Systematic Evidence Review
Number 11

Hormone Replacement Therapy and Risk of Venous Thromboembolism

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
2101 East Jefferson Street
Rockville, MD 20852
http://www.ahrq.gov

Contract No. 290-97-0018
Task Order No. 2
Technical Support of the U.S. Preventive Services Task Force

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August 2002

Preface

The Agency for Healthcare Research and Quality (AHRQ) sponsors the development of Systematic Evidence Reviews (SERs) through its Evidence-based Practice Program. With guidance from the third U.S. Preventive Services Task Force[*] (USPSTF) and input from Federal partners and primary care specialty societies, two Evidence-based Practice Centers—one at the Oregon Health Sciences University and the other at Research Triangle Institute-University of North Carolina—systematically review the evidence of the effectiveness of a wide range of clinical preventive services, including screening, counseling, immunizations, and chemoprevention, in the primary care setting. The SERs—comprehensive reviews of the scientific evidence on the effectiveness of particular clinical preventive services—serve as the foundation for the recommendations of the third USPSTF, which provide age- and risk-factor-specific recommendations for the delivery of these services in the primary care setting. Details of the process of identifying and evaluating relevant scientific evidence are described in the "Methods" section of each SER.

The SERs document the evidence regarding the benefits, limitations, and cost-effectiveness of a broad range of clinical preventive services and will help to further awareness, delivery, and coverage of preventive care as an integral part of quality primary health care.

AHRQ also disseminates the SERs on the AHRQ Web site (http://www.ahrq.gov/uspstfix.htm) and disseminates summaries of the evidence (summaries of the SERs) and recommendations of the third USPSTF in print and on the Web. These are available through the AHRQ Web site (http://www.ahrgq.gov/uspstfix.htm), through the National Guideline Clearinghouse (http://www.ncg.gov), and in print through the AHRQ Publications Clearinghouse (1-800-358-9295).

We welcome written comments on this SER. Comments may be sent to: Director, Center for Practice and Technology Assessment, Agency for Healthcare Research and Quality, 6010 Executive Blvd., Suite 300, Rockville, MD 20852.

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[*] The USPSTF is an independent panel of experts in primary care and prevention first convened by the U.S. Public Health Service in 1984. The USPSTF systematically reviews the evidence on the effectiveness of providing clinical preventive services--including screening, counseling, immunization, and chemoprevention--in the primary care setting. AHRQ convened the third USPSTF in November 1998 to update existing Task Force recommendations and to address new topics.

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Structured Abstract

Context: Although postmenopausal hormone replacement therapy is widely used, its risks and benefits are not well understood.

Objective: To assess the risk of venous thromboembolism with the use of postmenopausal hormone replacement therapy (HRT) by literature review and meta-analysis.

Data Sources: All relevant English-language studies identified in MEDLINE (1966 to December 2000), HealthSTAR (1975 to December 2000), Cochrane library databases, and reference lists of key articles. Studies of selective estrogen receptor modulators (SERMs) were identified in MEDLINE (1991 to December 2000).

Study Selection: All studies of postmenopausal HRT or SERMs reporting venous thromboembolism as an outcome or adverse event.

Data Extraction: Twelve studies of HRT (3 randomized controlled trials, 8 case-control studies, and one cohort study), and 5 randomized controlled trials of SERMs were identified. We extracted data on number of participants, interventions, event rates, and confounders. Two reviewers independently rated study quality based on established criteria.

Data Synthesis: We used Bayesian meta-analysis. Current HRT use was associated with an increased risk of venous thromboembolism (relative risk [RR], 2.14; CI, 1.64-2.81). The absolute rate increase was 1.5 venous thromboembolic events per 10,000 women in one year. Five case-control studies reported highest risk within the first year of use (odds ratios [OR], 2.9-6.7). Data from 5 randomized controlled trials of SERMs were not included in the meta-analysis. The 2 largest trials reported a similar increased risk of venous thromboembolism.

Conclusions: Postmenopausal HRT is associated with an increased risk of venous

thromboembolism, and this risk may be highest in the first year of use. SERMs are associated

with a similar increase in risk.

Chapter 1. Introduction

In this systematic evidence review (SER), we evaluate data on the relationship between the use of postmenopausal hormone replacement therapy (HRT) and selective estrogen receptor modulators (SERMs) and the risk for venous thromboembolism. We present results of a review of the literature and a meta-analysis of studies reporting data on postmenopausal HRT and venous trhomboembolism. This report is part of a larger project on the risks and benefits of HRT prepared for the U.S. Preventive Services Task Force (USPSTF) to assist them in making recommendations.

Burden of Suffering

The 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 HRT.   Although postmenopausal HRT is widely used,[1] it poses important health risks. One suspected risk is an increase in venous thromboembolic events. Initially, this relationship was based on studies of oral contraceptives[2] and was not supported by studies of HRT.[3-5] Findings from more recent studies, however, indicate an increase in risk.[6-13]

Prior Recommendations

Because the literature addressing this issue was limited, previous USPSTF (1996) reported that there was no conclusive evidence to support an association between postmenopausal HRT and thrombosis.[14]

Analytic Frameworks and Key Questions

The analytic frameworks in Figures 1 and 2 show the target populations, interventions, and health outcome measures we examined for the overall question of the benefits and risks of postmenopausal HRT. Arrow 3 in Figure 2 corresponds to issues of HRT and venous thromboembolism specifically covered in this report. One key question, "Does HRT increase the risk for venous thromboembolism?" guided our literature review.

We were concerned with HRT as chemoprevention, and therefore focused on the use of either estrogen alone or estrogen combined with progestins in healthy, postmenopausal women. The SERM literature we reviewed was restricted to raloxifene and tamoxifen use in healthy postmenopausal women.

Chapter 2. Methods

Literature Search Strategy

We searched MEDLINE (1966 to December 2000) and HealthSTAR (1975 to December 2000) databases. Additional articles were obtained by reviewing reference lists of pertinent studies and reviews. Multiple search terms were used because venous thromboembolism is usually reported as a secondary or adverse outcome in studies with unrelated primary outcomes. Search terms included *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* (Appendix 1a-c).

To identify randomized controlled trials (RCTs), we performed 3 separate searches of the Cochrane Controlled Trials Register using *estrogen replacement therapy*, *hormone replacement*, and *venous thromboembolism* as search terms in various combinations. Only one study,[12] previously identified in the MEDLINE search, was appropriate for inclusion. We performed additional MEDLINE searches (1991 to December 2000) to identify randomized controlled trials of tamoxifen and raloxifene in women without breast cancer. Using all 3 databases, (MEDLINE, HealthSTAR, and Cochrane) a total of 7 searches for literature addressing HRT, SERMs, and venous thromboembolism were performed.

Inclusion/Exclusion Criteria

The studies included in this review enrolled postmenopausal women, and included deep venous thrombosis (DVT), pulmonary embolism (PE), or both as either a primary or secondary outcome or as a reportable adverse event related to HRT or SERM use. When data were

available, we reported effects of dose, duration, and progestin use. Only articles with English-language abstracts were considered. We excluded studies where the population was selected based on prior thrombotic events or presence of conditions that are associated with higher risk of thrombosis, such as malignancies.

Size of Literature Reviewed

We identified 3,363 abstracts from our search of postmenopausal HRT and venous thromboembolism; most did not specifically address this topic and were excluded from full-text review (Appendix 2). Twelve abstracts met inclusion criteria and contained primary data (3 randomized controlled trials,[12,15,16] 8 case-control studies,[3,6-10,13,17] and one cohort study[11]). Three other studies[4,5,18] identified from a review article[19] did not meet inclusion criteria. We found 3 trials from 475 abstracts of tamoxifen[20-22] and 2 trials from 62 abstracts of raloxifene[23,24] that reported venous thromboembolic events.

Data Extraction and Synthesis

From each included study, we abstracted the number of participants, treatment (in randomized controlled trials) or definition and method of determining exposure (in case-control or cohort studies), rates of thromboembolic events, confounders controlled for, methods of outcome measurement, and study duration. Studies varied in their definition of exposure, method of determining exposure, confounders controlled for, and method of diagnosis. Two reviewers independently rated each study's quality using criteria developed by the USPSTF[25] (Appendix 3) and had 76% agreement. When reviewers disagreed, a final score was reached through

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consensus. Abstracted data and quality assessments were entered into evidence tables (Appendix 4).

We performed a meta-analysis of the 12 HRT studies meeting inclusion criteria. Two studies[11,12] reported hazard ratios from Cox proportional hazards models. A hazard ratio is the ratio of the instantaneous probability of an event in the treatment group compared to that of the control group, and can be thought of as the relative risk. One study[15] provided the raw data to calculate the unadjusted relative risk. The remaining studies[6-10,13,17] reported odds ratios from logistic regression models. Since venous thromboembolism is a fairly rare event, the odds ratio is a good estimate for the relative risk. For uniformity, therefore, we indicated the results from all studies as relative risks (RR).

Under the modeling assumptions made by each study, the logarithm of the relative risk (logRR) had a normal distribution. Standard errors for logRR were calculated from the 95% confidence intervals (CIs) given in the studies or, in the case of the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial,[15] from the raw data. The logRR and their standard errors provided the data points for the meta-analysis.

We tested both fixed-effects and random-effects models. A fixed-effects model is fit on the data and assumes only one source of variability (the variability within studies). It also assumes that the patient populations across studies are sufficiently similar and that the results are suitable to pool together. A random-effects model assumes a second source of variability among studies. Variation among studies implies that each study potentially estimates different effects sizes. Random-effects models are more conservative in the sense that they allow for more variability in treatment effects.[26]

We used the Bayesian data analysis framework for the meta-analysis and WinBUGS software to analyze the data.[27]   Because of the differences in study design between the 12 studies, a meta-analysis was performed for each study type, excluding the single cohort study.

We evaluated studies for selection bias using funnel plots [28] and investigated the sensitivity of the analysis to possible missing studies due to publication bias by "trim and fill."[29,30] Results were unaffected.

Chapter 3. Results

Hormone Replacement Therapy Studies

The 12 studies included in the meta-analysis are listed in Table 1. One of the 3 randomized controlled trials[12] reported an increased risk of venous thromboembolism with HRT, while the other studies[15,16] did not. Six of the 8 case-control studies observed an association.[6-10,13] The cohort study reported an increased risk of pulmonary embolism in users of HRT.[11] Characteristics of these studies are described in the following sections.

