analysis (14). We conducted our review in conjunction with the U.S. Preventive Services Task Force to update the Task Force's recommendations on hormone replacement therapy. This paper is part of a larger project on hormone replacement therapy; other risks and benefits are reported separately (15).

METHODS

With assistance from a medical librarian, we searched the following databases: MEDLINE (1966 to

December 2000), HealthSTAR (1975 to December 2000), and the Cochrane Controlled Trials Register. Because venous thromboembolism is usually reported as a secondary or adverse outcome in studies with unrelated primary outcomes, we used multiple search terms: *hormone replacement therapy, estrogen replacement, thromboembolism, thrombophlebitis, pulmonary embolism, blood clot, thrombosis, blood coagulation disorders, hemostasis, hypercoagulation, fibrinogen, fibrinolysis, anticoagulants, thrombolytic therapy, and randomized controlled trials*. Additional articles were obtained by reviewing reference lists of pertinent reports and reviews. We used only published data. Seven content experts reviewed this report.

The studies included in this review enrolled postmenopausal women and included deep venous thrombosis, pulmonary embolism, or venous thromboembolism as a primary or secondary outcome or as a reportable adverse event related to estrogen use. When data were available, we report effects of dosage, duration, and progestin use. Only articles with English-language abstracts were considered. We excluded studies with participants selected on the basis of previous

thrombotic events or presence of conditions that are associated with higher risk for thrombosis.

From each included study, we abstracted the number of participants, treatment (for randomized, controlled trial) or definition and method of determining exposure (for case-control and cohort studies), event rates, confounders controlled for, methods of outcome measurement, and study duration. Two reviewers independently rated each study's quality using criteria developed by the U.S. Preventive Services Task Force (Appendix, available at www.annals.org); ratings between reviewers had 76% agreement. Reviewer disagreements were resolved by consensus.

We performed a meta-analysis of the 12 studies of estrogen use meeting the inclusion criteria. Two studies (11, 12) reported hazard ratios derived from Cox proportional hazards models. A hazard ratio is the ratio of the instantaneous probability of venous thromboembolism in the treatment group compared with that in the control group and can be considered the relative risk. Two studies provided the raw data with which to calculate unadjusted relative risks (16, 17). One study provided data with which to calculate an age-adjusted relative risk (3). The remaining studies reported odds ratios from logistic regression models; for these studies, we used the most adjusted value provided (6–10, 13, 18). Because venous thromboembolism is a rare event, the odds ratio is a good estimate for the relative risk. Thus, for uniformity, we report pooled estimates as relative risk.

Under the modeling assumptions made by each study, the logarithm of the relative risk (log relative risk) had a normal distribution. Standard errors for log relative risk were calculated from the reported 95% confidence intervals or from the raw data. The log relative risk and SEs provided the data points for the meta-analysis.

We fit fixed-effects and random-effects models on the data using the Bayesian data analytic framework (19). We report only the random-effects model because the results of the two models were sufficiently similar. To analyze the data, we used WinBUGS software (20), which uses Gibbs sampling to simulate posterior probability distributions. Noninformative (proper) prior probability distributions were used ($N[0, 10^6]$ for log relative risks). Point estimates and 95% credible intervals were calculated from 5000 simulated draws (1000

draws from 5 chains) from the posterior distribution after adequate convergence.

Because the study designs among the 12 studies differed, a meta-analysis was performed for each study type, excluding the single cohort study. We constructed a regression model with study design as a variable and found no differences in results. Thus, we combined all 12 studies for a pooled analysis. In a sensitivity analysis, we combined only studies with a good or fair quality rating, studies enrolling participants with coronary artery disease, and studies excluding women with coronary artery disease.

We evaluated studies for selection bias using funnel plots (21), and we investigated the sensitivity of the analysis to possible missing studies due to publication bias by using the “trim and fill” method (22, 23). The results were unaffected.

