Review

Oral vs Transdermal Estrogen Therapy and Vascular Events: A Systematic Review and Meta-Analysis

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Background: Menopausal hormone therapy is widely used to alleviate climacteric symptoms but may increase the risk of venous and arterial vascular events.

Objective: The objective was to synthesize the evidence about the risk of vascular events in postmenopausal women who use oral estrogen therapy (ET) and transdermal ET.

Methods: We searched bibliographical databases through August 2013 for longitudinal comparative studies that enrolled postmenopausal women using either oral or transdermal ET and reported the outcomes of interest: venous thromboembolism (VTE), pulmonary embolism, deep venous thrombosis (DVT), myocardial infarction (MI), and stroke. Two reviewers independently selected and appraised studies. Outcomes were pooled using random effects meta-analysis and were reported as risk ratio (RR) and 95% confidence interval (CI).

Results: We included 15 observational studies at moderate risk of bias with follow-up of 3 to 20.25 years. When compared to transdermal ET, oral ET was associated with increased risk of a first episode of VTE (RR, 1.63; 95% CI, 1.40–1.90; $I^2 = 53\%$), DVT (RR, 2.09; 95% CI, 1.35–3.23; $I^2 = 0\%$), and possibly stroke (RR, 1.24; 95% CI, 1.03–1.48; a single case-controlled study), but not MI (RR, 1.17; 95% CI, 0.80–1.71; $I^2 = 74\%$).

Conclusion: Observational evidence warranting low confidence suggests that compared to transdermal ET, oral ET may be associated with increased risk of VTE and DVT, but not MI. (***J Clin Endocrinol Metab*** **100: 4012–4020, 2015)**

Menopausal hormonal therapy (MHT) is commonly used to manage bothersome menopausal symptoms affecting up to 75% of women (1). Estrogen therapy (ET) is used in women with hysterectomy and in combination with a progestogen in women with an intact uterus for protection against endometrial hyperplasia and cancer. MHT can be administered by various routes, including oral and transdermal. Concerns have been raised about thrombotic and ischemic complications of MHT.

ET is a known risk factor for venous thromboembolism (VTE) (2, 3), but observational studies suggest that this risk is significantly higher for oral estrogen compared to transdermal. However, this has not been tested in a randomized controlled trial (RCT). Oral ET undergoes first-pass metabolism in the liver, which is associated with a number of adverse hemostatic effects, whereas transdermal administration of ET largely avoids these effects. These adverse changes may impact vascular disease risk

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Abbreviations: CI, confidence interval; DVT, deep venous thrombosis; EPT, estrogen and progestogen therapy; ET, estrogen therapy; MHT, menopausal hormone therapy; MI, myocardial infarction; PE, pulmonary embolism; RCT, randomized controlled trial; RR, risk ratio; VTE, venous thromboembolism.

and include decreased low-density lipoprotein particle size, increased triglycerides and C-reactive protein, as well as increased production of certain coagulation factors (4–6).

The association of arterial vascular events such as myocardial infarction (MI) and ischemic stroke with the use of ET is even more complex and may relate to the dose, route of administration, and time since menopause, with women who are > 10 years from the menopausal transition at greatest risk for cardiovascular events (7, 8).

Evidence regarding the risk of vascular events in postmenopausal women comparing oral and transdermal ET is still unclear. We aim to synthesize existing evidence about the risk of vascular events in postmenopausal women using oral compared to transdermal ET.

Materials and Methods

We followed a predefined protocol developed by a task force from The Endocrine Society to conduct this systematic review and meta-analysis. We followed the standards set in the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (9).