Randomized Controlled Trials

None of the 3 randomized controlled trials[12,15,16] identified by our search were designed to study venous thromboembolism as a primary outcome (Appendix 4, Evidence Table 1). The Heart and Estrogen/progestin Replacement Study (HERS)[12] was designed to determine if daily HRT reduces the risk of coronary heart disease (CHD) events in postmenopausal women with pre-existing coronary artery disease. The primary outcome was non-fatal myocardial infarction or CHD death.   This 4-year study randomized 2,763 women with a mean age of 66.7 years. Daily use of conjugated equine estrogen, 0.625 mg, with medroxyprogesterone acetate, 2.5 mg, (Prempro) was compared to placebo. DVT and PE were both secondary outcomes. DVT diagnosis was by venography, impedance plethysmography, or ultrasound. Nuclear lung scan or pulmonary angiography were required for PE diagnosis. There were a total of 34 out of 1,380 (2.5%) thrombotic events in the treatment group and 13 out of 1,383 (0.9%) in the placebo group. Relative hazards were reported as 2.89 (95% CI, 1.50-5.58) for venous thromboembolism, 3.18 (CI, 1.43-7.04) for DVT, and 2.79 (CI, 0.89-8.75) for PE. A second

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publication from HERS reported idiopathic (relative hazard, 3.1; CI, 0.8-11.3) and non-idiopathic (relative hazard, 2.5; CI, 1.2-5.3) events separately.[31] Risk was highest in the first 2 years of estrogen use.

The PEPI trial[15] enrolled 875 healthy postmenopausal women, mean age 56.1 years, into one of 5 intervention groups and followed them for 3 years. The interventions included conjugated equine estrogen, 0.625 mg daily, alone or with a progestin in various forms and dosages compared to placebo. Primary outcomes were cardiovascular disease risk factors, including systolic blood pressure, high-density lipoprotein (HDL) cholesterol, serum insulin, and fibrinogen. Thromboembolic events were reported as adverse experiences during the follow-up phase and their method of measurement was not described. The definition of thrombotic events included DVT, PE, and superficial phlebitis. There were 10 events in the treatment group: 2 with DVT, 2 with PE, and 6 with superficial phlebitis. The placebo group had no reported events, and the difference between the groups was not statistically significant (P=0.42).

The Estrogen Replacement and Atherosclerosis (ERA)[16] trial randomized 309 women with angiographic-proven coronary heart disease to estrogen, estrogen and progestin, 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/progestin group, and 1 in the placebo group. There was no significant difference between the groups (P=0.16).

The quality ratings using USPSTF criteria were good for HERS and fair for the PEPI and ERA trials. While HERS reported venous thromboembolism as a secondary outcome and described how the diagnosis was made, both the PEPI and ERA trials reported it as an adverse

experience and did not describe how it was diagnosed. There were other differences, unrelated to quality ratings, between the trials. The HERS and ERA trials enrolled older, postmenopausal women with documented coronary artery disease (mean age 66.7 years), while PEPI enrolled younger, healthy postmenopausal women (mean age 56.1 years). HERS randomized more than 3 times as many participants as PEPI (2,763 vs 875) and nearly 9 times as many as the ERA trial (2,763 vs 309), allowing for greater power to detect events. The PEPI trial included superficial phlebitis and had only 4 DVT and PE cases. The HERS trial reported an increased risk similar to the observational studies.

Case-Control Studies

Six of the 8 studies (Appendix 4, Evidence Table 2) reported an increased risk of venous thromboembolism with estrogen use and 3 of them had results that were statistically significant.[6-10,13] Five studies reported an increased risk in the first year (Figure 3). Two of the 8 case-control studies did not report an increased risk.[3,17] One of these studies did not use multivariable analysis to control for potential confounders.[17]

Four studies used hospital-based controls[3,6,7,17] and 4 studies used population-based controls.[8-10,13] Women ranged in age from 45 to 79 years. Hormonal preparations varied among the studies. Five studies used various doses of conjugated estrogen,[3,6,8,9,17] one used transdermal estrogen,[10] a Scandinavian study included only estradiol formulations,[13] and the other did not report estrogen type.[7] The use of a progestin in conjunction with estrogen was not specified in 3 of the studies,[3,7,17] and dosage and type of progestin use in the remaining studies were not reported.[6,8-10,13]

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Exposure history and its ascertainment also varied among studies. HRT usage was described as current, past, never, ever, or nonuser, with variable definitions across the studies. For example, 2 case-control studies[13,17] defined current use as HRT use at the time of hospital admission, while another study[6] defined it as HRT use within the month prior to hospital admission. Still others[8-10] considered HRT use within the previous 6 months as current use. The methods of determining exposure included interview,[6,7] chart review,[17] chart review and questionnaire,[13] and review of various pharmacy databases.[8-10]

The method of outcome assessment also varied among studies. The most rigorous criteria required a positive venogram, ultrasound, or doppler for DVT diagnosis and a positive ventilation/perfusion (V/Q) scan for PE.[8] In addition, documentation of heparin and oral anticoagulation therapy was required. Another study[6] classified cases into categories (definite, probable, possible) based on evidence of venous thromboembolism. A "definite" classification required a positive V/Q scan, pulmonary angiogram, venography, duplex scanning, or radioisotope studies. The "probable" and "possible" classification required only certain signs, symptoms, or less invasive diagnostic procedures (electrocardiogram, chest radiograph, arterial blood gas). Despite this stratification, all cases from these 3 categories were included in the analysis. Another study[10] required that cases present with typical signs and symptoms and have a documented positive diagnostic procedure (V/Q scan, pulmonary angiogram, venogram, ultrasound) or necropsy, or have received treatment with anticoagulation for more than 2 months after hospital discharge.

Other studies were less rigorous and either did not indicate the method of outcome measurement,[7] used a random sample to validate 10% of the cases,[9] or simply stated that all cases had at least one diagnostic test (impedance plethysmography, fibrinogen scans, doppler

ultrasound, venogram, V/Q scan, or pulmonary angiogram) in addition to a clinical exam.[17] The

most recent study[13] reported the various diagnostic tests performed (venography, ultrasound,

V/Q scan, pulmonary angiography, autopsy, clinical diagnosis) on the cases, though no criteria

for study inclusion were cited.

The most common confounders controlled for in these studies were body mass index

(BMI)[6,7-10,13] and history of varicose veins.[6,8-10] Smoking was controlled for in only 3

studies.[8,9,13]

Some studies reported the effects of dose and regimen, although the numbers of study

participants were small. Three studies reported a higher risk for increased doses of estrogen

(>0.625 mg conjugated) compared to lower doses.[6,8,9] A higher risk (OR, 2.2-5.3) for estrogen

combined with progestin compared with estrogen alone was reported by 3 studies.[6,9,10] A

comparison of oral (OR, 4.6; CI, 2.1-10.1) and transdermal (OR, 2.0; CI, 0.5-7.6) estrogen was

reported by only one study.[6]

A study conducted in the United Kingdom[6] identified 103 women hospitalized with first-

time venous thromboembolism and compared them to 178 controls admitted for diagnoses

unrelated to HRT. Exclusion criteria included history of previous venous thromboembolism,

stroke, myocardial infarction, cancer, and use of anticoagulants or oral contraceptives in the

month preceding hospital admission. Patients reporting surgery, pregnancy, trauma, or

prolonged bed rest within the prior 6 weeks were also excluded. DVT and PE diagnoses were

confirmed by diagnostic maneuvers (V/Q scan, pulmonary angiogram, venography, duplex

scanning or radioisotope studies) or signs, symptoms, and less invasive diagnostic maneuvers

(electrocardiogram, chest radiograph, arterial blood gas). Hormone use any time in the month

prior to hospital admission was categorized as current use. Nonusers were defined as past or

never users of HRT. BMI, presence of varicose veins, and socioeconomic status were all controlled for. There were 44 exposed cases, resulting in an odds ratio of 3.5 (CI, 1.8-7.0).

The same author reported similar findings in a study[7] published in a letter. This nested case-control study used women previously recruited for a contraceptive study. Cases (n=18) and controls (n=161) were 45 to 64 years and were subject to the same inclusion and exclusion criteria as for the prior study. The hormone dosage and duration were not specified. When the same confounders were controlled for, an increased risk for current users compared to nonusers was reported (OR, 2.3; CI, 0.6-8.1).

A study[9] using the General Practice Research Database (n=347,253) in the United Kingdom also included hospitalized patients with first-time venous thromboembolism (n=292). In this study, cases were identified by admission diagnoses. The randomly sampled controls (n=10,000) from this study cohort were not hospitalized. Patients with history of venous thromboembolism, coagulopathy, neoplasm, ischemic heart disease, heart failure, vasculitis, and alcohol-related diagnoses were excluded. All study participants were 50 to 79 years old. Use of HRT was determined using the British National Formulary. Participants were placed into one of 3 categories of HRT usage: current (HRT usage any time within past 6 months), nonuse (no HRT prescription recorded in the formulary), and past use (HRT use greater than 6 months ago). Cases were verified using a 10% random sample of venous thromboembolism admission diagnoses by chart review of discharge diagnosis, clinical symptoms, and diagnostic procedures (not further described). All but one DVT case was confirmed. Of the 292 cases, 81% (n=236) had medical record codes for anticoagulation therapy. The adjusted odds ratio of 2.1 (CI, 1.4-3.2) was based on 37 exposed cases. Confounders controlled for included BMI, history of

varicose veins or superficial phlebitis, age, smoking, oophorectomy status, and year of enrollment.

An Italian study[10] with 6 estrogen users among 171 exposed cases enrolled a similar number (n=10,000) of controls and had similar definitions for HRT use as the above United Kingdom study.[9] It also used pharmacy records to determine exposure. However, in this study, 79% of the participants used transdermal estrogen. Despite this difference, this study reported a similar odds ratio of 2.3 (CI, 1.0-5.3).

A study using data from Group Health Cooperative in Seattle[8] reported similar findings (OR, 3.6; CI, 1.6-7.8). This study enrolled only 42 cases and 168 controls. Findings for DVT (OR, 4.0; CI, 1.6-9.7) and PE (OR, 2.5; CI, 0.5-12.2) were also reported separately.