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RESULTS

Search Results

We identified 3363 abstracts from our search of postmenopausal estrogen and venous thromboembolism; most abstracts did not specifically address this topic and were excluded from full-text review. Twelve abstracts met the inclusion criteria and contained primary data (3 randomized, controlled trials [12, 16, 17]; 8 case-control studies [3, 6–10, 13, 18]; and 1 cohort study [11]). Three other studies (4, 5, 24) identified from a review article (14) did not meet the inclusion criteria (Appendix Figure, available at www.annals.org).

Randomized, Controlled Trials

None of the 3 randomized, controlled trials had venous thromboembolism as a primary outcome (Table 1). The Heart and Estrogen/progestin Replacement Study (HERS) (12) was a 4-year secondary prevention trial of estrogen and progestin therapy in postmenopausal women with heart disease. Although the primary outcomes were nonfatal myocardial infarction or death from coronary heart disease, deep venous thrombosis and pulmonary embolism were reported as secondary

Table 1. Characteristics of Estrogen Studies*

Study, Year (Reference)	Clinical Setting	Age†	Estrogen Type	Estrogen Dosage	Adherence Rate; Method of Verification
		y		mg/d	
Randomized, controlled trials					
PEPI, 1995 (16)	Outpatients	56.1	Conjugated	0.625	>80% at 3 y; pill count
Hulley et al. (HERS), 1998 (12)	Outpatients	67	Conjugated	0.625	70% at 3 y; pill count
Herrington et al. (ERA), 2000 (17)	Outpatients	65.8	Conjugated	0.625	Not stated; pill count
Case-control studies					
Devor et al., 1992 (18)	Hospitalized case-patients and controls	≥45	Conjugated	Not specified	NA
Daly et al., 1996 (6)	Hospitalized case-patients and controls	45–64	Multiple forms	Multiple doses	NA
Daly et al., 1996 (7)	Hospitalized case-patients and controls	45–64	Not specified	Not specified	NA
Jick et al., 1996 (8)	Hospitalized case-patients and population-based controls	50–74	Multiple forms	Multiple doses	NA
Pérez Gutthann et al., 1997 (9)	Hospitalized case-patients and population-based controls	50–79	Multiple forms	Multiple doses	NA
Varas-Lorenzo et al., 1998 (10)	Hospitalized case-patients and population-based controls	45–79	Multiple forms	Multiple doses	NA
Høibraaten et al., 1999 (13)	Hospitalized case-patients and population-based controls	45–70	Estradiol	Multiple doses	NA
Boston Collaborative, 1974 (3)	Hospitalized case-patients and controls	45–69	Not specified	Not specified	
Cohort study					
Grodstein et al., 1996 (11)	Outpatients	30–55 (in 1976)	Conjugated	Multiple doses	NA

* BMI = body mass index; DVT = deep venous thrombosis; ERA = Estrogen Replacement and Atherosclerosis trial; HERS = Heart and Estrogen/progestin Replacement Study; NA = not applicable; PE = pulmonary embolism; PEPI = Postmenopausal Estrogen/Progestin Interventions trial.

† Data are presented as the mean age or the age range of participants.

outcomes. Deep venous thrombosis was diagnosed by using venography, impedance plethysmography, or ultrasonography; pulmonary embolism was diagnosed by nuclear lung scanning or pulmonary angiography. The treatment group had 34 venous thromboembolic events (2.5% of the 1380 participants), and the placebo group had 13 (0.9% of the 1383 participants) (Table 2). The hazard ratio for venous thromboembolism was 2.89 (95% confidence interval, 1.50 to 5.58). A second HERS report (25) presented idiopathic events (hazard ratio, 3.1 [confidence interval, 0.8 to 11.3]) and non-idiopathic events (hazard ratio, 2.5 [confidence interval, 1.2 to 5.3]) separately. Risk was highest in the first 2 years of estrogen use (Figure 1).

The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial (16) studied healthy postmenopausal women receiving estrogen replacement, alone or with a progestin, in various forms and dosages compared with placebo. Four measures of cardiovascular risk were the primary end points. Thromboembolic events were reported as adverse experiences during the follow-up phase; the study did not report the method for measuring events. The definition of venous thromboembolism included deep venous thrombosis, pulmonary embolism, and superficial phlebitis. Ten venous thromboembolic events occurred among the four estrogen treatment groups, and none occurred in the placebo group ($P > 0.2$).

