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Comparative venous thromboembolic safety of oral and transdermal postmenopausal hormone therapies among women Veterans

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Abstract

Objective: Hormone therapy (HT) is used by menopausal women to treat vasomotor symptoms. Venous thromboembolism (VTE) is an important risk of HT use, and more knowledge on the comparative safety of different estrogenic compounds is useful for women who use HT for these symptoms. The objective was to compare the risk of VTE among users of oral conjugated equine estrogen (CEE), oral estradiol (E2) and transdermal E2, in a cohort of women Veterans.

Methods: This retrospective cohort study included all women Veterans aged 40–89 years, using CEE or E2, without prior VTE, between 2003 and 2011. All incident VTE events were adjudicated. Time-to-event analyses using a time-varying HT exposure evaluated the relative VTE risk between estrogen subtypes, with adjustment for age, race, and BMI, with stratification for prevalent vs. incident use of HT.

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Addendum

All statements and opinions are solely of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States Government.

Authorship: M. Blondon, A.K. Timmons, A.J. Baraff, A.M. Korpak, N.L. Smith substantially contributed to concept and design, analysis, and interpretation of data. J.S. Floyd and L.B. Harrington substantially contributed to concept and design and interpretation of data. All authors critically wrote or revised the intellectual content and approved the final version.

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Results: Among 51,571 users of HT (74.5% CEE, 12.6% oral and 12.9% transdermal E2 at cohort entry), with a mean age of 54.0 years, the incidence of VTE was 1.9/1000 person-years. Compared with CEE use, in the multivariable regression model, there was no difference in the risk of incident VTE associated with oral E2 use (HR 0.96, 95% CI 0.64-1.46) or with transdermal E2 use (HR 0.95, 95% CI 0.60-1.49). Results were unchanged when restricting to incident users of HT.

Conclusions: Among women Veterans, the risk of VTE was similar in users of oral CEE, oral E2 and transdermal E2. These findings do not confirm the previously observed greater safety of transdermal and oral E2 over CEE.

Keywords

venous thrombosis; estrogens; hormone replacement therapy; menopause; epidemiology

Climacteric vasomotor symptoms affect about 1 in 2 peri- or postmenopausal women,¹ which transdermal and oral hormone therapy (HT) alleviate effectively, with good tolerance.² However, excess risks of breast cancer and venous thromboembolism (VTE) are among its most important and consequential harms.³⁻⁷ The risk of HT-associated VTE appears, however, to be modulated by its route, the estrogenic compound and dose and its progestogenic compound,^{4,5,8,9} with a transdermal route possibly having the least risk.¹⁰ A better knowledge of the relative safety of available preparations is important, because 4-14% of American postmenopausal women were still recently using HT.¹¹⁻¹³ The estrogen component of most HT preparations is oral conjugated equine estrogen (CEE), oral estradiol (E2) or transdermal E2.

Among a cohort of postmenopausal women Veterans using HT, we assessed the comparative VTE risks of the 3 mostly commonly used treatments: oral CEE, oral E2, and transdermal E2. Extrapolating findings from previous research on CEE risk, we hypothesized that current oral CEE use would be associated with a greater risk of a first VTE than current E2 use, either oral or transdermal.^{4,5,14}

Methods

Setting and Design

This cohort is set in the Veterans Health Administration (VHA) within the Department of Veterans Affairs (VA), a large, national healthcare delivery system for those with U.S. military service. We used VHA electronic health records (EHR) to identify a cohort of women using HT and to identify VTE events during follow-up and while on HT. The study received VA Puget Sound Health Care System institutional review board approval.