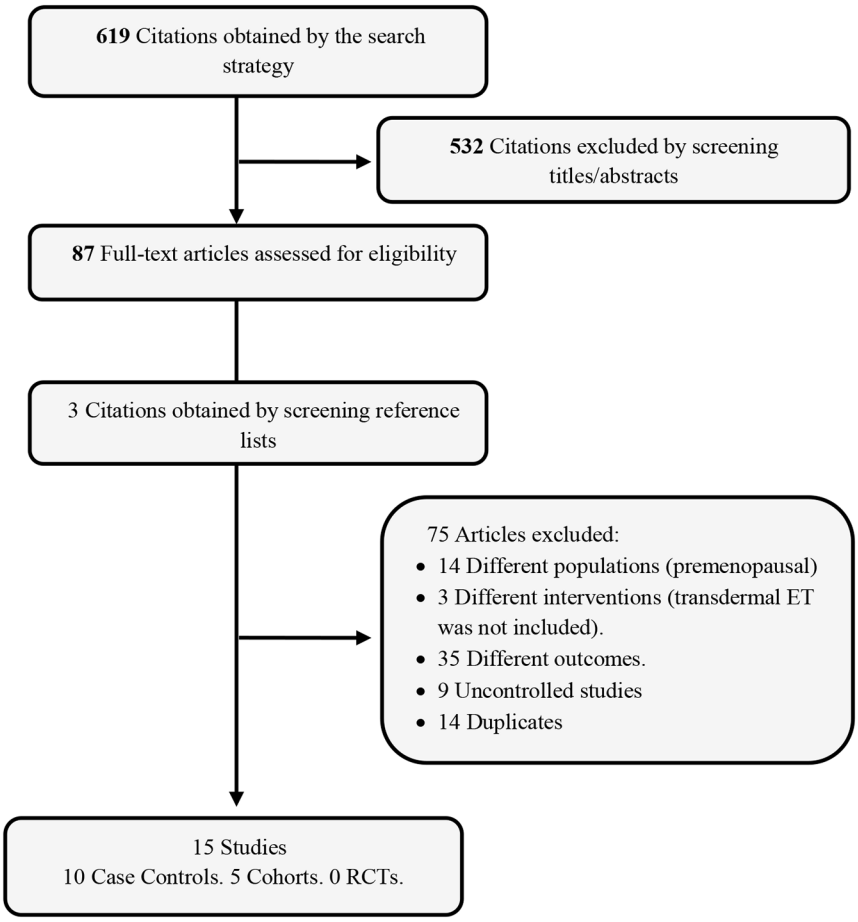

Figure 1. The process of study selection.

Eligibility criteria

We included comparative/controlled (prospective and retrospective) studies that enrolled postmenopausal women who received either oral or transdermal ET. The outcomes of interest were VTE, pulmonary embolism (PE), deep venous thrombosis (DVT), MI, and stroke. For studies to be included, they needed to report using both oral and transdermal ET. We excluded studies with no comparison group, case series, reviews, or expert opinion and studies reporting use of only oral or transdermal ET, but not both.

Literature search

We conducted a comprehensive search of several databases from the inception of each database to August 2013. The search was not restricted to English, and it employed controlled vocabulary supplemented with keywords. The databases included Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. The search was conducted by an experienced Mayo Clinic reference librarian (L.J.P.). A detailed search strategy is in Appendix 1. The electronic database search was supplemented with a manual database search, expert collaboration, and review of bibliographies of included studies.

Study selection and data extraction

Two reviewers independently evaluated the titles and abstracts, and then the full text for inclusion eligibility. Disagreements were harmonized by consensus and, if not possible, by arbitration with a third reviewer. We used an online reference management system (Distiller SR; Evidence Partners Inc). Non-English studies were translated with the help of native speakers. We calculated inter-rater agreement (κ) during the full-text screening to observe the agreement between reviewers. Two reviewers independently extracted data from each study and reconciled any differences by referring to the full text. Data were extracted on patient demographics, study characteristics (inclusion and exclusion criteria, location, detailed interventions, and follow-up duration), and outcome data. Authors of the original studies were contacted by email if clarification or additional data were needed.

Risk of bias assessment and quality of evidence

We used the Newcastle-Ottawa Scale (10) to appraise the risk of bias in case-control and cohort studies. The quality of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (11).