Table 1—Continued

Method of Outcome Measurement	Method of Determining Exposure	Adjusted Confounders	Follow-up Rate
			%
Not stated	NA	NA	97
For DVT: venography, plethysmography, or ultrasonography; for PE: nuclear lung scanning or pulmonary angiography	NA	NA	100
Not stated	NA	NA	80
Clinical examination and diagnostic procedures	Chart review	None	NA
Diagnosis at hospital admission	Interview	BMI, varicose veins, socioeconomic group	NA
For PE: ventilation–perfusion lung scanning, pulmonary angiography, or clinical examination; for DVT: venography, duplex scanning, radioisotope studies, or clinical examination	Interview	BMI, socioeconomic group	NA
For PE: ventilation–perfusion lung scanning; for DVT: venography, ultrasonography or Doppler ultrasonography, and treatment with anticoagulants	Pharmacy records	BMI, smoking status, varicose veins	NA
Discharge diagnosis, clinical symptoms, and diagnostic procedures	National formulary	BMI, smoking status, varicose veins or superficial phlebitis, age, oophorectomy status	NA
Clinical signs and symptoms and positive result on diagnostic test, treatment with anticoagulants, or necropsy	Prescription database	BMI, age, history of varicose veins or superficial phlebitis, hypertension, diabetes mellitus, and osteoarthritis	NA
Venography (<i>n</i> = 135); ventilation–perfusion lung scan (<i>n</i> = 33); autopsy finding (<i>n</i> = 9); ultrasonography (<i>n</i> = 7); pulmonary angiography (<i>n</i> = 2); clinical diagnosis (<i>n</i> = 2)	For case-patients: chart review and questionnaire; for controls: questionnaire	Hypertension, diabetes mellitus, coronary artery disease, smoking status, previous venous thromboembolism, BMI	NA
For DVT: not specified; for PE: lung scanning, angiography, or surgery	Interview	None	NA
Ventilation–perfusion lung scanning, pulmonary angiography, or necropsy	Questionnaire every 2 y	Age, BMI, hypertension, diabetes, smoking status, oral contraceptive use, parity, elevated cholesterol level	>90 (estimate)

The Estrogen Replacement and Atherosclerosis (ERA) trial (17) randomly assigned 309 women with angiographically proven coronary heart disease to estrogen, estrogen and progesterone, or placebo and performed follow-up coronary angiography after approximately 3 years to assess disease progression. A total of 8 venous thromboembolic events were reported—5 in the estrogen group, 2 in the estrogen–progesterone group, and 1 in the placebo group—with no significant difference among the groups ($P = 0.16$).

The quality ratings, which used U.S. Preventive Services Task Force criteria, were good for HERS and fair for the PEPI and ERA trials (Table 2). Although HERS reported venous thromboembolism as a secondary out-

come and described how the diagnosis was made, both the PEPI and ERA trials reported these events as an adverse experience and did not describe the method of diagnosis. The studies also differed in ways unrelated to quality ratings. The HERS and ERA trials enrolled older, postmenopausal women with documented coronary artery disease (mean age, 66.7 years), while the PEPI trial enrolled younger, healthy postmenopausal women (mean age, 56.1 years). The HERS trial ($n = 2763$) randomly assigned more than three times as many participants as the PEPI trial ($n = 875$) and nearly nine times as many as the ERA trial ($n = 309$), allowing for greater power to detect events. The PEPI trial included superficial phlebitis in its definition of venous thrombo-