Cohort of HT users

The cohort consists of peri- and postmenopausal women who were currently using HT on January 1, 2003 or who initiated HT use after that date through December 31, 2011, within the VA. Cohort entry date was January 1, 2003 for chronic (prevalent) users; for new (incident) users, this was the date the first observed HT prescription was dispensed. Using VA pharmacy benefit files, we identified 61,107 women with a record of a dispensed

prescription for HT, of which 57,862 had a pharmacy record for oral CEE, oral E2 or transdermal E2. Exclusion criteria, which were not mutually exclusive, were age <40 years or >89 years at the time of the first HT use (n=4,533), history of VTE (based on medical record note or ICD-9 codes, Supplementary Table S1, n=402), use of anticoagulants in the 6 months prior to cohort entry (n=552), conflicting sex data in the medical records (n=1,013) and recorded death before cohort entry (n=48). The final cohort comprised 51,571 women who were using HT at cohort entry.

Hormone Therapy Use

All dispensed medications from the VHA to beneficiaries are centrally recorded. Among hormonal drugs (class HS300), we identified and classified preparations for menopause hormone therapy into CEE, oral E2, transdermal E2, and other, such as estradiol cypionate. Further, we identified progestogen preparations among the HT users, which were either combined in the same preparation as the estrogen or separate.

After summarizing prescription patterns, we defined current exposure for the primary analysis as a compliance of 100% plus 30 days, based on the number of days supplied at the time of each medication fill. This means that a woman receiving 90 days of hormone therapy was considered a user until 120 days after the prescription fill.

We defined incident users as women with a first prescription of HT during the cohort time, and not having filled an HT prescription since at least 1 year prior to cohort entry (January 1, 2002). All other users were considered to be chronic (prevalent) users.

Incident VTE

We used ICD-9 diagnostic codes from VHA hospitalizations and outpatient encounters to identify women with potential VTE and to confirm that the event occurred while using HT. Pulmonary embolism (PE) and deep vein thrombosis (DVT) were identified using the codes in Supplementary Table S1. Trained abstractors then identified adjudicated potential events through a comprehensive and standardized review of the electronic health record (EHR), including provider notes and reports. Events were adjudicated as not qualifying, possible or definite. PE was considered definite in case of a positive pulmonary angiogram, CT or lung scan, and considered possible in case of a physician-reported diagnosis (in case of an imaging procedure done outside of the VA health care system) or an equivocal angiogram, CT or lung scan. DVT was considered definite in case of a positive venogram, compression ultrasound or CT and considered possible in case of a physician-reported diagnosis or an equivocal imaging. From 494 potential VTE events throughout the follow-up, 214 were considered definite (123 (57.5%)) or possible (91 (42.5%)) and occurred during exposure to HT. Only 10/91 possible VTE events had no evidence of anticoagulation after the diagnosis; these were kept as possible events because anticoagulation could have been dispensed outside of the VA health care system. There were 107 DVT-only events and 107 PE (with or without diagnosed DVT) events (Supplementary Table S2).

Covariates

Data collected in the 12 months prior to cohort entry were used for covariates, including ICD-9 codes (Supplementary Table S1), pharmacy data and VA specific medical data for age, BMI and race. The number of dispensed medications at baseline included all medications within 6 months prior to cohort entry.

Statistical Analyses

We described the data using means / standard deviations (SD) and simple proportions, stratified by the type of estrogens used at cohort entry. Incidence rates were estimated by the number of events over the total time at risk for each estrogen type.

Time-to-event models were used to characterize the association between estrogen types and risk of incident VTE among women using HT. Time at risk began at cohort entry and extended through the last prescription of HT, the occurrence of a primary outcome (VTE), death, or December 31, 2011, whichever came first. Current use of HT was modeled as a time-dependent variable. Switches between estrogen types were assumed to occur on the day of the prescription of the new estrogen type. Women stopping HT temporarily were excluded from the risk set for that period, and re-entered the risk set at the time of re-initiation.