Statistical analysis

For dichotomized outcomes, we estimated risk ratios (RRs) and 95% confi-

Table 1. Characteristics of Studies Included

First Author, Year (Ref.)	Location/Setting	Inclusion Criteria	Exclusion Criteria	Follow-Up Duration, mo	MHT		Outcome	Study Design
					Oral ET	Transdermal ET		
Roach, 2013 (13)	Six anticoagulation clinics in The Netherlands	Cases: 1082 patients with a first episode of DVT or PE, age >50 y. Controls: 1468 female partners of male patients with VTE	Severe psychiatric problems and inability to speak Dutch	76	CEE/MPA; E2/NETA	17-β estradiol; norethisterone acetate	First episode of DVT or PE	Case control
Renoux, 2010 (15)	United Kingdom/ General Practice Research Database (GPRD)	Cases: Incident cases of VTE, age 50–79 y. Controls: matched controls on age (±2 y)	All subjects with a diagnosis of VTE before age 50 y, or before up to date of practice	243	Estrogen alone or combined with progestogen. Low dose contained <0.625 mg conjugated equine estrogens or <2 mg 17-β estradiol; high dose contained 0.625 mg conjugated equine estrogens or 2 mg 17-β estradiol	Transdermal low-dose products contained <50 μg 17-β estradiol and high-dose products >50 μg	Incident cases of VTE, namely DVT or PE	Case control
Renoux, 2010 (21)	United Kingdom/ GPRD	Cases: women with first recorded diagnosis of stroke, age 50–79 y. Controls: matched cohort	Cases with no matched controls	166	Oral low-dose products contained ≤0.625 mg conjugated equine estrogens or ≤2 mg 17-β estradiol; high-dose products contained >0.625 mg conjugated equine estrogens or >2 mg 17-β estradiol	Transdermal low-dose products contained ≤50 μg 17-β estradiol; high-dose products contained >50 μg	First recorded diagnosis of stroke (ischemic, hemorrhagic, or not further specified)	Case control
Canonico, 2007 (16)	Multicenter, eight French hospitals	Cases: 208 cases with a first episode of idiopathic VTE. Controls: matched 426 hospital controls with diagnosis unrelated to estrogen use	History of VTE, contraindication for hormone therapy or predisposing factor for VTE, referred to clinical centers for estrogen advice or known thrombophilia	72	Micronized progesterone or pregnane derivatives, norpregnane derivatives, or nortestosterone derivatives. Pregnane derivatives included dydrogesterone or medrogestone, chlormadinone acetate, cyproterone acetate, or medroxyprogesterone acetate. Norpregnane derivatives included either nomegestrol acetate or promegestone	Micronized progesterone or pregnane derivatives, norpregnane derivatives, or nortestosterone derivatives. Pregnane derivatives included dydrogesterone or medrogestone, chlormadinone acetate, cyproterone acetate, or medroxyprogesterone acetate. Norpregnane derivatives included either nomegestrol acetate or promegestone	First documented episode of idiopathic VTE	Case control
de Vries, 2006 (22)	United Kingdom/ GPRD	Cases: 4537 women with first diagnosis of MI or AMI, age 52–74 y. Control: matched controls	NR	56	Unopposed estrogen, combined HT and tibolone	Unopposed estrogen, combined HT	First diagnosis of MI or AMI	Case control
Hippisley-Cox, 2003 (23)	Nine general practices recruited from the Trent Focus Collaborative Research Network, UK	Cases: first recorded diagnosis of CHD or first prescription for nitrates. Control: matched women who never had a recorded diagnosis of CHD	NR	60	Low dose: users of 1 mg 17-β estradiol, 0.625 mg oral conjugated equine estrogens, 5 μg ethinyl estradiol. High dose: higher amounts of estrogen	Low dose: 25 μg of transdermal 17-β estradiol per day or less. High dose: higher amounts of estrogen	First recorded diagnosis of CHD (including angina, MI, and coronary artery surgery)	Case control
Chilvers, 2003 (24)	Eight hospitals serving Derby, Leicester, Mansfield, and Nottingham. East Midlands, UK	Cases: Women with first AMI, age 35–65 y. Control: matched controls	Recurrent MI	44	Estrogen only. Combined	Estrogen only. Combined	First AMI	Case control

(*Continued*)

