

Does the route of administration for estrogen hormone therapy impact the risk of venous thromboembolism? Estradiol transdermal system versus oral estrogen-only hormone therapy

François Laliberté, MA,¹ Katherine Dea, MA,¹ Mei Sheng Duh, MPH, ScD,²
Kristijan H. Kahler, PhD, RPh,³ Melanie Rolli, MD,³ and Patrick Lefebvre, MA¹

Abstract

Objective: The aim of this study was to quantify the magnitude of risk reduction for venous thromboembolism events associated with an estradiol transdermal system (Vivelle-Dot) relative to oral estrogen-only hormone therapy agents.

Methods: A claims analysis was conducted using the Thomson Reuters MarketScan database from January 2002 to October 2009. Participants 35 years or older who were newly using an estradiol transdermal system or an oral estrogen-only hormone therapy with two or more dispensings were analyzed. Venous thromboembolism was defined as one or more diagnosis codes for deep vein thrombosis or pulmonary embolism. Cohorts of estradiol transdermal system and oral estrogen-only hormone therapy were matched 1:1 based on both exact factor and propensity score matching, and an incidence rate ratio was used to compare the rates of venous thromboembolism between the matched cohorts. Remaining baseline imbalances from matching were included as covariates in multivariate adjustments.

Results: Among the matched estradiol transdermal system and oral estrogen-only hormone therapy users (27,018 women in each group), the mean age of the cohorts was 48.9 years; in each cohort, 6,044 (22.4%) and 1,788 (6.6%) participants had a hysterectomy and an oophorectomy at baseline, respectively. A total of 115 estradiol transdermal system users developed venous thromboembolism, compared with 164 women in the estrogen-only hormone therapy cohort (unadjusted incidence rate ratio, 0.72; 95% CI, 0.57-0.91; $P = 0.006$). After adjustment for confounding factors, the incidence of venous thromboembolism remained significantly lower for estradiol transdermal system users than for estrogen-only hormone therapy users.

Conclusions: This large population-based study suggests that participants receiving Vivelle-Dot have a significantly lower incidence of venous thromboembolism than do participants receiving oral estrogen-only hormone therapy.

Key Words: Venous thromboembolism – Estradiol transdermal system – Vivelle-Dot – Oral estrogen – Hormone therapy.

Hormone therapy (HT), encompassing estrogen therapy and combined estrogen-progestogen therapy, is regularly used in the treatment of moderate to severe

Received December 21, 2010; revised and accepted February 3, 2011.

From the ¹Groupe d'analyse Ltée, Montréal, Quebec, Canada; ²Analysis Group Inc, Boston, MA; and ³Novartis Pharmaceuticals Corporation, East Hanover, NJ.

This manuscript was presented in part at The North American Menopause Society (NAMS) 21st annual meeting, Chicago, IL, October 6-9, 2010.

Funding/support: This research was funded by Novartis Pharmaceuticals Corporation.

Financial disclosure/conflicts of interest: F. Laliberté, K. Dea, and P. Lefebvre are employees of Groupe d'analyse Ltée, which has received research grants from Novartis Pharmaceuticals Corporation. M.S. Duh is an employee of Analysis Group Inc., which has also received research grants from Novartis Pharmaceuticals Corporation. K.H. Kahler and M. Rolli are employees of Novartis Pharmaceuticals Corporation.

Address correspondence to: Patrick Lefebvre, MA, Groupe d'analyse Ltée, 1000 rue de la Gauchetière Ouest, Bureau 1200, Montréal, Québec, Canada H3B 4W5. E-mail: plefebvre@analysisgroup.com

menopause-related symptoms such as hot flashes and vulvovaginal atrophy.¹ An estimated 75% of women older than 50 years are affected by hot flashes and night sweats, also known as vasomotor symptoms, the most bothersome symptoms of menopause.² To treat mild vasomotor symptoms, lifestyle changes, such as maintaining cool air temperature and a healthy body weight and using relaxation techniques, either alone or in conjunction with nonprescription remedies, are generally recognized as first-line treatment options.³ However, among women reporting vasomotor symptoms, 40% to 60% report symptoms of moderate to severe intensity, whereas up to 20% report nearly intolerable symptoms.^{3,4}