We used Cox proportional hazards models for all analyses, with an alpha threshold of 0.05. The following potential confounders were selected *a priori* for adjustment and stratification in the regression models: age, race, BMI, previous use of HT, and concomitant progestogen use. Missing data, found for BMI (2.7%) and race (10.4%), were multiple-imputed by chained equations using 20 imputations. The primary analysis included definite and possible VTE events. We conducted secondary analyses in a sample restricted to new users of HT and stratified by the use of progestogen. Sensitivity analyses included a complete case analysis (without imputation), an analysis restricting to only definite VTE diagnoses and an analysis assuming a strict 100% compliance.

Results

The cohort comprised 51,571 women with a median age of 52 years (IQR 48-58), mostly of white (74%) and Black (22%) race (Table 1), and 45% were married. Participants were well distributed across all regions (Northeast 16%, Southeast 23%, Central 19%, South Central and Mountain 20%, Southwest and West 23%). The prevalence of co-morbidities was high, with 40% and 41% of the women having a diagnosis of obesity and hypertension respectively and 5% with a history of cancer. Women had been prescribed an average of 4 different drugs in the 6 months prior to cohort entry. In particular, 25.8%, 24.3% and 49.3% were using statins, opioid drugs, and psychotropic drugs, respectively.

Oral CEE users (74.5%) were somewhat older and more likely to be prevalent users at baseline than oral E2 (12.6%) or transdermal E2 (12.9%) users, but comorbidities were well balanced among groups. Over the course of cohort time, we observed a trend for more prescriptions of oral E2 and transdermal E2 (supplementary Figure 1) than for oral CEE, but

most women were still receiving oral CEE at cohort closure (December 2011). The mean duration of follow-up with use of HT was 2.2 years.

Primary analysis

In the whole cohort, we observed an incidence of possible or definite VTE of 1.9/1000 person-years. As expected, obesity and advanced age were risk factors for VTE: the hazard ratio (HR) for a BMI $\geq 30\text{kg/m}^2$ (compared with a BMI $<25\text{kg/m}^2$) was 1.62 (95%CI 1.15-2.28) and the HR for an age >75 years (compared with ≤ 60 years) was 2.72 times (95%CI 1.78-4.15).

Compared with CEE use, there was no difference in the adjusted risk of incident VTE associated with oral E2 use (HR 0.96, 95%CI 0.64-1.46) or with transdermal E2 use (HR 0.95, 95%CI 0.60-1.49; Table 2).

Secondary analyses

In the analysis restricting to incident users, comparisons of VTE risks between subtypes of estrogens were conducted among new users of HT, by excluding women who were already taking HT at cohort entry. Relative risk point estimates were less precise but essentially unchanged, with no differences in risk of VTE between estrogen subtypes (Table 2). There was no apparent effect modification by the use of progestogen, but the number of events in the combined HT group was low (Table 3).

Sensitivity analyses

Findings were unchanged in the sensitivity analysis restricted to definite VTE outcomes, when assuming a 100% strict compliance (Supplementary Table S3), or in the complete case analysis (data not shown).

Discussion

In this pharmacoepidemiological comparative cohort study of VHA women, about 2 in 1000 women using HT per year experienced a VTE, with a similar burden of risk among the different estrogen subtypes and between oral vs. transdermal routes. Similar relative risks among the HT subtypes were also observed in an analysis restricted to new users of HT.

Two observations support the internal validity of our cohort. First, the observed incidence in our cohort is consistent with expectations, as population-based studies report similar sex and age-specific rate estimates.¹⁵ Participants in the Women's Health Initiative (WHI) trials had greater incidences (3.0-3.5/1000 women-years), but were on average older than those in our cohort.^{16,17} Second, obesity and an older age were both risk factors for VTE in the cohort, as expected.