Table 1. Continued

First Author, Year (Ref.)	Location/Setting	Inclusion Criteria	Exclusion Criteria	Follow-Up Duration, mo	MHT		Outcome	Study Design
					Oral ET	Transdermal ET		
Daly, 1996 (18)	Hospitals in the area of the Oxford Regional Health Authority	Cases: Women with PE, DVT, or both, age 45–64 y. Control: hospital controls	History of PE, DVT, stroke, or MI, bed rest for longer than 1 wk after surgery, pregnancy, trauma, or illness	22	Low dose: oral preparations (0.625 mg conjugated equine estrogens, 1 mg 17-β estradiol/estradiol valerate, or 1.5 mg piperazine estrone sulfate). High dose: 2.5 mg conjugated equine estrogens or 2 mg 17-β estradiol/estradiol valerate	Low dose: transdermal preparations delivering 50 μg 17-β estradiol. High dose: 100 μg 17-β estradiol	Idiopathic VTE	Case control
Douketis, 2005 (19)	Twelve clinical centers (eight in Canada, two in Italy, two in The Netherlands)	Cases: patients with idiopathic DVT. Control: patients in whom DVT was excluded, and who did not have any aforementioned DVT risk factors	PE; amenorrhea due to ovarian failure; cognitive impairment, language barrier, current users of selective estrogen receptor modulators, estrogen antagonists	36	Estrogen only; combined	Estrogen only; combined	Idiopathic DVT	Case control
Scarabin, 2003 (26)[a]	Seven teaching hospitals in France	Cases: 155 postmenopausal women aged 45–70 y. Control: 381 matched hospital controls	Previous episode of VTE; predisposing factor for VTE	36	Low-dose preparation containing 0.625 mg conjugated equine estrogens, 1 mg estradiol, or 1 mg estradiol valerate. High-dose preparation containing 1.25 mg conjugated equine estrogens, or 1.5 mg and 2 mg estradiol or 2 mg estradiol valerate	Low-dose preparations delivering less than 50 μg estradiol per 24 h; high-dose preparations delivering 50 μg and 100 μg estradiol per 24 h	First documented episode of idiopathic VTE	Case control
Laliberté, 2011 (14)	Thomson Reuters Market Scan database	Postmenopausal women aged 35 years or older newly using an estradiol transdermal system or an oral estrogen-only hormone therapy with 2 or more dispensings were analyzed	Previously diagnosed with a VTE before the index date	Mean, SD (121.2, 55.2)	Oral ET (eg, Cenestin, Estrace, Premarin)	Transdermal ET (17-β estradiol transdermal system; Vivelle-Dot)	VTE and hospitalization-related VTE	Cohort
Olie, 2011 (12)	Hormones and cardiovascular disease team, CEPH Centre for research in Epidemiology and Population Health, France	All postmenopausal women aged 45 to 70 y who came to the outpatient clinic of the hemostasis unit	Superficial vein thrombosis, upper extremity DVT, central retinal vein obstruction	79	Current users of HT were classified according to the route of estrogen administration (oral or transdermal) and the type of concomitant progestogen	Current users of HT were classified according to the route of estrogen administration (oral or transdermal) and the type of concomitant progestogen	Documented recurrent VTE event	Cohort
Canonico, 2010 (20)	E3N French prospective cohort	80 308 postmenopausal women including 549 with documented idiopathic first VTE	Not menopausal, history of cancer or predisposing factors for VTE	120	Most current users of oral and transdermal estrogens received 17β -estradiol. Women were classified as users of micronized progesterone, pregnane derivatives, norpregnane derivatives, or nortestosterone derivatives	Most current users of oral and transdermal estrogens received 17β-estradiol. Women were classified as users of micronized progesterone, pregnane derivatives, norpregnane derivatives, or nortestosterone derivatives	Idiopathic first VTE	Cohort

(*Continued*)

Table 1. Continued

First Author, Year (Ref.)	Location/Setting	Inclusion Criteria	Exclusion Criteria	Follow-Up Duration, mo	MHT		Outcome	Study Design
					Oral ET	Transdermal ET		
Sweetland, 2012 (17)	National Health Service breast screening clinics in UK	Postmenopausal UK women	History of cancer, blood clot or treatment for clotting, VTE, or had surgery within 12 wk before recruitment	Total of 3.3 million person-years, with a mean of 3.1 years per woman	Oral or transdermal (patch or gel) dose of estrogen with or without progestogen (patch or tablet)	Oral or transdermal (patch or gel) dose of estrogen with or without progestogen (patch or tablet)	First diagnosis VTE	Cohort
Løkkegaard, 2008 (25)	Danish national registry of women from all hospitalizations in Denmark	Postmenopausal women (51 y old)	Women with CVD or hormone-related cancers	50	Estrogen only therapy, cyclic combined estrogen/progestogen therapy, long-cycle combined estrogen/progestogen therapy, continuous combined estrogen/progestogen therapy, tibolone, and raloxifene; estrogen	Estrogen only therapy, cyclic combined estrogen/progestogen therapy, long-cycle combined estrogen/progestogen therapy, continuous combined estrogen/progestogen therapy, tibolone, and raloxifene; estrogen	The first event of MI	Cohort