Women treated with oral estrogen-containing HT have an increased risk of developing venous thromboembolism (VTE), one the most serious and potentially fatal complications associated with HT.⁵⁻¹³ VTE is often manifested as deep vein thrombosis (DVT) with or without pulmonary embolism (PE), but the manifestations of VTE also include upper

extremity and intraabdominal DVT, cerebral sinus thrombosis (venous stroke), and superficial venous thrombophlebitis.¹⁴

The effect of HT on the risk of developing VTE may differ by route of administration. Oral estrogen-containing HT is currently the most commonly used route of administration in the United States.³ The transdermal patch form of estrogen HT avoids the digestive tract and the first-pass metabolism through the liver. This confers upon the transdermal formulation the advantages of both administering unmetabolized estradiol directly to the bloodstream and requiring lower doses compared with oral agents.³ Unlike that of the patch form, the hepatic metabolism of oral estrogen may lead to an imbalance between procoagulant factors and antithrombotic mechanisms.^{15,16} For example, previous studies comparing the route of estrogen therapy on hemostatic variables associated with VTE in postmenopausal women have reported that oral therapy was associated with an increased resistance to activated protein C, a risk factor for VTE, compared with transdermal formulation.^{17,18}

To the best of our knowledge, the association of VTE with the use of estrogen-only transdermal HT (estradiol transdermal system [ETS]; Vivelle-Dot) compared with oral estrogen-only HT (eg, Cenestin, Estrace, Premarin) has not been examined in a commercially insured population in the United States. Therefore, the objective of the current study was to quantify the magnitude of risk reduction for VTE events associated with ETS relative to oral estrogen-only HT agents in a real-world setting.

METHODS

Data source

Health insurance claims from the Thomson Reuters MarketScan database were used to conduct the analysis. The MarketScan database combines two separate databases (ie, the Commercial Claims and Encounters database and the Medicare Supplemental and Coordination of Benefits database) to cover all age groups and contains claims from approximately 100 employers, health plans, and government and public organizations representing about 30 million covered lives. All census regions are represented, but the South and North Central (Midwest) regions are predominant. The MarketScan data used in the current analysis covered the period from January 2002 to October 2009.

The data elements used in the present study included health plan enrollment records, participant demographics, inpatient and outpatient medical services, and outpatient prescription drug dispensing records. Finally, the data included in the MarketScan database are deidentified and are in compliance with the Health Insurance Portability and Accountability Act of 1996 to preserve participant anonymity and confidentiality.

Study design

A retrospective matched-cohort design was used to quantify the magnitude of risk reduction for VTE events associated with ETS relative to oral estrogen-only HT agents. The matched cohort design was preferred to ensure that both groups were well balanced at baseline to reduce the confounding by indi-

cation bias. To be included in the study sample, the patients were required to meet the following criteria: (1) at least two dispensings of either ETS or an oral estrogen-only HT agent (index treatment), (2) continuous health plan enrollment during the observation period, and (3) age 35 years or older at the date of first dispensing (index date) of index therapy. In addition, the participants were required to have continuous health plan enrollment for at least 180 days before the index date (baseline period). Participants were excluded from the study if they received any other estrogen HT agents, including vaginal estrogen agents, other ETSS, other estrogen-only HT (eg, IM injection, gel, spray), and estrogen combinations during the 180-day baseline period (including the index date) or if they had been previously diagnosed with a VTE before the index date.

The participant observation period spanned from the date of the first ETS or oral estrogen-only HT dispensing (index date) to the 90th day after the treatment interruption or discontinuation, defined as a gap of more than 90 days since the last dispensing (ie, continuous drug exposure plus 90 d), participant disenrollment, or end of data availability (October 31, 2009), whichever occurred earliest.

Outcomes measures

The primary outcomes measures of the study included the risk of any VTE and hospitalization-related VTE. VTE events were defined as one or more diagnosis codes for DVT (International Classification of Diseases, 9th revision [ICD-9] codes: 451.1×, 451.2, 453.4×, 453.8, 453.9) or PE (ICD-9 code: 415.1×). A hospitalization-related event was defined as any hospitalization with an admitting diagnosis of VTE. Additional exploratory endpoints included VTE and hospitalization-related VTE stratified into (1) DVT and (2) PE events, as well as the time of the first occurrence of a VTE event (ie, time-to-event analysis).