Our comparative findings contrast with previous literature and our hypothesis of lower VTE risks associated with oral and transdermal E2, compared with oral CEE. The WHI studies clearly demonstrated that oral CEE causes an excess of VTE.^{16,17} Quite consistently, the body of observational studies suggests that while oral HT increases VTE, transdermal estrogen does not.^{8,9} Coherently, transdermal estrogen does not influence biological in vitro

thrombin generation.¹⁸ Similarly, we have observed in a previous case-cohort study from Washington State that risks of VTE were lower for oral E2 than CEE, along a reduced thrombin generation potential.^{5,14} A decreased VTE risk for E2 than CEE was also found in a recent population-based UK cohort.⁸

We do not believe that our null findings are explained by methodological biases. Our study has a low potential for (1) non-differential measurement error of exposure, given the high-quality and detailed pharmacy data providing information on drug dispense, for (2) misclassification of VTE outcomes, which were individually validated, or for (3) a bias of depletion of susceptibles, given similar findings from the incident user analysis.¹⁹ The progestogen also influences the risk of VTE, in a complex fashion, but our study results were similar in combined vs. estrogen only HT.^{8,20} It may be that our sample is prone to confounding by lifestyle variables that cannot be adjusted for, such as diet and physical activity. It may also be that, among women with a high number of co-medications, in particular psychotropic and opioid drugs, differential effects of estrogen and routes are truly not present.

Although our findings do not confirm the hypothesis of differential associations of estrogen types with risks of VTE, we observed a shift of prescription, with less CEE and more transdermal E2 over time in our cohort. Such prescription patterns emanate from the previous overall literature, which suggests a lower risk of VTE with transdermal E2 than with oral estrogens, especially CEE.^{5,8,14} Current national guidelines advise transdermal E2 as the first-line hormone therapy in menopausal women with symptomatic climacteric symptoms and other VTE risk factors, such as obesity or advanced age.^{21,22}

In this cohort, most women used estrogens without progestogen, although the proportion of previous hysterectomy was discrepantly low. This is related to measurement error in the proportion of hysterectomy, which was likely underestimated: these data were collected within 12 months before cohort entry and may only have been coded at the time of surgery, prior to that period. When abstracting 20 medical charts of women with no evidence of hysterectomy and no progestogen use, we found that 80% of them had undergone a hysterectomy prior to the 12 months before cohort entry or outside of the VA, indicating a poor capture of this intervention in our data.

Strengths of our study include the use of high-quality pharmacy fill data, the adjudication of VTE events, and the comparative design avoiding a non-use group, to minimize confounding by indication. We acknowledge that, despite a large sample size, the number of events was modest with somewhat imprecise relative risk estimates in secondary and sensitivity analyses. We also included prevalent HT users in the primary analysis, which can introduce bias, such as attrition of susceptibles; secondary analyses restricting to new users of HT suggested relative risks were similar to those from the primary analyses, but power to detect differences was limited. As in all observational studies, residual confounding and selection bias remain possible. Further, the external validity of results based on this cohort of women Veterans receiving healthcare within the VA—especially given the comorbidity burden—may be limited.

Conclusion

Our study among women Veterans did not confirm previously observed differences in the risk of VTE associated with HT, comparing oral CEE, oral E2 and transdermal E2.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Characteristics of Participants at the time of Cohort Entry, stratified by the used type of estrogen.

	All participants	Oral CEE		Oral E2		Transdermal E2
	N=51,571	n = 38,421		n = 6,501		n = 6,649
Demographic						
Age, mean (SD)	53.9 (9.5)	54.7 (9.8)		52.4 (8.3)		51.3 (7.4)
BMI, %						
< 20	3.2	3.4		2.8		2.8
20 - <25	23.5	23.6		23.7		22.9
>=25 - <30	33.1	32.8		33.1		35.0
>= 30	40.1	40.2		40.4		39.2
Race, %						
American Indian/Alaska Native	1.2	1.2		1.3		1.2
Asian/Pacific Islander	2.0	2.0		1.9		1.9
Black/African-American	22.3	21.9		17.7		29.2
White	74.5	74.9		79.2		67.7
Comorbidities ^a						
Hypertension, %	41.1	42.8		36.2		36.2
Current Smoker, %	17.5	17.5		17.3		17.7
Cancer, %	4.3	4.1		4.7		5.1
Diabetes, %	10.8	11.1		9.1		10.2
Cardiovascular Disease, % ^b	1.7	1.8		1.3		1.5
Statin Use at Baseline, %	25.8	26.6		23.4		23.8
Menopausal Symptoms, %	32.8	31.8		33.4		38.3
Hysterectomy, %	3.4	2.1		5.0		9.6
HT Use						
Incident User, %	49.4	44.2		62.4		66.8
Progestogen use at Cohort Entry, %	24.8	28.5		16.8		10.8
HT Dose, % ^c						
Low	19.6	21.3		13.6		15.8
Medium	63.0	64.3		69.1		49.1
High	17.4	14.4		17.4		35.1
Other Drug Use ^d						
No. unique drugs dispensed, mean (SD)	4.3 (3.5)	4.4 (3.5)		4.1 (3.4)		4.3 (3.6)