Abbreviations: GPRD, General Practice Research Database; HT, hormone therapy; AMI, acute MI; NR, not reported; CEE, conjugated equine estrogen; MPA, medroxyprogesterone acetate; CHD, coronary heart disease; CVD, cardiovascular disease; E2, estradiol; NETA, norethisterone acetate; E3N, Etude Epidémiologique auprès de femmes de l'Education Nationale.

[a] This study was only included in the subgroup analysis.

dence intervals (CIs) using binomial distribution. We then pooled the log-transformed RRs using the DerSimonian and Laird random-effect models with the heterogeneity estimated from the Mantel-Haenszel model. The I^2 statistic was used as a measure for overall heterogeneity, where $I^2 > 50\%$ indicates high heterogeneity. All analyses were conducted using STATA, version 13 (StataCorp LP).

Subgroup analysis

Predetermined subgroups were identified to explain heterogeneity; subgroup analysis was done based on the hormone therapy regimen (ET vs estrogen and progestogen therapy [EPT]) and dose of oral ET (low vs high dose). Oral ET containing <0.625 mg of conjugated equine estrogens or <2 mg of 17-β estradiol was defined as low dose; oral ET containing ≥0.625 mg of conjugated equine estrogens or >2 mg of 17-β estradiol was defined as high dose. Transdermal low-dose products contained ≤50 μg of 17-β estradiol, and high-dose products contained >50 μg.

Results

The initial database search resulted in 619 citations, from which 15 studies were eligible. Average weighted κ for study selection was 0.81. The detailed study selection process is described in Figure 1.

All of the studies were observational (10 case-control and five cohort studies), and none were randomized. Studies enrolled 22 489 women who received oral ET and 5671 women who received transdermal ET, with a follow-up period ranging from 3 to 20.25 years.

In all studies, the clinical endpoint was the first idiopathic episode of VTE, DVT, PE, stroke, or MI, except for one study that reported recurrent VTE events (12). Detailed description of the included case-control studies and cohort studies is summarized in Table 1.

Risk of bias assessment

The overall risk of bias of included studies was moderate. Samples were representative in most studies with no baseline imbalance, and nearly all studies adjusted for at least one important confounder. Tables 2 and 3 describes detailed risk of bias assessment of the included studies.

Meta-analysis

Figure 2 shows the results of the meta-analysis for risk of VTE, DVT, PE, stroke, and MI associated with oral compared to transdermal ET. The quality of evidence for most of the outcomes was low to very low due to the observational nature of the studies and inconsistency. Table 4 shows a detailed GRADE profile for the reported outcomes.

Risk of VTE

Nine studies (12–20) with mean age of 57.7 ± 6.3 years reported VTE. Compared to transdermal ET, oral ET was associated with an increased risk of VTE (RR, 1.66; 95% CI, 1.42–1.93; $I^2 = 53.2\%$). The quality of evidence was considered very low due to the observational study design and inconsistency. For the risk of DVT or PE alone, two studies (14, 19) reported increased risk of DVT associated with oral compared to transdermal ET (RR, 2.09; 95% CI, 1.1.35–3.23; $I^2 = 0\%$). One study (14) reported no sig-