Statistical analysis

The lack of randomization in such an observational study may have led to confounding across the ETS and the oral estrogen-only HT cohorts. To ensure balanced participant characteristics and risk factors for VTE at baseline, participants receiving ETS were matched 1:1 with participants receiving oral estrogen-only HT based on both (1) exact matching factors and (2) propensity scores using a caliper of 5%. The exact matching factors included age (5-y intervals), baseline concomitant medication use (antihypertensive, antihyperlipidemic, progestin, and anticoagulant), Charlson comorbidity index, year of the index date, menopausal, and postmenopausal disorders, hysterectomy, oophorectomy, and risk factors for VTE (major surgery, hypertension, and coagulation defect). The propensity score was generated in a first step using probability estimates from a logistic regression model in which the ETS treatment assignment was the binary dependent variable (yes/no) and baseline covariates were used as predictors of receiving ETS or oral estrogen-only HT treatment.

The risk of VTE complications among participants using ETS relative to those using oral estrogen-only HT was evaluated using incidence rate. The incidence rates of VTE events

were calculated as the number of participants with an event divided by participant-years of observation, censored at the time of the first event. The VTE rates were compared between ETS and oral estrogen-only HT cohorts using unadjusted and adjusted incidence rate ratios (IRR). The unadjusted IRR was calculated as the unadjusted incidence rate in the ETS group divided by that in the oral estrogen-only HT group. The 95% CIs of unadjusted IRRs were calculated based on the Poisson probability distribution to account for the person-time design and to appropriately model the outcome variable. Conditional Poisson regression models accounting for the matched pair data were used to compare the rates of VTE events and VTE events resulting in hospitalizations for ETS with those of oral estrogen-only HT cohorts. In the multivariate adjustments, progestin and other estrogen agents used during the observation period and any remaining baseline imbalances (ie, $P < 0.05$) from matching were included as covariates.

A sensitivity analysis restricting the study population to the subset of postmenopausal women who received only ETS compared with women only receiving oral estrogen HT was also conducted. This secondary analysis was restricted to nonpregnant women 50 years or older not using progestin agents or contraceptive pills during the baseline period. Moreover, to restrict the sensitivity analysis to the “pure”

users of ETS and oral estrogen-only HT, the observation period was censored 1 day before any progestin or other HT dispensings were observed during the follow-up period.

Descriptive statistics were used to describe the baseline characteristics and dosing patterns of the ETS and oral estrogen-only HT cohorts, including the mean (SD) for continuous data and relative frequencies for categorical data. Baseline continuous variables were compared using paired t tests, whereas baseline categorical variables were compared using Pearson χ^2 tests or the McNemar test. Kaplan-Meier analyses and log-rank tests were also performed to compare the time of first occurrence of VTE between the two cohorts. A two-sided α level of 0.05 was used to declare statistical significance. All statistical analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

Figure 1 presents the participants' disposition flow chart. Among the 30,547 women treated with ETS and 159,281 treated with oral estrogen-only HT, a total of 27,018 (88.5%) ETS users were matched with 27,018 oral estrogen-only HT users. The baseline characteristics of the matched cohorts are summarized in Table 1. The mean (SD) ages of the matched