The most recent of the case-control studies[13] reported a crude odds ratio of 3.54 (CI, 1.54-8.2) for less than one year of HRT use. There was no risk increase with HRT use longer than one year (OR, 0.66; CI, 0.39-1.10).   Of the 176 cases, there were 19 with less than one year of HRT exposure and 26 with more than one year of HRT exposure. Among all current HRT users, the adjusted risk was 1.22 (CI, 0.76-1.94). This study, based in Scandinavia,[13] differed from the earlier case-control studies. Only estradiol, in various formulations, was used by the cases and controls (n=352) and doses were not reported. The single exclusion criterion was a history of cancer; consequently, 52% (n=92) of the cases had predisposing factors for venous thromboembolism, and 48% (n=84) were idiopathic. Also, it was the only study to use a questionnaire to obtain exposure history.

One of the 8 case-control studies[17] did not report an increased risk (OR, 0.79; CI, 0.30-2.08). This study compared 121 cases of venous thromboembolism identified by hospital discharge diagnosis to 236 age-matched controls.   Participants were identified as current users

or nonusers, and only 6 cases were exposed to HRT. This study did not use multivariable analysis to control for potential confounders. In addition, there was a significant difference in length of stay between cases and controls in the hospitalized patients enrolled (19.5 days vs 9.2 days). This study also did not report the dosage and duration of hormone use.

The case-control studies had variable quality score ratings (3 good, 3 fair, 2 poor). Some were compromised by small numbers of cases and failure to control for important confounders. For example, 2 studies had 4 and 6 exposed cases, and did not control for smoking.[6,10] Despite higher numbers of exposed cases, the Scandinavian study[13] did not report estradiol doses or method of outcome measurement. In most studies, HRT use (type, dose, duration) and method of determining exposure were inadequately or inconsistently measured. Two studies used pharmacy records to determine HRT exposure.[8,9] Patient interview is subject to potential recall bias, and pharmacy databases indicate active prescriptions but do not confirm medication compliance. The discrepancy in definition of hormone use is potentially significant because some of the studies indicate increased risk with shorter duration of HRT use. One study was not peer-reviewed,[7] and one had significant differences between the cases and controls.[17]

Cohort Study

The only cohort study identified from our search[11] used 16 years of data from the Nurse's Health Study (Appendix 4, Evidence Table 3). This study reported primary PE only. PE was determined by questionnaire and confirmed by a high probability V/Q scan, positive pulmonary angiogram, or necropsy. HRT use was categorized as current, past, or never, though none of these usage categories was further defined. Reported dosages of estrogen were 0.3 mg, 0.625mg, and 1.25 mg, and use of progestins was not reported. Confounders controlled for in

the analysis included age, BMI, hypertension, diabetes, smoking, oral contraceptive use, parity, and elevated cholesterol. There were 22 PEs in the current-use group, resulting in a relative risk of 2.1 (CI, 1.2-3.8), and 19 PEs in the past-use group, resulting in a relative risk of 1.3 (CI, 0.7-2.4). No trends were observed for the various estrogen dosages. In terms of duration, current users of 5 years or more had a relative risk of 1.9 (CI, 0.9-4.0), and those with fewer than 5 years of use had a relative risk of 2.6 (CI, 1.2-5.2) for PE. These figures were based on 10 and 12 cases, respectively. This study had a good quality rating.

Meta-Analysis of HRT Studies

The 12 HRT studies were included in a meta-analysis. Relative risks and 95% confidence intervals for venous thromboembolism outcomes are indicated in Figure 4. The test of heterogeneity indicated that the studies were not heterogeneous ($P>0.10$). Combining the 12 studies, the overall relative risk for venous thromboembolism in postmenopausal women using HRT from the fixed-effects model was 2.08 (CI, 1.68-2.54). The results were similar with a random-effects model (RR, 2.14; CI 1.64-2.81). Combining the 8 case-control studies[3,6-10,13,17] the RR was 1.97 (CI, 1.54-2.47) for the fixed-effects model and 2.05 (CI, 1.40-2.95) for the random-effects model. For the 3 randomized controlled trials,[12,15,16] the RR estimate was highly variable because there were no events in the placebo group of the PEPI trial. From the fixed-effects model the mean RR was 3.15 (CI, 1.55-5.69), and from the random-effects model the median RR was 3.08 (CI, 0.21-45.14). Six studies that reported risk according to duration of use found the highest risks in the first 1 to 2 years (combined relative risk for first year was 3.49; CI, 2.33-5.59).[6,8-10,12,13]

Studies of Selective Estrogen Receptor Modulators (SERMs)

Five randomized controlled trials[20-24] of raloxifene and tamoxifen were identified and reviewed (Table 2 and Appendix 4, Evidence Table 4). The quality of the studies varied (2 fair, 3 poor). The 3 studies rated as poor [21,22,24] did not describe the method of diagnosis. One of them had high dropout rates,[21] one had important loss to follow-up,[22] and one was underpowered to detect outcomes.[24] The larger trials[20,23] were rated as fair.

The largest study of raloxifene, the Multiple Outcomes of Raloxifene Evaluation (MORE) study,[23] demonstrated a 3-fold increase in the risk of venous thromboembolism with daily use of raloxifene. This 3-year trial randomized 7,705 postmenopausal, osteoporotic women (mean age 66.5 years) into one of 3 groups: placebo, 60 mg/d of raloxifene, and 120 mg/d of raloxifene. The primary outcome was newly diagnosed breast cancer, with venous thromboembolism reported as an adverse event rather than a secondary outcome. Identification of thrombotic event was through chart review and was not restricted to idiopathic events. There were a total of 49 events in the raloxifene groups and 8 in the placebo group, resulting in a relative risk of 3.1 (CI, 1.5-6.2). There was no significant difference in the rate of events between the two raloxifene groups. These findings are consistent with studies of HRT. They differ with an earlier, but much smaller, randomized trial of one-year duration[24] comparing raloxifene (60 mg and 120 mg) with placebo. The earlier study reported no thromboembolic events in the 143 postmenopausal participants (mean age 68.4 years).

Three randomized controlled trials[20-22] of tamoxifen for breast cancer prevention have variable findings. All of the studies compared 20 mg of daily tamoxifen to placebo and excluded women with prior history of venous thromboembolism. The largest of the 3 studies, the Breast

Cancer Prevention Trial (BCPT),[20] randomized 13,000 women. Sixty-seven percent of participants were 40 to 59 years, 24 percent were 60 to 69 years, 6 percent were 70 or older, and the remainder were 35 to 39 years. Mean follow-up time was 4 years. Women in the tamoxifen group had a 3-fold risk of PE (n=18) compared to those in the placebo group (n=6) (RR, 3.01; CI, 1.15-9.27). This risk was more pronounced in women age 50 years or older (RR, 3.19; CI, 1.12-11.15) compared to participants 49 years or younger (RR, 2.0; CI, 0.11-119.62). DVT risk was also increased, though not significantly (RR, 1.60; CI, 0.91-2.86).

A trial conducted in Italy[21] randomized 5,400 women and followed them for a median length of 3.8 years. Study participants ranged in age from 35 to 70 years, with 76% between 45 and 59 years. The difference in frequency of vascular events between the tamoxifen group (n=38) and placebo groups (n=18) was significant (*P*=0.0053). Of 64 events, only 11 were DVT or PE; the remaining events were either superficial phlebitis or other thromboses.

A third trial, conducted in the United Kingdom,[22] enrolled nearly 2,500 women (ages 30 to 70 years), who were randomly assigned to tamoxifen or placebo groups with median follow-up of 5.8 years. No significant differences in events were observed between the placebo (n=4) and treatment groups (n=7).

There may be several reasons for the differences in risk among the 3 tamoxifen trials. The British [22] and Italian[21] studies allowed participants to continue HRT if they were already taking it or to start HRT therapy if indicated. The BCPT [20] did not allow HRT use within 3 months of randomization. Another difference was the age of study participants. Sixty-one percent were younger than 50 years old in the British trial[22] compared with 40% and 38% for the BCPT[20] and Italian[21] trial, respectively. There were 3 fatal PEs in the BCPT, reportedly associated with comorbid conditions, but it is unclear if these deaths were actually from PE or the comorbidities.

The Italian trial[21] had a proportion of women under age 50 similar to the BCPT and observed more vascular events in the tamoxifen group than in the placebo group. However, the majority of these events were superficial phlebitis and not DVT.

Chapter 4. Discussion

Conclusions

Our literature review and meta-analysis of 12 eligible studies indicated that postmenopausal HRT is associated with a 2-fold increase in risk of venous thromboembolism in current users (RR, 2.14; CI, 1.64-2.81). Using a baseline risk of 1.3 events 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]   A summary of the evidence is described in Table 3. The 2 largest trials of SERMs reported a similar statistically significant increased risk.[20,23]

The findings of recent studies of HRT and SERMs differ substantially from studies published earlier that showed no association.[3-5] However, these 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, using data from the Walnut Creek Contraceptive Drug Study, was designed to identify adverse outcomes of chronic oral contraceptive use.[4]   The study reported 17 idiopathic cases of venous thromboembolism in users of oral contraceptives or those with "other estrogenic use," however, it is not clear if "other estrogenic use" represented postmenopausal HRT.   Of the 17 cases, more than half were younger than 45 years old. A randomized controlled trial[5] followed an inpatient population of women from a hospital for chronic diseases for 10 years, limiting generalizability to a community-based ambulatory population. While the earliest case-control study included in our meta-analysis did not have significant findings, it did show a trend toward increased events.[3]

More recently, the Coronary Drug Project (CDP)[32] was reanalyzed, and an increased risk (RH, 1.62; 1.62-2.29) was reported.[33] This randomized controlled trial of men with known coronary artery disease compared 2 doses of estrogen (2.5 mg/d and 5.0 mg/d) to placebo and was discontinued after an increase was observed in mortality, nonfatal myocardial infarction, and adverse effects.

Also, unpublished, preliminary data from the Women's Health Initiative also indicate an increased risk of venous thromboembolism with hormone replacement.[34,35] The significance of these findings will be more apparent as the study progresses.

Limitations of the Literature

Studies included in this review had several important limitations. The diagnosis of DVT or PE is difficult, and the literature addressing this topic is complicated. A recent review[36] of noninvasive strategies of DVT diagnosis indicated that venous ultrasound is most accurate. However, multiple variables, such as proximal versus distal, symptomatic versus asymptomatic, and first versus recurrent DVT all affect the accuracy of the test.

The Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study[37] reported several findings about the utility of V/Q scans for PE diagnosis. A high probability scan usually indicated PE, but few patients diagnosed with PE had a high probability scan. Using pulmonary angiography for comparison, a high probability scan was 41% sensitive and 97% specific. Combining intermediate or high probability scans, these numbers were 82% and 52%, respectively. Also, intermediate probability scans did not contribute to PE diagnosis. Finally, most of the patients in this study, with and without PE, had abnormal V/Q scans.