Table 2. Risk of Bias in the Included Case-Control Studies

First Author, Year (Ref.)	Is the Case Definition Adequate?	Representativeness of the Cases	Selection of Controls	Definition of Controls	Comparability of Cases and Controls	Ascertainment of Exposure	Same Method of Ascertainment for Cases and Controls	Non-Response Rate
Roach, 2013 (13)	Requires some independent validation	Consecutive or obviously representative series of cases	Community controls	No history of disease (endpoint)	Study controls for additional factors	Written self-report or medical record only	Yes	Requires some independent validation
Renoux, 2010 (15)	Yes, with record linkage or based on self-report	Consecutive or obviously representative series of cases	Hospital controls	No history of disease (endpoint)	Study controls for additional factors	Written self-report or medical record only	Yes	Response rates different between groups and no description
Renoux, 2010 (21)	Yes, with record linkage or based on self-report	Consecutive or obviously representative series of cases	Hospital controls	No history of disease (endpoint)	Study controls for the most important factor	Secure record (eg, surgical record)	Yes	Non-respondents described
Canonico, 2007 (16)	Yes, with independent validation	Consecutive or obviously representative series of cases	Hospital controls	No history of disease (endpoint)	Study controls for additional factors	Secure record (eg, surgical record)	Yes	Same rate for both groups
de Vries, 2005 (22)	Yes, with record linkage or based on self-report	Consecutive or obviously representative series of cases	Community controls	No history of disease (endpoint)	Study controls for the most important factor	Secure record (eg, surgical record)	Yes	Response rates different between groups and no description
Hippisley-Cox, 2003 (23)	Yes, with record linkage or based on self-report	Consecutive or obviously representative series of cases	Hospital controls	No history of disease (endpoint)	Study controls for additional factors	Secure record (eg, surgical record)	Yes	Response rates different between groups and no description
Chilvers, 2003 (24)	Yes, with record linkage or based on self-report	Consecutive or obviously representative series of cases	Community controls	No history of disease (endpoint)	Study controls for the most important factor	Secure record (eg, surgical record)	Yes	Non-respondents described
Daly, 1996 (18)	Yes, with independent validation	Consecutive or obviously representative series of cases	Hospital controls	No history of disease (endpoint)	Study controls for the most important factor	Secure record (eg, surgical record)	Yes	NR
Douketis, 2005 (19)	Requires some independent validation	Consecutive or obviously representative series of cases	Hospital controls	No history of disease (endpoint)	Study controls for additional factors	Secure record (eg, surgical record)	Yes	NR

Abbreviation: NR, not reported.

nificant increase in risk of PE with oral compared to transdermal ET (RR, 2.0; 95% CI, 0.81–4.95).

Risk of stroke

Only one case-control study (21) with a mean age of 70.3 ± 7.3 years reported the outcome of stroke. Compared to transdermal ET, oral ET was associated with an increased risk of stroke (RR, 1.24; 95% CI, 1.03–1.48).

Risk of coronary events (MI)

Four studies (22–25) with a mean age of 60.5 ± 11.1 years reported the incidence of MI. Meta-analysis showed

Table 3. Risk of Bias in the Included Cohort Studies

First Author, Year (Ref.)	Representativeness of the Exposed Cohort	Selection of the Nonexposed Cohort	Ascertainment of Exposure	Demonstration That Outcome of Interest Was Not Present at Start of Study	Comparability of Cohorts on Basis of Design or Analysis	Assessment of Outcome	Was Follow-Up Long Enough for Outcomes to Occur?	Adequacy of Follow-Up of Cohorts
Laliberté, 2011 (14)	Truly representative of community or population	Drawn from same community as exposed cohort	Secure records	Yes	Study controls for any additional factors	Record linkage	Yes	Unclear
Olie, 2011 (12)	Truly representative of community or population	Drawn from same community as exposed cohort	Secure records	Yes	Study controls for any additional factors	Record linkage	Yes	Unclear
Canonico, 2010 (20)	Truly representative of community or population	Drawn from same community as exposed cohort	Secure records	Yes	Study controls for most important factor	Independent blind assessment	Yes	Complete follow-up, all subjects accounted for
Sweetland, 2012 (17)	Truly representative of community or population	Drawn from same community as exposed cohort	Secure records	Yes	Study controls for most important factor	Record linkage	Yes	Unclear
Løkkegaard, 2008 (25)	Truly representative of community or population	Drawn from same community as exposed cohort	Secure records	Yes	Study controls for most important factor	Record linkage	Complete follow-up, all subjects accounted for	No