^aRecorded in the 12 months prior to cohort entry

^bCardiovascular disease is composed of coronary artery disease, cerebrovascular disease, or peripheral artery disease

^cCategories correspond to CEE dose equivalents of <0.625, =0.625, and >0.625

d
In the 6 months prior to cohort entry

BMI = body mass index ; HT = hormone therapy ; SD = standard deviation ; CEE = conjugated equine estrogens ; E2 = estradiol

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Table 2.

Associations of Estrogen Subtypes with Risk of Incident Venous thromboembolism

	Incidence			Hazard Ratios		
	Events	Person Years / 1000	Incidence Rate per 1000PY	Unadjusted (95%CI)	Age Adjusted (95%CI)	Fully Adjusted ^a (95%CI)
PRIMARY ANALYSIS						
Oral CEE	165	85.1	1.94	Ref	Ref	Ref
Oral E2	27	15.6	1.73	0.89 (0.59-1.33)	0.97 (0.64-1.46)	0.96 (0.64-1.46)
Transdermal E2	22	13.3	1.65	0.85 (0.55-1.33)	0.95 (0.60-1.48)	0.95 (0.60-1.49)
RESTRICTED TO INCIDENT(NEW) USERS						
CEE Oral	47	28.8	1.63	Ref	Ref	Ref
E2 Oral	11	7.8	1.41	0.85 (0.44-1.65)	0.86 (0.44-1.66)	0.83 (0.42-1.62)
E2 Transdermal	11	6.6	1.66	1.02 (0.53-1.97)	1.03 (0.53-1.99)	1.02 (0.52-1.99)

^a Adjusted for age, race, and BMI; stratified by previous use of HT, and progestogen use

BMI = body mass index ; HT = hormone therapy ; CEE = conjugated equine estrogens ; E2 = estradiol

Table 3. Associations of Estrogen Subtypes with Risk of Venous thromboembolism, stratified by the use of progestogen

Incidence			Hazard Ratios		
Events	Person Years / 1000	Incidence Rate per 1000PY	Unadjusted (95%CI)	Age Adjusted(95%CI)	Fully Adjusted ^a (95%CI)
Estrogen Only, n = 38800					
CEE Oral	66.7	2.07	Ref	Ref	Ref
E2 Oral	26	13.3	0.94 (0.62-1.44)	1.05 (0.69-1.61)	1.06 (0.69-1.63)
E2 Transdermal	20	12.0	0.81 (0.51-1.29)	0.92 (0.57-1.47)	0.96 (0.59-1.54)
Estrogen + Progestogen, n = 12771					
CEE Oral	27	18.4	Ref	Ref	Ref
E2 Oral	1	2.3	0.29 (0.04-2.11)	0.28 (0.04-2.10)	0.30 (0.04-2.22)
E2 Transdermal	2	1.3	1.03 (0.25-4.34)	1.02 (0.24-4.29)	1.06 (0.25-4.46)

^a Adjusted for age, race, and BMI; stratified by previous use of HT

BMI = body mass index ; HT = hormone therapy ; CEE = conjugated equine estrogens ; E2 = estradiol