In the current studies, race was either not indicated[6-11] or participants were predominantly white.[12,15,17] Preliminary findings from the Black Women's Health Study indicate a possible increased risk (OR, 1.4; CI, 1.1-1.6) with postmenopausal HRT in African American women.[38]

Our method of reviewing abstracts and journal articles could have missed venous thromboembolic events that were not reported or reported in a limited way. Obtaining unpublished data from investigators may have provided more studies for the meta-analysis, but this was beyond the scope of our literature review.

Future Research

Our review supports an association between HRT and venous thromboembolism, although many questions remain. The pathophysiology is not well understood and requires further study. It is currently thought the effect of estrogen on the vascular endothelium and on coagulation factors might influence the potential for a thromboembolic event.[39,40] These hypercoagulable states might also be opposed by estrogen-induced clot lysis properties and an imbalance in these processes, in some women, might result in thromboembolism.[41] A follow-up analysis of the PEPI trial observed that patients with venous thromboembolism had lower baseline fibrinogen levels than those without.[42] The significance of these findings is unclear.

An Italian study suggests that continuous transdermal estradiol results in better hemostatic balance of clotting factors than cyclic estradiol therapy.[43] Some studies in our review indicated that higher doses of estrogen[6,8,9] and use of progestins [6,9,10] increase risk. However, the effects of dose (low vs conventional), delivery (transdermal vs oral), and adding

progestins have not been extensively studied. Additional research is necessary to determine the optimal HRT regimen.

Identifying individuals at highest risk needs further investigation. HERS reported increased risk in patients with hip or lower extremity fracture, cancer, hospitalization, or surgery.[31] Other expected risk factors (hypertension, smoking, BMI) were not predictive. Later onset of menopause (above age 52 years) was also associated with increased risk. The use of statin medications and aspirin was protective. However, it is not clear if all of these findings can be extrapolated to women without coronary artery disease. The Estrogen in Venous Thromboembolism Trial (EVTET) reported that women with a prior history of venous thromboembolism while taking hormone replacement are at increased risk for a recurrent event.[44] Women with the Factor V Leiden mutation who use HRT are also at increased risk for atherothrombolic[45] and venous thromboembolic events.[46] Further study is needed to determine the utility of screening for coagulopathies prior to starting hormone replacement.

Acknowledgements

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Appendix 1a. Search Strategy for Effects of Hormone Replacement Therapy on Coagulation

1   exp hormone replacement therapy
               estrogen replacement therapy
2   hormone replacement.tw. (Text word from title and abstract of article)
3   estrogen replacement.tw.
4   exp estrogens/ad,tu   (ad = administration & dosage)
                                    (tu = therapeutic use)

equilenin	estrogens, catechol
equilin	estrogens, conjugated
estradiol	estrogens, non-steroidal
estrone	estriol
estramustine	chlorotrianisene
coumestrol	dienestrol
diethylstilbestrol hexestrol	
zearalenone	zeranol

5   exp estrogens, synthetic/ad,tu

epimestrol	ethinyl estradiol
mestranol	quinestrol

6   1 **or** 2 **or** 3 **or** 4 **or** 5

7   exp blood coagulation disorders

antithrombin 111 deficiency	disseminated intravascular coagulation
Bernard-Soulier syndrome	platelet storage pool deficiency
protein C deficiency	coagulation protein disorders
protein S deficiency	purpura, thrombocytopenic
thrombasthenia	thrombocythemia, hemorrhagic
vitamin K deficiency	

8   exp blood coagulation
               fibrinolysis
9   hypercoagulation.tw.
10   exp hemostasis
               blood coagulation
               platelet activation
11   exp thromboembolism
               cerebral embolism and thrombosis
               embolism, paradoxical
12   thrombophlebitis
13   pulmonary embolism
14   exp fibrinogen

fibrinogens, abnormal	fibrin fibrinogen degradation products
fibrinopeptide A	fibrinopeptide B

15   fibrinolysis
16   blood clot$.tw.
17   exp thrombosis

coronary thrombosis	purpura, thrombotic thrombocytopenic
thromboembolism	venous thrombosis

18   regional blood flow
19   blood flow velocity
20   exp anticoagulants

4-hydroxycoumarins	acenocoumarol	ancrod

Appendix 1a. Search Strategy for effects of Hormone Replacement Therapy on Coagulation (continued)

citric acid	coumarins	dermatan sulfate
dextran sulfate	dextrans	dicumarol
edetic acid	enoxaparin	ethyl biscoumacetate
gabexate	heparin	heparin, low-molecular weight
heparinoids	nadroparin	pentosan sulfuric polyester
phenindione	phenprocoumon	protein C
protein S	tedelparin	tetrathionic acid
warfarin		

21   thrombo$.tw.
22   thrombolytic therapy
23   exp hemorrhage

blood loss, surgical	ecchymosis	cerebral hemorrhage
epitaxis	eye hemorrhage	gastrointestinal hemorrhage
hemarthrosis	hematocele	hematoma
hematuria	hemobilia	hemoperitoneum
hemoptysis	hemothorax	postoperative hemorrhage
retrobulbar hemorrhage	purpura shock, hemorrhagic	
uterine hemorrhage		

24   7 **or** 8 **or** 9 **or** 10 **or** 11 **or** 12 **or** 13 **or** 14 **or** 15 **or** 16 **or** 17 **or** 18 **or** 19 **or** 20 **or** 21 **or** 22 **or** 23

25   6 **and** 24

26   **limit** 25 to human
27   **limit** 26 to english language
28   (*looked at english abstracts for foreign language articles*)

Appendix 1b. Search Strategy for Hormone Replacement Therapy Randomized Controlled Trials

1	exp hormone replacement therapy
	estrogen replacement therapy
2	hormone replacement.tw. (text word taken from title and abstract of article)
3	estrogen replacement.tw.
4	exp estrogens/ad,tu (ad = administration & dosage; tu = therapeutic use)

          equilenin   estrogens, catechol
          equilin   estrogens, conjugated
          estradiol   estrogens, non-steroidal
          estriol   estrone

5   exp estrogens, synthetic/ad,tu

          estrogens, non-steroidal epimestrol
          chlorotrianisene   ethinyl estradiol
          coumestrol   mestranol
          dienestrol   quinestrol
          diethylstilbestrol   hexestrol
          zearalenone   zeranol

6   1 **or** 2 **or** 3 **or** 4 **or** 5

7   **limit** 6 to randomized controlled trials (*check for document type*)

8   randomized controlled trials
9   randomized.tw.

10   8 or 9

11   6 and 10

12   7 or 11

13   **limit** 12 to human

14   **limit** 13 to english language
15   *looked at english abstracts of foreign articles*

Appendix 1c. Search Strategy for Selective Estrogen Receptor Modulators (SERMs)

1 (tamoxifen or raloxifene).mp.

2 Bone density/ or "bone density".mp.

2 exp osteoporosis/ or "osteoporosis".mp.

4 exp fractures/ or fracture$.mp.

5 exp hormone replacement therapy/

6 estrogen replacement.mp.

7 2 or 3 or 4 or 5 or 6

8 1 and 7

9 limit 8 to (human and english language)

10 exp breast neoplasms/

11 9 not 10

12 from 11 keep

Appendix 2. Hormone Replacement Therapy and Venous Thromboembolism Search Results