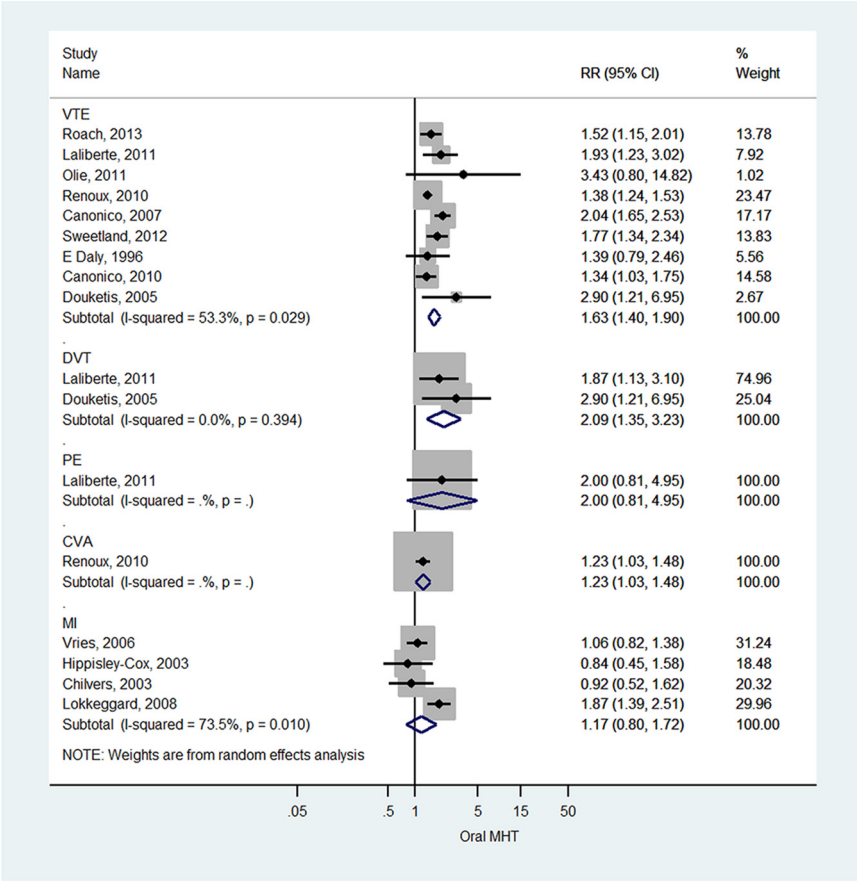

Figure 2. Meta-analysis of risk of vascular events in postmenopausal women using oral estrogen vs transdermal ET.

no statistically significant difference between oral and transdermal ET (RR, 1.17; 95% CI, 0.80–1.72; I^2 = 73.5%). Sensitivity analysis was done to exclude two studies that evaluated tibolone, with no change in the results (RR = 0.884; 95% CI, 0.58–1.345; I^2 = 0%).

Subgroup analysis

Stratified analysis was conducted based on estrogen dose (low vs high dose) and regimen of MHT (ET vs EPT). Two studies (15, 26) stratified the risk of VTE, and one study (21) stratified the risk of stroke according to dose of ET and regimen (ET vs EPT). One study (25) stratified the risk of MI according to dose of ET. The only significant interaction suggested that low-dose oral vs low-dose transdermal was associated with increased risk of stroke (whereas high-dose oral vs high-dose transdermal was not associated with a difference in risk). No significant interaction was detected for other subgroups. The results of the subgroup analysis are presented in Table 5.

Discussion

Main finding

We found a small number of observational studies at moderate risk of bias, suggesting a significant increase in risk of VTE and DVT with oral ET compared to transdermal ET in postmenopausal women. There was no significant association with PE or MI. In one case-control study, oral ET was also associated with a significantly increased risk of stroke. Subgroup analysis showed no significant interaction between dose of ET or regimen (ET vs EPT) and risk of vascular events.

Two previously published systematic reviews summarized both randomized and observational studies (27) and randomized trials only (28), comparing MHT users to nonusers. Olie et al (27) noted an increased risk of VTE with oral ET compared to nonusers in a meta-analysis of both observational studies and RCTs. Sare et al (28) found no difference in risk of VTE, MI, or stroke between oral and transdermal ET compared to placebo on a subgroup analysis, although the number of trials using transdermal ET in this systematic review of RCTs was small. However, these were indirect comparisons of the route of administration of ET because the studies included in these reviews only compared MHT users to nonusers, and the reviews did not include studies directly comparing the two routes of administration. In our review, we exclusively included the 15 observational studies that performed a direct comparison between oral and transdermal routes of administration of ET.