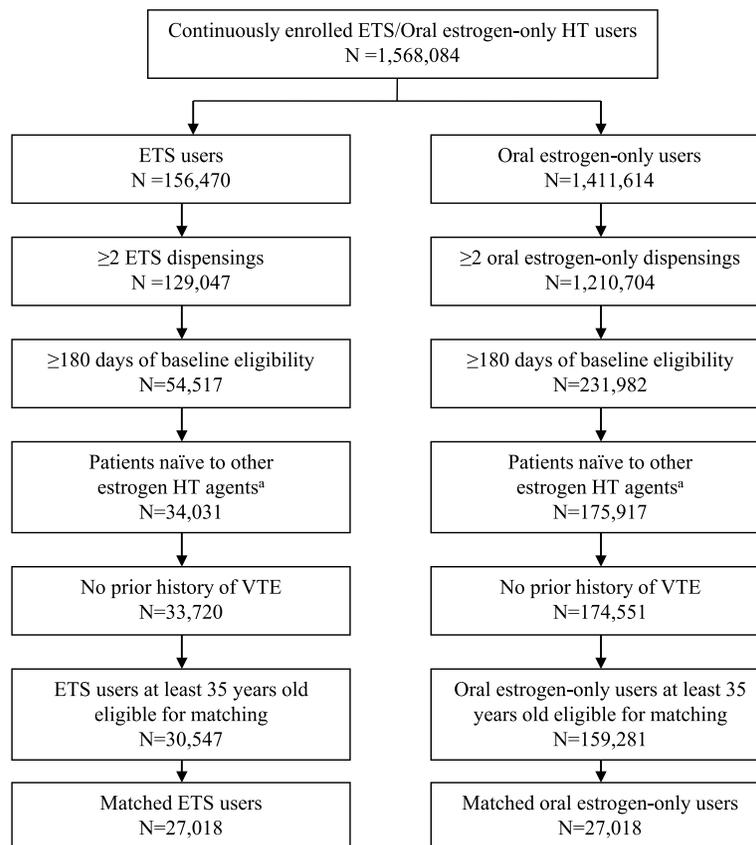


FIG. 1. Participants' disposition flow chart.^a This excludes participants taking any other estrogen HT agents based on the 180-day baseline period, including vaginal estrogen, other ETS (eg, Fempatch, Alora), other estrogen-only HT (eg, injection, gel, spray), estrogen and androgen combination, and estrogen and progestin combination. ETS, estradiol transdermal system; HT, hormone therapy; VTE, venous thromboembolism.