Table 2. Studies of Estrogen Included in the Meta-Analysis*

Study, Year (Reference)	Events in Exposed Participants	Events in Nonexposed Participants	Relative Risk (95% Confidence Interval)	Event Rate in Estrogen Users†	Number Needed To Treat for Harm‡	Quality Rating
	<i>n/n</i>			<i>n/10 000 women</i>	<i>n</i>	
Randomized, controlled trials						
PEPI, 1995 (16)	10/682	0/165	5.10 (0.30–86.66)§	47.6	210	Fair
Hulley et al. (HERS), 1998 (12)	34/1380	12/1383	2.89 (1.50–5.58)	12.2	256	Good
Herrington et al. (ERA), 2000 (17)	7/204	1/105	3.70 (0.45–30.44)§	114.4	123	Fair
Case-control studies						
Devor et al., 1992 (18)	6/20	112/334	0.79 (0.30–2.08)	Not reported	Not reported	Poor
Daly et al., 1996 (6)	44/88	59/193	3.5 (1.8–7.0)	2.7	5882	Fair
Daly et al., 1996 (7)	4/18	14/143	2.3 (0.6–8.1)	Not reported	Not reported	Poor
Jick et al., 1996 (8)	21/63	21/105	3.6 (1.6–7.8)	3.2	4347	Good
Pérez Gutthann et al., 1997 (9)	37/1116	243/8689	2.1 (1.4–3.2)	2.7	7142	Good
Varas-Lorenzo et al., 1998 (10)	6/238	164/9765	2.3 (1.0–5.3)	2.9	3448	Good
Høibraaten et al., 1999 (13)	50/143	126/385	1.22 (0.76–1.96)	Not reported	Not reported	Fair
Boston Collaborative, 1974 (3)	3/63	15/774	2.26 (0.61–8.41)§	Not reported	Not reported	Poor
Cohort study						
Grodstein et al., 1996 (11)	22/155 669¶	27/320 339¶	2.1 (1.2–3.8)	2.0**	25 000**	Good

* ERA = Estrogen Replacement and Atherosclerosis trial; HERS = Heart and Estrogen/progestin Replacement Study; PEPI = Postmenopausal Estrogen/Progestin Interventions trial.

† Event rates reported in the studies were standardized per 10 000 exposed women in 1 year.

‡ Women needed to treat for 1 year to cause one additional event.

§ Relative risk was not reported in the study but was calculated from the data provided.

|| Age-adjusted relative risk.

¶ The denominator represents person-years.

** Current users.

embolism and had only four cases of deep venous thrombosis or pulmonary embolism.

Case-Control Studies

Six (6–10, 13) of the 8 case-control studies reported an increased risk for venous thromboembolism with estrogen use; in 3 of the 6 studies, the results were statistically significant (Table 2). Five studies reported an increased risk in the first year of use (Figure 1). Two of the 8 case-control studies did not report an increased risk (3, 18); 1 of these studies did not use multivariable analysis to control for potential confounders (18).

Four studies used hospital-based controls (3, 6, 7, 18), and 4 others used population-based controls (8–10, 13). Enrolled women were 45 to 79 years of age. Hormonal preparations varied among the studies. Five studies used various doses of conjugated estrogen (3, 6, 8, 9, 18), 1 used transdermal estrogen (10), a Scandinavian study included only estradiol formulations (13), and the other study did not report estrogen type (7). Three of the studies did not specify the use of a progestin together with estrogen (3, 7, 18); the remaining studies did not report dosage and type of progestin use (6, 8–10, 13).

Exposure history and ascertainment of exposure his-

tory also varied among studies. Estrogen replacement was described as current use, past use, never use, ever use, or nonuse, with definitions varying across studies. The methods of determining exposure included interview (3, 6, 7), chart review alone (18), chart review and questionnaire (13), and review of various pharmacy databases (8–10).

The method of outcome assessment also varied. Studies with the most rigorous criteria required a positive result on venography, ultrasonography, or Doppler ultrasonography for diagnosis of deep venous thrombosis and required a positive result on ventilation-perfusion scanning for pulmonary embolism diagnosis as well as documentation of therapy with heparin and oral anti-coagulants (8). Another study classified cases into categories (definite, probable, possible) on the basis of evidence of venous thromboembolism, although cases from all three categories were included in the analysis (6). Other studies did not indicate the method of outcome measurement (3, 7), used a random sample to validate 10% of the cases (9), or simply stated that all cases had at least one diagnostic test in addition to a clinical examination (18).