MEDLINE 1966 to December 2000

HealthSTAR 1975 to December 2000

Cochrane Controlled Trials Register

```
                    ┌─────────────────────────┐
                    │     3,363 Abstracts     │
                    └─────────────────────────┘
                    ┌───────────┴────────────┐
        ┌───────────────────┐      ┌──────────────────┐
        │    26 Included    │      │  3,337 Excluded  │
        └───────────────────┘      └──────────────────┘
            ┌──────┴───────┐
┌───────────────────────┐  ┌──────────────────────────────────┐
│     14 Excluded       │  │ 12 studies met criteria for      │
│ 3 inappropriate       │  │         evidence tables          │
│   endpoints           │  │            3 RCTs                 │
│ 11 letters,           │  │          8 case control          │
│ editorials, reviews   │  │            1 cohort              │
└───────────────────────┘  └──────────────────────────────────┘
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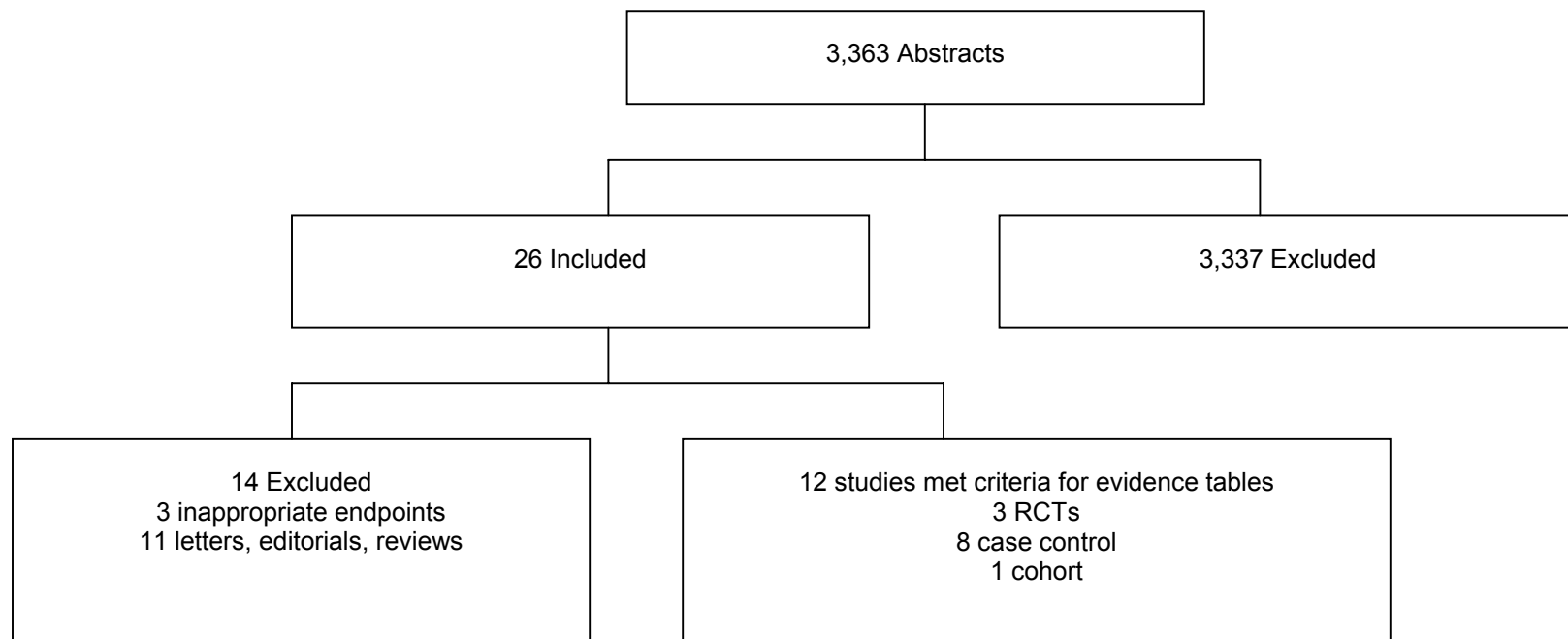
Appendix 3. Criteria for Grading the Internal Validity of Individual Studies

Design-Specific Criteria and Quality Category Definitions[25]

Presented below are a set of minimal criteria for each study design and then a general definition of three categories- "good," "fair," and "poor" – based on those criteria. These specifications are not meant to be rigid rules but rather are intended to be general guidelines, and individual exceptions, when explicitly explained and justified, can be made. In general, a "good" study is one that meets all criteria well. A "fair" study is one that does not meet (or it is not clear that it meets) at least one criterion but has no known "fatal flaw." "Poor" studies have at least one fatal flaw.

Case Control Studies
Criteria:
- Accurate ascertainment of cases
- Nonbiased selection of cases/controls with exclusion criteria applied equally to both
- Response rate
- Diagnostic testing procedures applied equally to each group
- Measurement of exposure accurate and applied equally to each group
- Appropriate attention to potential confounding variable

Definition of ratings based on criteria above:

Good: Appropriate ascertainment of cases and nonbiased selection of case and control participants; exclusion criteria applied equally to cases and controls; response rate equal to or greater than 80 percent; diagnostic procedures and measurements accurate and applied equally to cases and controls; and appropriate attention to confounding variables.

Fair: Recent, relevant, without major apparent selection or diagnostic work-up bias but with response rate less than 80 percent or attention to some but not all important confounding variables.

Poor: Major selection or diagnostic work-up biases, response rates less than 50 percent, or inattention to confounding variables.

Randomized Controlled Trials and Cohort Studies

Criteria:
- Initial assembly of comparable groups:
   -for RCTs: adequate randomization, including first concealment and whether potential confounders were distributed equally among groups
   -for cohort studies: consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to follow-up or overall high loss to follow-up
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- Important outcomes considered
- Analysis: adjustment for potential confounders for cohort studies, or intention to treat analysis for RCTs.

Appendix 3.   Criteria for Grading the Internal Validity of Individual Studies (continued)

Definition of ratings based on above criteria:

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention to confounders in analysis. In addition, for RCTs, intention to treat analysis is used.

Fair: Studies will be graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred in follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention to treat analysis is done for RCTS.

Poor: Studies will be graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.

Figure 1. Benefits of Hormone Replacement Therapy

Analytic Framework 1
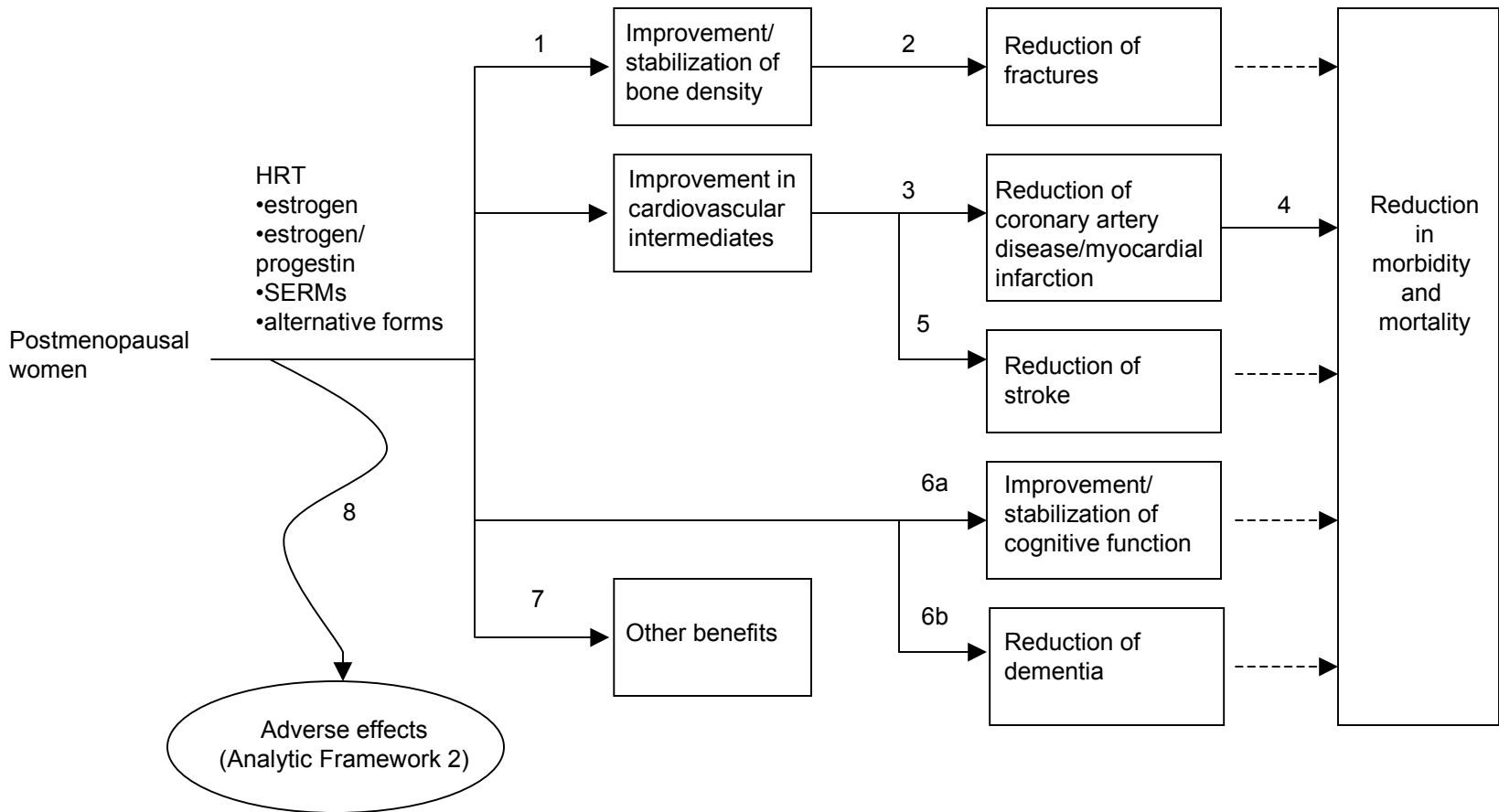
Note: SERMs indicates Selective estrogen receptor modulators

Figure 2. Adverse Effects of Hormone Replacement Therapy

Analytic Framework 2

Note: DVT indicates Deep-vein thrombosis; PE, pulmonary embolus; SERMs, Selective estrogen receptor modulators

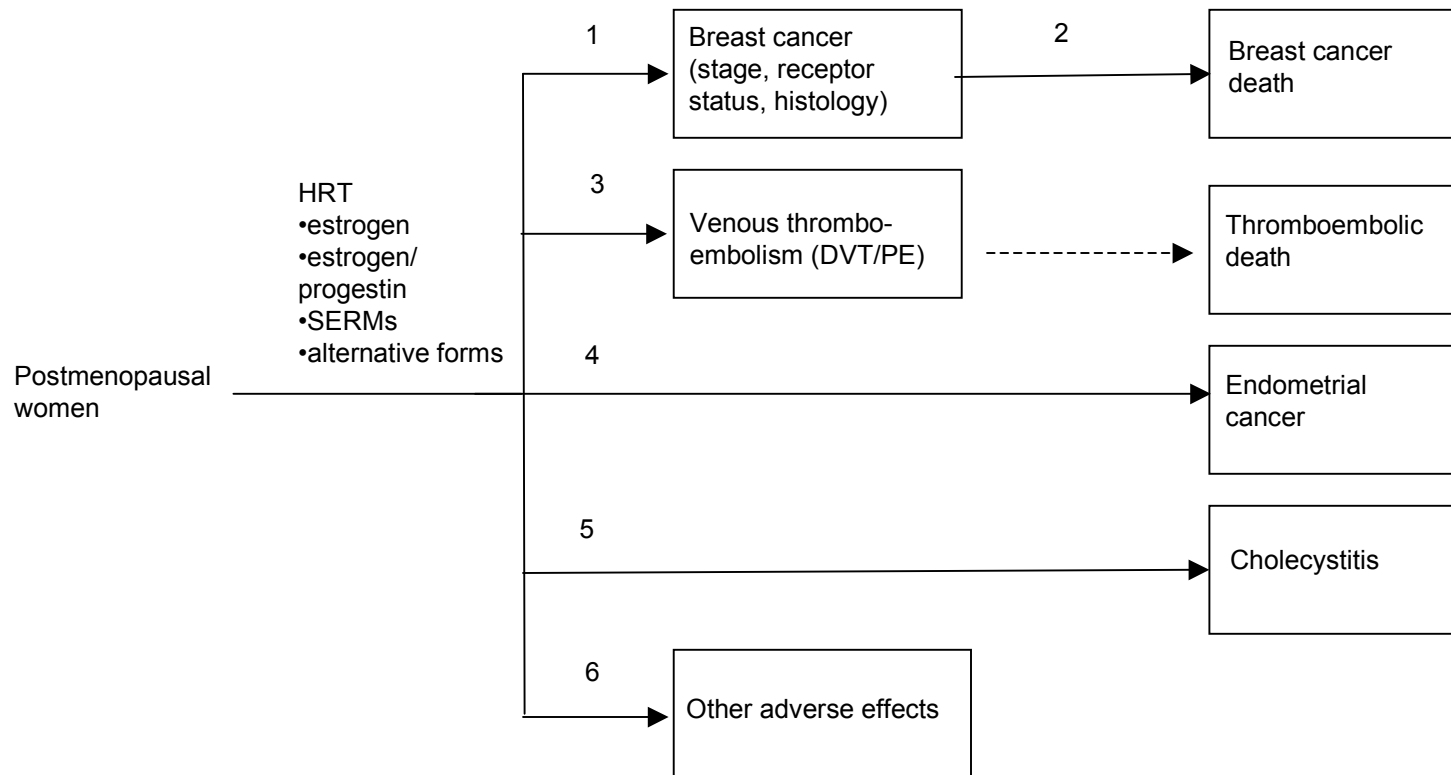**Figure 3. Risk for Venous Thromboembolism by Year of HRT Use**

34
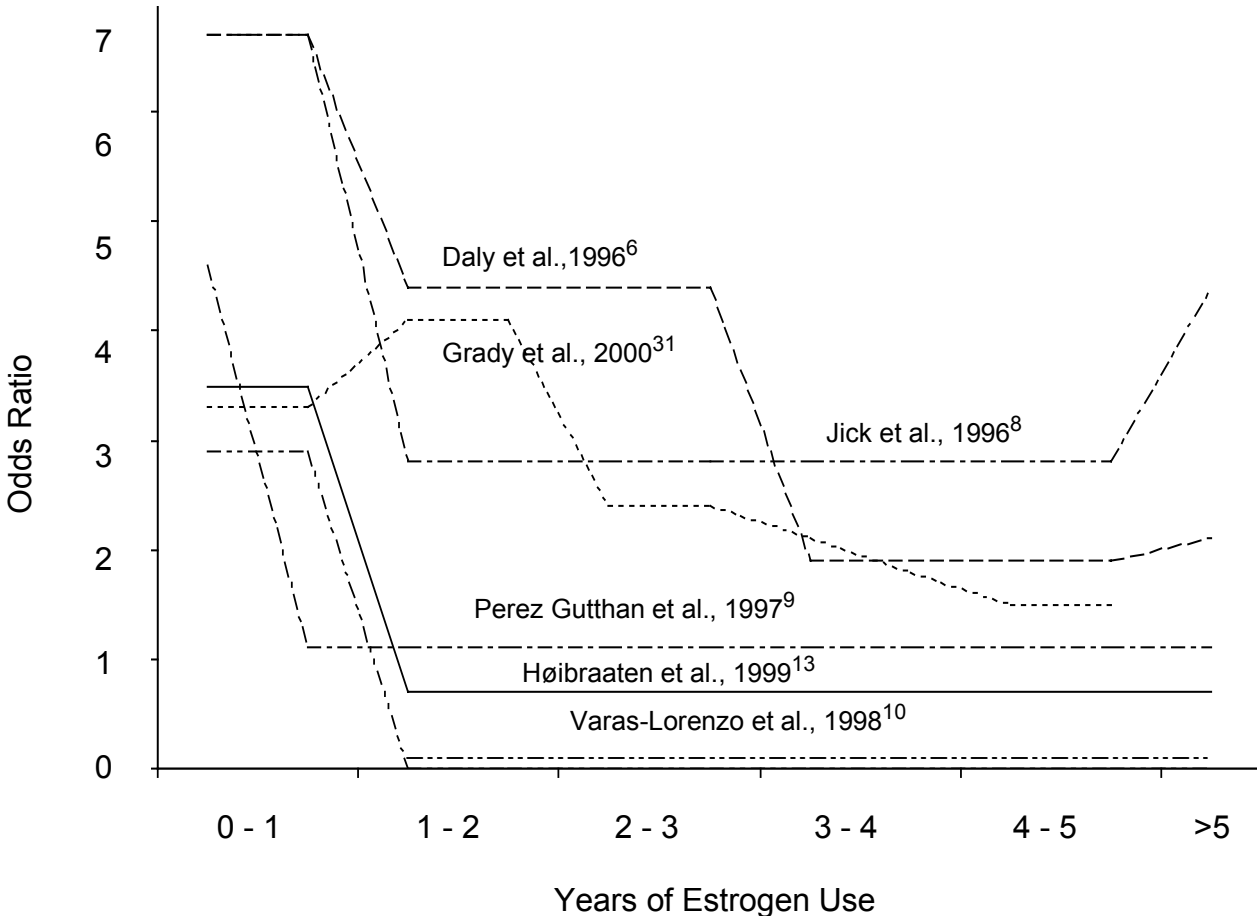
Figure 4. Meta-analysis of Estrogen Studies
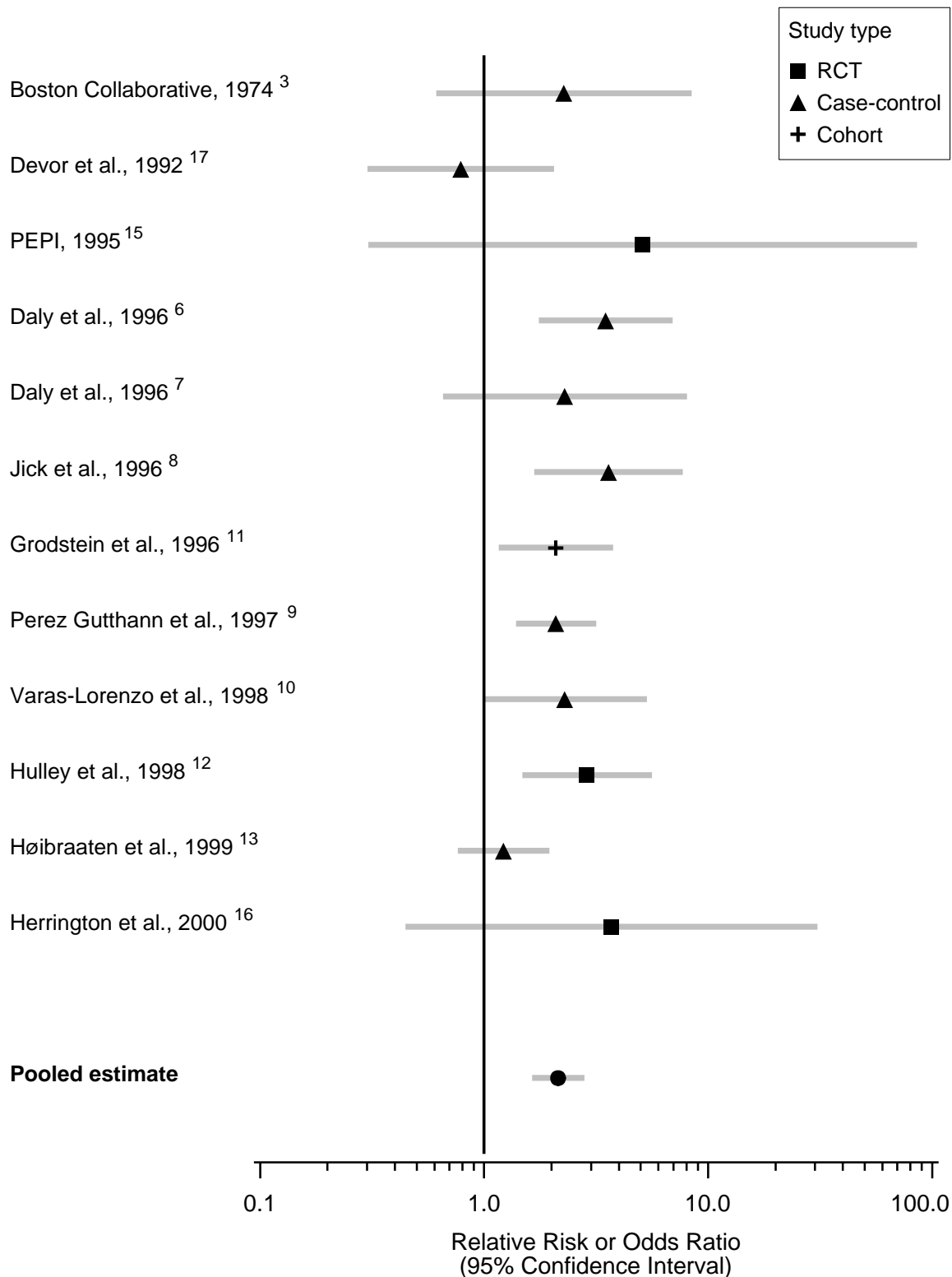
Table 1. Studies of Hormone Replacement Therapy Included in Meta-analysis

Study	Number of Subjects (N)	Exposed Cases (N)	Relative Risk (95% CI)	Event Rate Estrogen Users*	Number Needed to Harm†	Quality Rating
Randomized Controlled Trials	**Treatment/Placebo**					
PEPI, 1995[15]	701/174	10	5.10 (0.30-86.66)‡	47.6	210	Fair
Hulley et al., (HERS) 1998[12]	1,380/1,383	34	2.89 (1.50-5.58)	12.2	256	Good
Herrington et al., (ERA) 2000[16]	100/104	7	3.70 (0.45 - 30.44)‡	114.4	123	Fair
Case-control Studies	**Cases/Controls**					
Devor et al., 1992[17]	357 /236	6	0.79 (0.30-2.08)	Not Reported	Not Reported	Poor
Daly et al., 1996[6]	103 /178	44	3.5 (1.8-7.0)	2.7	5,882	Fair
Daly et al., 1996[7]	18 /168	4	2.3 (0.6-8.1)	Not Reported	Not Reported	Poor
Jick et al., 1996[8]	42 /168	21	3.6 (1.6-7.8)	3.2	4,347	Good
Perez Gutthann et al., 1997[9]	292 /10,000	37	2.1 (1.4-3.2)	2.7	7,142	Good
Varas-Lorenzo et al., 1998[10]	171 /10,000	6	2.3 (1.0-5.3)	2.9	3,448	Good
Høibraaten et al., 1999[13]	176 /352	50	1.22 (0.76-1.96)	Not Reported	Not Reported	Fair
Boston Collaborative, 1974[3]	152 /774	3	2.26 (0.61-8.41)‡	Not Reported	Not Reported	Poor
Cohort Studies	**Total Subjects**					
Grodstein et al., 1996[11]	112,593	41	2.1 (1.2-3.8)	2.0§	25,000§	Good

* calculated per 10,000 exposed women in one year