TABLE 1. Baseline characteristics of matched cohorts^a

Characteristics	ETS cohort		Oral estrogen-only cohort		P ^b
Number of participants	27,018		27,018		
Age, mean (SD), y	48.9	(7.1)	48.9	(7.1)	0.601
Eligibility prior index date, mean (SD), d	818	(605)	811	(610)	0.064
Region, n (%)					
South	14,713	(54.5)	14,804	(54.8)	0.001
West	6,398	(23.7)	6,040	(22.4)	
North Central	4,684	(17.3)	4,938	(18.3)	
Northeast	1,097	(4.1)	1,123	(4.2)	
Unknown	126	(0.5)	113	(0.4)	
Type of insurance, n (%)					
PPO	16,680	(61.7)	16,734	(61.9)	0.929
HMO	4,496	(16.6)	4,460	(16.5)	
POS	2,517	(9.3)	2,471	(9.1)	
Comprehensive	1,556	(5.8)	1,561	(5.8)	
CDHP	625	(2.3)	609	(2.3)	
Unknown	535	(2.0)	590	(2.2)	
POS with capitation	351	(1.3)	347	(1.3)	
EPO	181	(0.7)	184	(0.7)	
HDHP	77	(0.3)	62	(0.2)	
Menopausal and postmenopausal disorders, n (%)	6,038	(22.3)	6,038	(22.3)	1.000
Hysterectomy, n (%)	6,044	(22.4)	6,044	(22.4)	1.000
Oophorectomy, n (%)	1,788	(6.6)	1,788	(6.6)	1.000
Charlson comorbidity index, n (%)					
0	24,505	(90.7)	24,505	(90.7)	1.000
1	1,997	(7.4)	1,997	(7.4)	
2	433	(1.6)	433	(1.6)	
3	76	(0.3)	76	(0.3)	
4	3	(0.0)	3	(0.0)	
≥5	4	(0.0)	4	(0.0)	
VTE risk factors, n (%)					
Surgical resection of abdominal or pelvic cancer	6,476	(24.0)	6,481	(24.0)	0.799
Major surgery	4,843	(17.9)	4,843	(17.9)	1.000
Hyperlipidemia	3,425	(12.7)	3,359	(12.4)	0.358
Hypertension	2,994	(11.1)	2,994	(11.1)	1.000
Multiple trauma	2,849	(10.5)	2,825	(10.5)	0.746
Use of oral contraceptive pill	2,379	(8.8)	2,203	(8.2)	0.004
Abdominal surgery	2,173	(8.0)	2,090	(7.7)	0.159
Other serious infections	1,795	(6.6)	1,834	(6.8)	0.511
Age, >60 y	1,560	(5.8)	1,567	(5.8)	0.783
Diabetes	799	(3.0)	815	(3.0)	0.617
Malignant cancer	603	(2.2)	592	(2.2)	0.724
Obesity	430	(1.6)	387	(1.4)	0.135
Arrhythmia	402	(1.5)	408	(1.5)	0.859
COPD	392	(1.5)	431	(1.6)	0.164
Use of tobacco	344	(1.3)	373	(1.4)	0.271
Treatment with SERMs	287	(1.1)	270	(1.0)	0.414
Pneumonia	282	(1.0)	299	(1.1)	0.504
Pregnancy	222	(0.8)	209	(0.8)	0.553
Hip, pelvis, or leg fracture	210	(0.8)	204	(0.8)	0.804
Rheumatoid arthritis	200	(0.7)	197	(0.7)	0.916
Inflammatory bowel disease	137	(0.5)	135	(0.5)	0.952
Varicose veins	120	(0.4)	116	(0.4)	0.845
Atrial fibrillation	54	(0.2)	58	(0.2)	0.773
Transient ischemic attack	27	(0.1)	26	(0.1)	1.000
Ischemic stroke	25	(0.1)	16	(0.1)	0.200
Congestive heart failure	19	(0.1)	31	(0.1)	0.119
Central venous catheter	15	(0.1)	20	(0.1)	0.500
Coagulation defect	7	(0.0)	7	(0.0)	1.000
Treatment with erythropoiesis-stimulating agents	7	(0.0)	7	(0.0)	1.000
Spinal cord injury	6	(0.0)	3	(0.0)	0.508
Total hip replacement	6	(0.0)	1	(0.0)	0.125
Thrombophilia	5	(0.0)	7	(0.0)	0.500
Total knee replacement	4	(0.0)	8	(0.0)	0.388
Myocardial infarction	2	(0.0)	2	(0.0)	1.000
Immobility	2	(0.0)	1	(0.0)	1.000
Concomitant medications, n (%)					
Antihypertensive	2,840	(10.5)	2,840	(10.5)	1.000
Antihyperlipidemic	2,619	(9.7)	2,619	(9.7)	1.000
Progestin	2,076	(7.7)	2,076	(7.7)	1.000

(Continued on next page)

TABLE 1. (Continued)

Characteristics	ETS cohort		Oral estrogen-only cohort		<i>P</i> ^b
Anticoagulant	19	(0.1)	19	(0.1)	1.000
Healthcare resources utilization, mean (SD)					
Outpatient services, visits	7.5	(6.7)	7.3	(6.9)	<0.001
Inpatient services, visits	0.2	(0.4)	0.2	(0.4)	0.131
Pharmacy services, dispensings	10.6	(10.1)	10.6	(10.3)	0.961
Healthcare costs, dollars, mean (SD)					
Outpatient services	2,782	(4,221)	2,710	(4,207)	0.018
Inpatient services	2,269	(5,003)	2,322	(5,111)	0.029
Pharmacy services	723	(1,368)	703	(1,464)	0.071
Year of index date, n (%)					
2002	742	(2.7)	742	(2.7)	1.000
2003	1,876	(6.9)	1,876	(6.9)	
2004	3,002	(11.1)	3,002	(11.1)	
2005	3,636	(13.5)	3,636	(13.5)	
2006	3,771	(14.0)	3,771	(14.0)	
2007	4,455	(16.5)	4,455	(16.5)	
2008	6,533	(24.2)	6,533	(24.2)	
2009	3,003	(11.1)	3,003	(11.1)	

ETS, estradiol transdermal system; PPO, preferred provider organization; HMO, health maintenance organization; POS, point of service; CDHP, consumer-directed health plans; EPO, exclusive provider organization; HDHP, high-deductible health plan; VTE, venous thromboembolism; COPD, chronic obstructive pulmonary disease; SERMs, selective estrogen receptor modulators.