The most common confounders controlled for in these studies were body mass index (6–10, 13) and his-

tory of varicose veins (6, 8–10). Only three studies controlled for smoking status (8, 9, 13).

Some studies reported the effects of dose and regimen, although the study samples were small. Three studies (6, 8, 9) reported a higher risk with increased estrogen dose (>0.625 mg of conjugated estrogen compared with lower doses). Three studies reported a higher risk (odds ratio, 2.2 to 5.3) for use of estrogen combined with a progestin compared with use of estrogen alone (6, 9, 10). Only one study (6) reported a comparison of oral estrogen (odds ratio, 4.6 [confidence interval, 2.1 to 10.1]) with transdermal estrogen (odds ratio, 2.0 [confidence interval, 0.5 to 7.6]).

The quality-score ratings varied among the case-control studies (3 received a rating of good, 3 were considered fair, and 2 were considered poor). In some studies, the accuracy of results was compromised by small numbers of events and failure to control for important confounders. For example, 2 studies had 4 and 6 exposed cases (6, 10), respectively, and did not control for smoking status. Despite having more exposed cases, the Scandinavian study (13) was compromised because it did not report estradiol doses or method of outcome measurement. In most studies, estrogen exposure (type, dose, and duration) and method of determining exposure were inadequately or inconsistently measured. Two studies used pharmacy records to determine estrogen exposure (8, 9). Patient interviews are subject to potential

recall bias, and pharmacy databases indicate active prescriptions but do not confirm medication adherence. Discrepant definitions of hormone use are potentially significant because some of the studies indicated increased risk for venous thromboembolism with shorter duration of estrogen use. One study was not peer reviewed (7), and 1 had important differences in patient characteristics between the case-patients and controls (18).

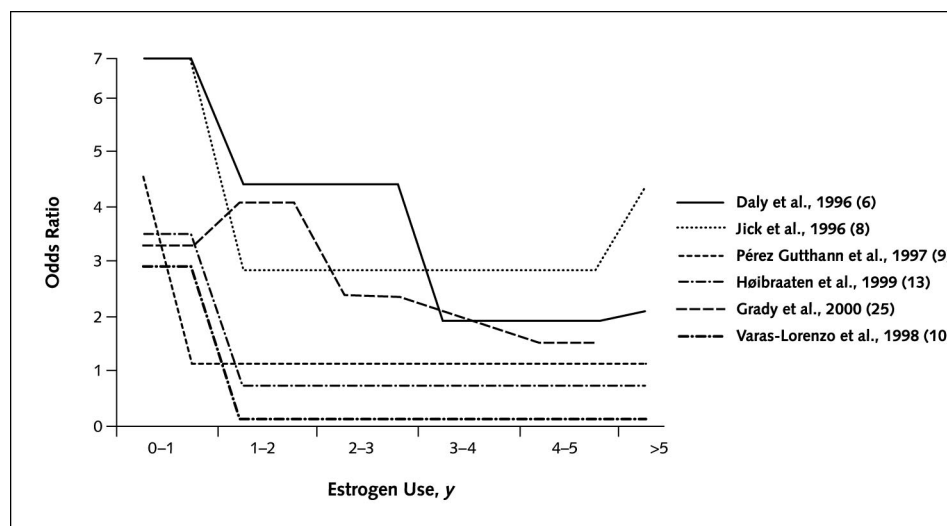
Cohort Studies

The only cohort study identified from our search used 16 years of data from the Nurses' Health Study and reported primary pulmonary embolism only (11). The current-use group had 22 pulmonary emboli (relative risk, 2.1 [confidence interval, 1.2 to 3.8]). No trends were observed for the various estrogen dosages. Among current users, risk was lower in persons taking estrogen for at least 5 years (relative risk, 1.9 [confidence interval, 0.9 to 4.0]) than in persons using estrogen for less than 5 years (relative risk, 2.6 [confidence interval, 1.2 to 5.2]). This study had a good quality rating.