† women needed to treat for one year to cause one additional event

‡ calculated

§ current users

Note: ERA indicates Estrogen Replacement and Atherosclerosis; HERS, Heart and Estrogen/progestin Replacement Study; PEPI, Postmenopausal Estrogen/Progestin Interventions

Table 2. Trials of Selective Estrogen Receptor Modulators Reporting Thrombotic Events

Study	Subjects (N)	Treatment Events (N)	Placebo Events (N)	Relative Risk (95% CI)	Number Needed to Harm†	Quality Rating
Raloxifene						
Lufkin et al., 1998 [24]	143	0	0	Undefined	Undefined	Poor
Cummings et al., 1999 [23] (MORE)	7,705	49	8	VTE 3.1 (1.5-6.2)	155	Fair
Tamoxifen						
Fisher et al., 1998 [20] (BCPT)	13,388	53	28	VTE 1.91 (1.21-3.02)*	266	Fair
				DVT 1.60 (0.91-2.86)		
				PE 3.01 (1.15-9.27)		
Powles et al., 1998 [22]	2,471	7	4	VTE 1.75 (0.51-5.98)†	419	Poor
Veronesi et al., 1998 [21]	5,408	7	4	VTE 1.76 (0.51-6.01)†	896	Poor

* women-years/1 VTE

† calculated

Note: BCPT indicates Breast Cancer Prevention Trial; DVT, Deep Vein Thrombosis; MORE, Multiple Outcomes of Raloxifene Evaluation; PE, Pulmonary Embolism; VTE, Venous Thromboembolism.

Table 3. Summary of Evidence

Key Question	Evidence Codes	Quality of Evidence
Does HRT increase the risk for venous thromboembolism?	I	RCTs: Poor to good. Venous thromboembolism is a secondary outcome, groups randomized for cardiac outcomes, method of outcome assessment not reported.
	II-2	Case-control: Poor to good. Analysis based on small numbers of cases, important confounders such as smoking not considered in some
	II-2	Cohort: Good.

*Study design categories[14]
I: Randomized, controlled trials
II-1: Controlled trials without randomization
II-2: Cohort or case-control analytic studies
II-3: Multiple time seies, dramatic uncontrolled experiments
III: Opinions of respected authorities, descriptive epidemiology

Author, Year	Setting/ Population	Eligibility	Number Consid-ered	Exclusions*	Number Randomized	Treatment (n) Placebo(n)	Mean Age	Hormone Type/dosage(s)
Hulley (HERS), 1998[12]	Outpatient and community; 20 U.S. sites; primary outcome nonfatal myocardial infarction or coronary artery disease death	Post menopausal, < 80 yrs, coronary artery disease, intact uterus.	68,561	Cardiac event within 6 mos of randomization; use of HRT within 3 mos of initial visit; history of VTE; history of breast or endometrial cancer.	2,763	1,380/1,383	67 Range 44-79 yrs.	CEE 0.625 mg/ MPA 2.5 mg
PEPI, 1995[15]	Outpatient; 7 U.S. academic centers; primary outcomes: high density lipoproteins, systolic blood pressure, insulin, fibrinogen.	Post menopausal, 45-64 yrs, with or without a uterus.	Not stated	Myocardial infarction within 6 mos; congestive heart failure, cerebrovascular accident, transient ischemic attach, prior breast or endometrial cancer; use of HRT within 3 mos.	875	701/174	56.1 Range 45-64 yrs.	CEE 0.625 mg; CEE 0.625 mg +cyclic MPA 10 mg; CEE 0.625 mg +continuous MPA 2.5 mg; CEE 0.625 mg+cyclic MP 200 mg
Herrington, et al (ERA), 2000[16]	Outpatient; 6 clinical sites; primary outcome: coronary artery diameter.	Postmenopausal on current estrogen therapy, 1 or more coronary stenoses ≥30% of luminal diameter.	Not stated	Breast or endometrial cancer; previous or planned coronary bypass surgery; history of DVT or PE; uncontrolled hypertension or diabetes.	309	CEE=100/ CEE/MPA= 104/placebo= 105	65.8 Range 42-80 yrs	CEE 0.625 mg or CEE 0.625/MPA 2.5 mg

*Not all exclusions listed
**calculated
CEE indicates Conjugated equine estrogen; DVT, Deep Vein Thrombosis; HRT, Hormone Replacement Therapy; MPA, Medroxyprogestone acetate; PE, Pulmonary Embolism; VTE, Venous Thromboembolism

Evidence Table 1. HRT and Venous Thromboembolism--Randomized Controlled Trials

Author, Year	Placebo	Compliance Rate/Method	Secondary Outcome Measured	Method of Secondary Outcome Measurement	Study Duration	Follow-up Rate	Relative Hazard (95% CI)	Significance	Quality of Studies
Hulley (HERS), 1998[12]	Identical placebo	70% at 3 yrs; pill count	VTE,DVT, PE	DVT: venography, plethysmography, ultrasound PE: nuclear lung scan, pulmonary angiography	4.1 yrs	100%	VTE 2.89 (1.50-5.58) DVT 3.18 (1.43-7.04) PE 2.79 (0.89-8.75)	*P*<.05 *P*<.05 *P*>.05	Good: VTE a secondary outcome;groups randomized for cardiac outcomes; included non-idiopathic VTE as outcome; not all important confounders
PEPI, 1995[15]	Identical placebo	>80% at 3 yrs; pill count	DVT and PE not specified outcomes	Not stated	3 yrs	97%	not reported	*P*=0.42	Poor: VTE reported as "adverse" experience. DVT (n=2), PE (n=2), and superficial phlebitis (n=6).
Herrington, et al (ERA), 2000[16]	Identical placebo	Not stated; pill count	DVT and PE not specified outcomes	Not stated	3 yrs	80%	VTE= 3.70 (0.45-30.44)**	*P*=0.16	Fair: VTE reported as adverse experience. Method of VTE diagnosis not described.

*Not all exclusions listed
**calculated
CEE indicates Conjugated equine estrogen; DVT, Deep Vein Thrombosis; HRT, Hormone Replacement Therapy; MPA, Medroxyprogestone acetate; PE, Pulmonary Embolism; VTE, Venous Thromboembolism

Evidence Table 2. HRT and Venous Thromboembolism--Case-Control Studies

Author, year	Setting/ Population	Selection of cases	Selection of controls	No. Cases/ Controls	Selected Exclusions*	Age range	Hormone type/ dosage(s)
Devor, 1992[17]	University hospital; San Diego, CA	VTE by hospital discharge diagnosis	Hospitalized on same service, matched to age and hospitalization date	121/236	Not specified	≥ 45yrs	CEE/ 0.625,1.25 mg; Transdermal estradiol/ 25,50, 100 mcg
Daly, 1996[6]	Hospital based; UK	First time VTE	Hospitalized for diagnosis unrelated to HRT	103/178	History of VTE; surgery, trauma, pregnancy, bedrest within prior 6 wks; use of anticoagulants or	45-64 yrs	CEE/ 0.625 mg; Estradiol/ 1mg,2mg; EE/1.5 mg; Transdermal/50,100 mcg
Daly, 1996[7]	Hospital based; UK	First time VTE	Hospitalized for diagnosis unrelated to HRT	18/161	Same as above	45-64 yrs	Not specified