^aBased on the baseline period of 180 d before the index date.

^bContinuous variables were compared using a *t* test for matched pairs. Categorical variables with two levels were compared using the McNemar test for matched pairs and categorical variables with more than two levels were compared using the Pearson χ^2 test.

cohorts were 48.9 (7.1) years. In each cohort, 6,044 (22.4%) and 1,788 (6.6%) women had a hysterectomy and an oophorectomy at baseline, respectively. Overall, the baseline distribution of VTE risk factors was well balanced between the two cohorts. The most frequent (>10%) baseline risk factors for VTE were surgical resection of abdominal or pelvic cancer, major surgery, hyperlipidemia, hypertension, and multiple trauma.

Table 2 presents the dosing patterns and concomitant medication use of the matched cohorts during the observation period. The mean (median) drug exposure for the ETS and oral estrogen-only HT cohorts was 391 (264) and 401 (272) days, respectively. Women treated with ETS received, on average, 7.8 dispensings compared with 7.5 for the estrogen-only HT cohort. Progestin medication was concomitantly used by 23.6% and 19.6% of the ETS and oral estrogen-only HT users, respectively ($P < 0.001$).

Based on the matched analysis, a total of 115 ETS users developed VTE compared with 164 women in the estrogen-only HT cohort (unadjusted IRR, 0.72; 95% CI, 0.57-0.91; $P = 0.006$; Table 3). After adjustment for confounding factors, ETS remained statistically significantly associated with a reduced incidence (33% reduction) of VTE events compared with oral estrogen-only HT (adjusted IRR, 0.67; 95% CI, 0.49-0.92; $P = 0.013$; Table 3). The incidence rate reduction for hospitalization-related VTE events among the ETS users was even more pronounced, with the adjusted incidence being 62% lower for ETS users relative to oral estrogen-only HT users (adjusted IRR, 0.38; 95% CI, 0.18-0.79; $P = 0.010$; unadjusted IRR, 0.56; 95% CI, 0.34-0.92; $P = 0.022$; Table 3).

Exploratory stratified analyses by type of event (ie, DVT versus PE) revealed that the magnitude of the risk reduction

associated with ETS relative to oral estrogen-only HT was more important for PE (unadjusted IRR, 0.52; 95% CI, 0.32-0.87; $P = 0.012$; adjusted IRR, 0.46; 95% CI, 0.22-0.97; $P = 0.041$) than for DVT (unadjusted: IRR, 0.79; 95% CI, 0.61-1.03; $P = 0.082$; adjusted: IRR, 0.72; 95% CI,

TABLE 2. Dosing patterns and concomitant medications during the observation period

Variables	ETS cohort		Oral estrogen-only cohort		<i>P</i> ^a
Number of participants	27,018		27,018		
Eligibility after index date, mean (SD), d	744.4	(607)	735.5	(602)	0.136
Drug exposure, mean (SD), d	391.1	(366)	400.9	(378)	0.002
Number of dispensings per participant, mean (SD)	7.8	(9.0)	7.5	(8.6)	<0.001
Day supply per dispensing, mean (SD)	40.7	(22.0)	45.0	(24.5)	<0.001
Concomitant HT medication, n (%)					
ETS (Vivelle-Dot)	NA		438	(1.6)	
Oral estrogen-only HT	1,572	(5.8)	NA		
Progestin	6,388	(23.6)	5,300	(19.6)	<0.001
Other estrogen agents	3,377	(12.5)	2,586	(9.6)	<0.001
Vaginal estrogen	1,242	(4.6)	1,078	(4.0)	0.001
Other ETS (eg, Fempatch, Alora)	1,202	(4.4)	346	(1.3)	<0.001
Other estrogen-only HT	442	(1.6)	285	(1.1)	<0.001
Estrogen-androgen combination	445	(1.6)	656	(2.4)	<0.001
Estrogen-progestin combination	319	(1.2)	383	(1.4)	0.016
Other medication, n (%)					
Antihypertensive	3,864	(14.3)	4,458	(16.5)	<0.001
Anticoagulant	218	(0.8)	242	(0.9)	0.269
Antihyperlipidemic	4,185	(15.5)	4,548	(16.8)	<0.001

ETS, estradiol transdermal system; HT, hormone therapy; NA, not applicable.