Table 4. GRADE Evidence Profile for the Study Outcomes

Outcome	No. of Studies	Quality Assessment						Effect	
		Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Relative (95% CI)	Quality
VTE	9	Observational studies	Not serious	Serious	Not serious	Not serious	None	RR, 1.63 (1.40 to 1.90)	⊕◯◯◯, very low
MI	4	Observational studies	Not serious	Serious	Not serious	Serious	None	RR, 1.17 (0.80 to 1.72)	⊕◯◯◯, very low
Stroke	1	Observational studies	Not serious	Serious	Not serious	Not serious	None	RR, 1.23 (1.03 to 1.48)	⊕◯◯◯, very low
DVT	2	Observational studies	Not serious	Not serious	Not serious	Not serious	None	RR, 2.09 (1.35 to 3.23)	⊕⊕◯◯, low
PE	1	Observational studies	Not serious	Not serious	Not serious	Serious	None	RR, 2.00 (0.81 to 4.95)	⊕◯◯◯, very low

Table 5. Subgroup Analysis: Vascular Events Risk Stratified Based on MHT Regimen (ET vs EPT) and Dose of ET

Outcome	Effect Size	95% CI		I^2 %	Interaction *P* Value
		LL	UL		
VTE					
Estrogen dose					.21
High-dose oral vs high-dose transdermal[b]	1.74	0.94	3.21	82.6	
Low-dose oral vs low-dose transdermal[a]	1.53	0.84	2.77	84.6	
MHT regimen					.23
Oral estrogen only vs transdermal estrogen only	1.37	1.21	1.56	0	
Oral estrogen-progestogen vs transdermal estrogen-progestogen	1.83	1.17	2.83	82.7	
Stroke					
Estrogen dose					.03
High-dose oral vs high-dose transdermal[b]	0.86	0.59	1.24	NA	
Low-dose oral vs low-dose transdermal[a]	1.37	1.12	1.69	NA	
MHT regimen					.3
Oral estrogen only vs transdermal estrogen only	1.2	0.98	1.49	NA	
Oral estrogen-progestogen vs transdermal estrogen-progestogen	1.49	1.04	2.15	NA	
MI					
Estrogen type					.2
Oral estrogen only vs transdermal estrogen only	2.32	1.53	3.53	NA	
Oral estrogen-progestogen vs transdermal estrogen-progestogen	1.59	1.05	2.43	NA	

Abbreviations: LL, lower level; UL, upper level; NA, not available.

[a] Oral low dose if it contained <0.625 mg of conjugated equine estrogens or <2 mg of 17-β estradiol and transdermal low-dose products contained ≤50 μg of 17-β estradiol.

[b] Oral high dose if it contained 0.625 mg of conjugated equine estrogens or 2 mg of 17-β estradiol and transdermal high-dose products >50 μg.

Clinical implications

The risk of VTE is about 1 per 1000 person-years for women in their 50s, and it increases with age and risk factors such as obesity, fracture, renal disease, existing cardiovascular disease, and both acquired and congenital thrombophilias (29). VTE accounts for approximately one in three potentially fatal cardiovascular events in postmenopausal hormone therapy users (5). Because this is a significant health concern for postmenopausal women, minimizing this risk is paramount. The greater impact on coagulation activation with oral compared to transdermal estrogen has been demonstrated in multiple studies (30). This meta-analysis suggests a safety advantage with the use of transdermal as compared to oral ET, particularly in women at risk for thrombosis. In addition to route of administration, the dose of estrogen and choice of progestogen may also influence risk (4, 31).

The mechanism by which ischemic stroke occurs in younger, postmenopausal hormone therapy users may differ from that of MI, in that the former is most commonly associated with thrombosis and the latter with development and progression of atherosclerosis (31), which may explain the differing results between these cardiovascular endpoints noted in the present study.

Strength and limitations

The strength of this systematic review and evidence synthesis is driven from the rigorous methodological approach that included a predefined protocol guided by The Endocrine Society, a comprehensive literature search that spanned multiple databases without language restriction, and duplicate study selection and appraisal. The main limitation of the study is the observational nature of the included studies, which increases the risk of bias and reduces the trustworthiness of the results.

Conclusion

Observational evidence warranting low confidence suggests that, compared to transdermal ET, oral ET may be associated with increased risk of VTE, DVT, and possibly stroke, but not MI.

Acknowledgments

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Disclosure Summary: The authors have nothing to declare.

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