Jick, 1996[8]	Group Health Plan; Seattle, WA	First VTE diagnosis and positive study for DVT or PE and treatment with heparin and oral anticoagulants	Random within study cohort, matched to age and index date of case	42/168	History of prior VTE; trauma/surgery 6 mos prior to VTE	50-74 yrs	CEE or EE/ 0.325, 0.625, 1.25 mg
Perez-Gutthann, 1997[9]	Population based within General Practice Research Database, UK	First time VTE with hospital admission	Random within study cohort	292/10,000	History of VTE, coagulopathy; recent fracture, injury, sugery, hospital admission	50-79 yrs	CEE/ 0.625,1.25 mg; Transdermal estradiol/ 25,50, 100 mcg
Varas-Lorenzo, 1998[10]	Population based within Regional Health System; Italy	First time VTE by hospital discharge diagnosis	Random within study cohort	171/10,000	History of VTE, coagulopathies, pregnancy	45-79 yrs	Transdermal 79% Oral 21%
Høibraaten, 1999[13]	University hospital; Oslo, Norway	VTE by hospital discharge diagnosis	Random within population of Oslo	176/352	Any cancer diagnosis	45-70 yrs; Mean 59 yrs	Estradiol in various formulations
Boston Collaborative, (1974)[3]	24 Boston area hospitals	VTE by hospital discharge diagnosis	Hospitalized for diagnosis unrelated to HRT	18/774	History of VTE; post-op or post-traumatic VTE	45-69 yrs	Not specified

*Not all exclusions listed

**calculated

Note: CE indicates Conjugated estrogen; EE, Esterified; ERT, Estrogen Replacement Therapy; HRT, Hormone Replacement Therapy; PE, Pulmonary Embolism; VTE, Venous Thromboembolism.

Evidence Table 2. HRT and Venous Thromboembolism--Case-Control Studies

Author, year	Duration of estrogen use	Progestin use	Definition of HRT/ERT exposure usage	Method of determining exposure	Method of outcome measurement	Confounders controlled for
Devor, 1992[17]	Not specified	Not specified	Current=HRT use at time of admission; Nonuser not defined	Chart review	Clinical exam diagnostic procedure	None
Daly, 1996[6]	1-12 mos, 13-36 mos, 37-60 mos, 61 or more mos	Dosage/type not specified	Current=HRT use within months prior to admission; Nonuser=never or past user	Interview	Admitting diagnosis	Body mass index, varicose veins, socioeconomic group
Daly, 1996[7]	Not specified	Dosage/type not specified	Current=HRT use within months prior to admission; Nonuser=never or past user	Interview	PE: V/Q scan; pulmonary angiogram clinical exam DVT: venography, duplex scanning, radioisotope studies,	Body mass index, socioeconomic group
Jick, 1996[8]	1 yr or less, 1.1-4.9 yrs, 5 yrs or more	Dosage/type not specified	Current=ERT within prior 6 mos; Nonusers=ever users or past users	Pharmacy records	PE: V/Q scan; DVT: venogram, ultrasound, doppler and treatment with anticoagulants	Body mass index, smoking, varicose veins
Perez-Gutthann, 1997[9]	1-6 mos, 6-12 mos, >12 mos	Dosage/type not specified	Current=HRT use within 6 mos; Nonuser=no prescription in database; Past user=no HRT within 6	National Formulary	Discharge diagnosis, clinical symoptoms and diagnostic procedures	Body mass index, smoking, varicose veins/superficial phlebitis, age, oophorectomy status
Varas-Lorenzo, 1998[10]	Nonuse, 1-12 mos, >12 mos	Dosage/type not specified	Current=Prescription within past 6 mos; Nonuser=no prescription on record; Past=Prescription >6 mos ago	Prescription database	Clinical signs and symptoms and positive diagnostic procedure, or necropsy, or treatment with anticoagulants	Body mass index, history of varicose veins or superficial phlebitis, hypertension, diabetes, age, osteoarthritis
Høibraaten, 1999[13]	<12 mos, >12mos	Dosage/type not specified	Current=HRT use at time of admission; Nonuse not defined	Cases-chart review and questionnaire Controls-questionnaire	Venography n=135; V/Q scan n=33; Ultrasound n=7; pulmonary angiography n=2; autopsy n=9; clinical dx n=2	Hypertension, diabetes, coronary artery disease, smoking, prior VTE, body mass index
Boston Collaborative, (1974)[3]	Not specified	Not specified	Not specified	Interview	DVT: not specified; PE: lung scan, or angiography or surgery	None

*Not all exclusions listed

**calculated

Note: CE indicates Conjugated estrogen; EE, Esterified; ERT, Estrogen Replacement Therapy; HRT, Hormone Replacement Therapy; PE, Pulmonary Embolism; VTE, Venous Thromboembolism.

Evidence Table 2. HRT and Venous Thromboembolism--Case-Control Studies

Author, year	Confounders not controlled for	Adjusted OR (95% CI)	Exposed cases	Duration trends	Number Needed to Harm	Quality of studies
Devor, 1992[17]	Body mass index, varicose veins, smoking	VTE 0.79 (0.30-2.08)	6	Not analyzed	Not able to calculate	Poor: not accurate ascertainment of cases, included VTE cases not present at admission; important confounders not included, significant difference between hospital length of stay between cases and
Daly, 1996[6]	Smoking	VTE 3.5 (1.8-7.0)	44	Highest risk with first year of use	6,060 woman yrs/1 VTE	Fair: did not control for smoking; 22 cases recruited retrospectively; analysis of dosages,route, and ERT/HRT based on small numbers.
Daly, 1996[7]	Smoking, varicose veins	VTE 2.3 (0.6-8.1)	4	Not analyzed	Not able to calculate	Poor: type and dose of HRT not included; not peer reviewed, published as letter to editor.
Jick, 1996[8]	Not Stated	VTE 3.6 (1.6-7.8) DVT 4.0 (1.6-9.7) PE 2.5 (0.5-12.2)	21	Highest risk with first year of use	4,347 woman yrs/1 VTE	Good: although analysis of dosages and ERT/HRT were based on small numbers and method of determining exposure was through formulary records.
Perez-Gutthann, 1997[9]	Not Stated	2.1 (1.4-3.2) Current vs. Nonuser	37	Highest risk with first year of use	6,993 woman yrs/1 VTE	Good: although analysis of dosages and ERT/HRT were based on small numbers and method of determining exposure was through formulary records.
Varas-Lorenzo, 1998[10]	Smoking	2.3 (1.0-5.3) Current vs. Nonuser	6	Highest risk with first year of use	5,000 woman yrs/1 VTE	Fair: did not include smoking, analysis based on 6 current users of ERT/HRT.