Bayesian Data Interpretation

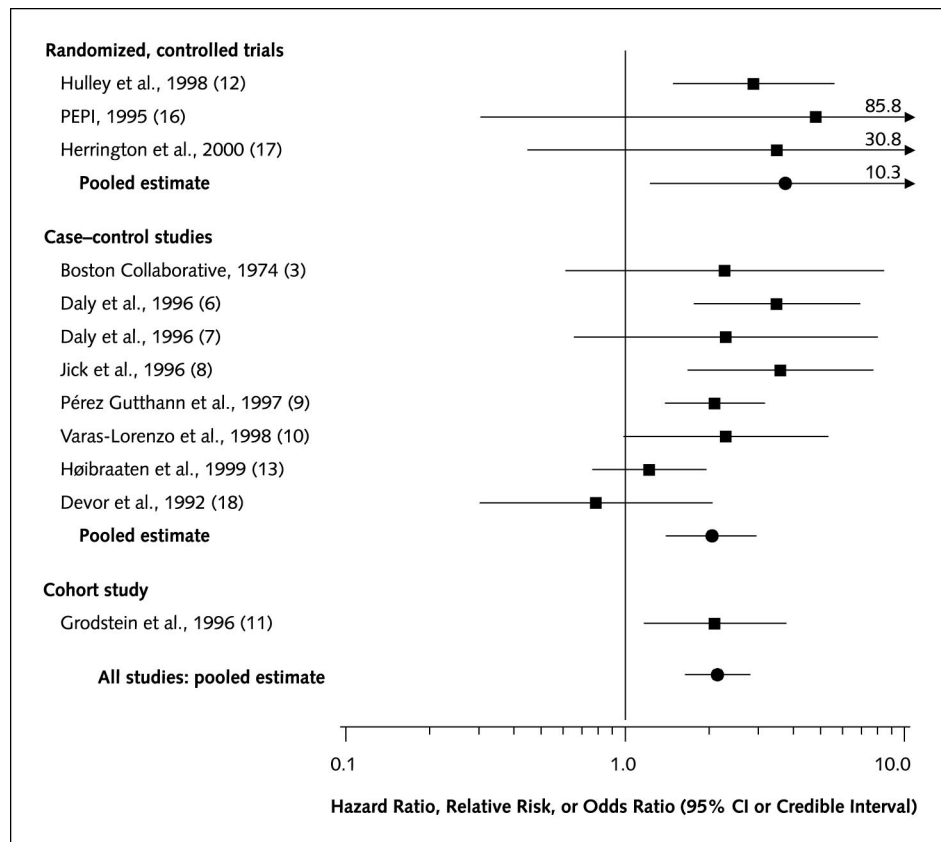
Results of the 12 estrogen studies were combined by using meta-analysis (Figure 2). The test of heterogeneity indicated that the studies were not heterogeneous ($P = 0.196$). For the 3 randomized, controlled trials (12, 16,

Figure 1. Risk for venous thromboembolism by year of estrogen use.



Odds ratios for thromboembolic events were higher in the first or second year than in subsequent years in all six studies reporting results by year of use.

Figure 2. Meta-analysis of estrogen studies.



The pooled estimate of venous thromboembolism risk for all 12 studies meeting eligibility criteria was 2.14 (95% credible interval, 1.64 to 2.81). Numbers above the lines ending in arrows indicate the outer limits of the confidence intervals. PEPI = Postmenopausal Estrogen/Progestin Interventions trial.

17), the relative risk estimate was 3.75 (95% credible interval, 1.23 to 10.26). When only the 8 case-control studies were combined (3, 6–10, 13, 18), the relative risk was 2.05 (credible interval, 1.40 to 2.95). The overall relative risk for venous thromboembolism in postmenopausal women using estrogen was 2.14 (credible interval, 1.64 to 2.81). This risk did not change significantly when the idiopathic or overall hazards reported by the HERS trial were used (25). Among the 6 studies reporting first-year risk (6, 8–10, 12, 13), the pooled relative risk for an event in the first year was 3.49 (credible interval, 2.33 to 5.59). The estimated relative risk from the same 6 studies for an event after the first 12 months was 1.91 (credible interval, 1.18 to 3.52).