Høibraaten, 1999[13]	Varicose veins	1.22 (0.76 - 1.94) Current vs. Nonuser	50	Highest risk with first year of use	Not analyzed	Fair: no clear method of outcome measurement. Dose of HRT not reported.
Boston Collaborative, (1974)[3]	Body mass index, varicose veins, smoking	2.26 (0.61 - 8.41)**	3	Not analyzed	25,000	Poor: No clear method of outcome measurement. Dose and duration of HRT use not reported. Confounders not controlled for.

*Not all exclusions listed

**calculated

Note: CE indicates Conjugated estrogen; EE, Esterified; ERT, Estrogen Replacement Therapy; HRT, Hormone Replacement Therapy; PE, Pulmonary Embolism; VTE, Venous Thromboembolism.

Author, Year	Grodstein, 1996[11]
Study type	Prospective
Population	112,593 nurses
Setting	11 U.S. states
Exclusions*	History of PE
Age range	30-55 yrs in 1976
Method of Determining Exposure	Questionnaire every 2 yrs
Definition of HRT Use	Current Past Never
HRT Dosage(s)	CEE: 0.3 mg; 0.625 mg; 1.25 mg
Progestin Use	Not specified
Outcome Measured	PE
Method of Determining Outcome	V/Q scan, pulmonary angiogram or necropsy
Study Duration	16 yrs
Follow-up Rate	Estimated > 90%
Confounders Controlled For	Age, body mass index, hypertension, diabetes, smoking, oral contraceptive use, parity, elevated cholesterol
Current Users with PE (n)	30-39 yrs n=1 40-49 yrs n=4 50-59 yrs n=10 >60 yrs n=7
Past Users with PE (n)	30-39 yrs n=0 40-49 yrs n=4 50-59 yrs n=8 >60 yrs n=7
Current User Relative Risk (95% CI)	2.1 (1.2-3.8)
Past User Relative Risk (95% CI)	1.3 (0.7-2.4)
Relative Risk by duration of usage	Current user: >5 yrs =1.9 (0.9-4.0); Current user: < 5 yrs =2.6 (1.2-5.2)
Number Needed to Harm	Current user: 17,932 woman yrs/1 VTE; Past user: 27,691 woman yrs/1VTE
Quality of Study	Good-No trends observed in dosages. Relative risk slightly increased when venous diagnoses excluded

*Not all exclusions listed
Note: CEE indicates Conjugated equine estrogen; PE, Pulmonary Embolism; VTE,
Venous Thromboembolism

Author, Year	Setting/ Population	Eligibility	Number Considered	Exclusions	Number Randomized	Treatment (n) Placebo (n)
Tamoxifen						
Fisher (BCPT), 1998[20]	Outpatient;131 U.S. and Canadian sites	No breast cancer and 60 yrs or older, or 35-59 yrs with increased risk for breast cancer	98,018	Breast cancer;use of HRT, oral contraceptives, or androgens within 3 mos of randomization; history of VTE or	13,388	6,681/6,707
Powles,1998[22]	Outpatient Breast Clinic; Great Britain	Age 30-70 yrs and increased risk for breast cancer due to family history	2,508	History of any cancer, DVT, or PE	2,494	1,250/1,244
Veronesi, 1998[21]	Outpatient; mostly Italian sites	Age 35-70 yrs with hysterectomy	13,419	Severe illness, cardiac disease, endometriosis, history of DVT	5,408	2,700/2,708
Raloxifene						
Lufkin, 1998[24]	Outpatient; two U.S. sites	Age 45-75 yrs, postmenopausal	not available	History of DVT, thromboembolic diagnoses, cancer, coronary disease	143	48 (60 mg)/ 47 (120 mg)/ 48 (placebo)
Cummings (MORE), 1999[23]	180 community and medical clinics; mainly U.S. and Europe	Age <80 yrs; 2 yrs postmenopausal with osteoporosis	22,379	History of breast or endometrial cancer, stroke, VTE, any cancer; abnormal uterine bleeding; secondary causes	7,705	5,129/2,576

*Calculated
Note: DVT indicates Deep Vein Thrombosis; HRT, Hormone Replacement Therapy;
PE, Pulmonary Embolism; VTE, Venous Thromboembolism.

Author, Year	Mean Age	SERM Type/ Dosage(s)	Placebo RX	Compliance Rate/Method	Secondary Outcome Measured	Method of Secondary Outcome Measurement	Study Duration
Tamoxifen							
Fisher (BCPT), 1998[20]	39% 35-49yrs 30% 50-59 yrs 30% > 60 yrs	Tamoxifen 20 mg/d	Placebo	Not stated	DVT and PE not specified outcomes	Not stated	5 years
Powles,1998[22]	Median age 47 yrs	Tamoxifen 20 mg/d	Identical placebo	Interview, confirmed by random blood testing of tamoxifen group	DVT and PE not specified outcomes	Not stated	Interim analysis at 70 months
Veronesi, 1998[21]	Median age 51 yrs	Tamoxifen 20 mg/d	Identical placebo	Not stated	DVT and PE not specified outcomes	Not stated	Interim analysis at 46 months
Raloxifene							
Lufkin, 1998[24]	68 yrs	Raloxifene 60 mg/d or 120 mg/d + calcium 750 mg/d and Vitamin D	Calcium 750 mg/d and Vitamin D	Not stated	DVT and PE not specified outcomes	Not stated	One year
Cummings (MORE), 1999[23]	65 yrs	Raloxifene 60 mg/d or 120 mg/d + calcium 500 mg/d and 400-600 IU cholecalciferol	Placebo + Calcium 500 mg/d and 400-600 IU cholecalciferol	92% took > 80% medication; method not stated	DVT and PE not specified outcomes; reported as adverse effect	Chart review	40 months

*Calculated
Note: DVT indicates Deep Vein Thrombosis; HRT, Hormone Replacement Therapy;
PE, Pulmonary Embolism; VTE, Venous Thromboembolism.

Author, Year	Follow-up Rate	Relative Risk (95% CI)	Number Needed to Harm	Quality of Studies
Tamoxifen				
Fisher (BCPT), 1998[20]	92.3% tamoxifen 92.4% placebo	PE 3.01 (1.15-9.27) DVT 1.60 (0.91-2.86) VTE 1.91 (1.21-3.02)	266 woman yrs/1 VTE	Fair: diagnostic criteria for VTE unclear.
Powles,1998[22]	89%	Unadjusted OR 1.75 (0.51-5.98)*	419 woman yrs/1 VTE	Poor: VTE not designated as a secondary outcome; diagnostic criteria for VTE unclear; important loss to follow-up.
Veronesi, 1998[21]	>90%	Unadjusted OR 1.76 (0.51-6.01)*	896 woman yrs/1 VTE	Poor: VTE not designated as a secondary outcome;diagnostic criteria for VTE unclear; high dropout rate.
Raloxifene				
Lufkin, 1998[24]	>90%	Undefined	Undefined	Poor: VTE not designated as a secondary outcome; diagnostic criteria for VTE unclear; underpowered to detect VTE outcome.
Cummings (MORE), 1999[23]	At 3 yrs: 78% raloxifene 75% placebo	VTE 3.1 (1.5-6.2)	155 woman yrs/1 VTE	Fair: VTE not designated as an apriori outcome.

*Calculated
Note: DVT indicates Deep Vein Thrombosis; HRT, Hormone Replacement Therapy;
PE, Pulmonary Embolism; VTE, Venous Thromboembolism.