When we combined only the studies with a good or fair quality rating (6, 8–13, 16, 17), the relative risk was 2.25 (credible interval, 1.66 to 3.16). When we excluded all but the good-quality studies (8–12), the rel-

ative risk was 2.44 (credible interval, 1.77 to 3.40). The pooled relative risk for studies that excluded participants with known coronary artery disease (6–10, 16) was 2.73 (credible interval, 1.78 to 4.24); meanwhile, the relative risk was 3.32 (credible interval, 1.29 to 6.99) for studies whose participants had coronary artery disease (12, 17) (Appendix Table, available at www.annals.org).

DISCUSSION

Our literature review and meta-analysis of 12 studies demonstrate that current use of postmenopausal estrogen is associated with a twofold increased risk for venous thromboembolism (relative risk, 2.14 [credible interval, 1.64 to 2.81]). With a baseline risk for venous thromboembolism of 1.3 per 10 000 woman-years, based on a study with 10 000 controls, an additional 1.5 events per 10 000 women each year would be expected

(9). When we considered duration of use, the absolute incremental risk was 3.2 additional events for the first 12 months and 1.2 additional events after 12 months.

Six studies that reported risk according to duration of use (6, 8–10, 12, 13) found the highest risks in the first 1 to 2 years (combined relative risk for year 1, 3.49 [credible interval, 2.33 to 5.59]). Risk was higher among studies that included women with coronary artery disease (pooled relative risk, 3.32 [credible interval, 1.29 to 6.99]).

The apparent trend in pooled relative risk estimates by study quality (pooled relative risk for good-quality studies, 2.44; for good- and fair-quality studies, 2.25; and for all studies, 2.14) is explained by two outlying studies—one fair-quality study (13) and one poor-quality study (18)—rather than overall differences by study quality. The two outlying studies also explain most differences between the pooled estimates for randomized, controlled trials and case-control studies. Nevertheless, the pooled relative risk estimates were consistently between 2 and 3.

The findings of recent studies of estrogen replacement therapy differ from studies published earlier that showed no association with venous thromboembolism (3–5). However, the earlier studies have several methodologic limitations, and two of the studies (4, 5) did not meet our inclusion criteria for the meta-analysis. A case-control study of data from the Walnut Creek Contraceptive Drug Study (4) was designed to identify adverse outcomes of long-term oral contraceptive use. A randomized, controlled trial (5) followed an inpatient sample of women with chronic diseases for 10 years, limiting generalizability to a community-based ambulatory population. Although the earliest case-control study included in our meta-analysis (3) had no significant findings, it showed a trend toward increased venous thromboembolic events.

More recently, reanalysis of data from the Coronary Drug Project (CDP) (26) showed an increased risk for venous thromboembolism (hazard ratio, 1.62 [confidence interval, 1.62 to 2.29]) (27). This randomized, controlled trial of men with known coronary artery disease compared two dosages of estrogen therapy (2.5 mg/d and 5.0 mg/d) with placebo; the study was discontinued after the investigators observed increases in the number of deaths, nonfatal myocardial infarctions, and adverse effects in estrogen users.

Data are available for two of the selective estrogen receptor modulators (tamoxifen and raloxifene), although women in trials of these drugs tended to be younger than those in the estrogen studies. The largest of the three randomized, controlled trials of tamoxifen for breast cancer prevention, the Breast Cancer Prevention Trial (BCPT), reported a higher risk for pulmonary embolism in the tamoxifen group than in the placebo group (relative risk, 3.01 [confidence interval, 1.15 to 9.27]). The risk for deep venous thrombosis was also increased, although not significantly (relative risk, 1.60 [confidence interval, 0.91 to 2.86]) (28). A trial in Italy (29) also reported different frequency of vascular events between the tamoxifen and placebo groups ($P < 0.001$). A smaller trial in the United Kingdom (30) reported no significant differences in risk for venous thromboembolism between the tamoxifen and placebo groups.

The largest study of raloxifene, the Multiple Outcomes of Raloxifene Evaluation (MORE) (31), demonstrated a threefold increased risk for venous thromboembolism with daily raloxifene use. This 3-year trial contrasts with an earlier, smaller randomized trial 1 year in duration (32) that reported no thromboembolic events.

Studies included in our review had several important limitations. Methods for diagnosing venous thromboembolism were inconsistent among studies. Deep venous thrombosis and pulmonary embolism are difficult to diagnose, and the literature on this topic is complicated. A recent review of noninvasive strategies for diagnosing deep venous thrombosis (33) indicated that venous ultrasonography is most accurate, although several variables could have compromised the accuracy of these results. The Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) (34) reported that most patients, with or without pulmonary embolism, had abnormal results on ventilation-perfusion scanning. Because accurate diagnosis of deep venous thrombosis is difficult, misclassification of cases is possible and could affect study outcomes in either direction. However, if a patient is more likely to undergo diagnostic testing on the basis of a clinician's knowledge of her estrogen use, differential misclassification could contribute to the observed increase in risk.

Eligibility criteria differed among studies. Two of the trials (12, 17) enrolled older women with coronary artery disease. In general, the observational studies en-

rolled younger, healthier women and excluded those with atherosclerotic disease. Such differences among study samples could explain the increased thromboembolic risk reported in the intervention trials compared with the observational studies. Referral bias is more likely with observational studies, resulting in increased suspicion and subsequent diagnostic testing in women using estrogen replacement.

Several studies did not indicate ethnicity/race (6–11), and other studies enrolled predominantly white participants (12, 16, 18). Preliminary findings from the Black Women's Health Study (35) indicate a possible increased risk for venous thromboembolism (odds ratio, 1.4 [confidence interval, 1.1 to 1.6]) with use of postmenopausal estrogen replacement in African-American women (35).

Our review supports an association between estrogen replacement therapy and venous thromboembolism, although many questions remain. The pathophysiology is not well understood; however, the effect of estrogen on the vascular endothelium and on coagulation factors might affect the potential for a thromboembolic event (36, 37). These hypercoagulable states might also be opposed by properties of estrogen-induced clot lysis, and an imbalance in these processes in some women might result in thromboembolism (38). A follow-up analysis (39) of the PEPI trial observed that patients with venous thromboembolism had lower baseline fibrinogen levels than patients without venous thromboembolism. The significance of these findings is unclear. An Italian study suggests that continuous transdermal estradiol use results in better hemostatic balance of clotting factors than cyclic estradiol therapy (40).

Identification of persons at highest risk requires further investigation. The HERS trial (25) reported increased risk in patients with hip or lower-extremity fracture, cancer, hospitalization, or surgery. Other expected risk factors (hypertension, smoking, or body mass index) did not predict venous thromboembolic events. Later onset of menopause (>52 years of age) was also associated with increased risk. Use of statin medications and use of aspirin had protective effects. However, whether all of these findings can be extrapolated to women without coronary artery disease is unclear. The Estrogen in Venous Thromboembolism Trial (EVTET) reported that women with a history of venous thromboembolism using estrogen replacement therapy are at increased risk

for a recurrent event (41). Women with the factor V Leiden mutation who use estrogen are also at increased risk for atherothrombotic events (42) and venous thromboembolic events (43). Further study must determine when to screen for coagulopathies in postmenopausal women before starting estrogen replacement therapy.

An emerging emphasis on women's health, coupled with an aging population, makes it increasingly important for primary care physicians to be familiar with the risks and benefits of postmenopausal estrogen replacement. The most recent studies support an increased risk for venous thromboembolism. Preliminary data from the Women's Health Initiative (44, 45) also indicate an increased risk for venous thromboembolism with estrogen replacement therapy. All postmenopausal women considering use of estrogen replacement or selective estrogen receptor modulators should be informed of this potential adverse effect.

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