^aContinuous variables were compared using a *t* test for matched pairs. Categorical variables were compared using the McNemar test for matched pairs.

TABLE 3. Incidence rate and incidence rate ratio of VTE: ETS cohort (N = 27,018) relative to oral estrogen-only cohort (N = 27,018)

Outcome measure	No. of events ^a		Incidence rate (per 100 participant-y)		Univariate analysis		Multivariate analysis conditional Poisson ^{b,c}	
	ETS	Oral estrogen-only	ETS	Oral estrogen-only	Unadjusted IRR (95% CI)	P	Adjusted IRR (95% CI)	P
VTE								
DVT or PE	115	164	0.40	0.56	0.72 (0.57-0.91)	0.006	0.67 (0.49-0.92)	0.013
DVT	99	128	0.34	0.43	0.79 (0.61-1.03)	0.082	0.72 (0.51-1.02)	0.062
PE	23	45	0.08	0.15	0.52 (0.32-0.87)	0.012	0.46 (0.22-0.97)	0.041
Hospitalization-related VTE								
DVT or PE	24	44	0.08	0.15	0.56 (0.34-0.92)	0.022	0.38 (0.18-0.79)	0.010
DVT	19	22	0.07	0.07	0.89 (0.48-1.64)	0.698	1.12 (0.47-2.66)	0.794
PE	9	27	0.03	0.09	0.34 (0.16-0.73)	0.005	0.23 (0.08-0.66)	0.006

VTE, venous thromboembolism; ETS, estradiol transdermal system; PE, pulmonary embolism; DVT, deep vein thrombosis; IRR, incidence rate ratio.

^aThe observation period was truncated at the time of the first VTE event.

^bCovariates adjusted for in the multivariate conditional Poisson regression models included baseline healthcare costs, census region, baseline oral contraceptive pill use, and binary variables for progestin and other estrogen agents used concomitantly during the ETS and the oral estrogen-only drug exposure, including vaginal estrogen, other ETSs (eg, Fempatch, Alora), other estrogen-only hormone therapy (eg, injection, gel, spray), estrogen-androgen combination, and estrogen-progestin combination.

^cBecause of the rarity of hospitalization-related VTE events and the limited degree of freedom for estimation, the list of covariates for adjustment in the hospitalization-related VTE models was limited to baseline healthcare costs and progestin used concomitantly during the ETS and the oral estrogen-only drug exposure.

0.51-1.02; $P = 0.062$). Similar findings were observed for the subset of DVT or PE events resulting in hospitalizations (Table 3).

The Kaplan-Meier rates of VTE events at 6, 12, and 24 months were 0.24%, 0.42%, and 0.68% for the ETS cohort versus 0.31%, 0.59%, and 1.13% for the oral estrogen-only HT cohort, respectively, (log-rank $P = 0.006$; Fig. 2). The Kaplan-Meier rates of hospitalization-related VTE event were also significantly lower throughout the study period for ETS relative to oral estrogen-only HT (Fig. 3).

Sensitivity analysis

The risk reduction for VTE events associated with ETS relative to estrogen-only HT was even more pronounced in the sensitivity analysis (9,264 women in each group), in which a total of 29 ETS users developed VTE compared with 56 women in the estrogen-only HT cohort (unadjusted IRR, 0.58; 95% CI, 0.37-0.92; $P = 0.019$; Table 4). After adjustment for confounding factors, ETS remained independently

associated with a lower risk for VTE events by 56% compared with oral estrogen-only HT (adjusted IRR, 0.44; 95% CI, 0.25-0.77; $P = 0.004$; Table 4). Additional exploratory analysis of hospitalization-related VTE events also corroborated the lower incidence rate associated with ETS relative to oral estrogen-only HT (unadjusted IRR, 0.33; 95% CI, 0.12-0.90; $P = 0.030$; adjusted IRR, 0.34; 95% CI, 0.10-1.19; $P = 0.092$; Table 4).

DISCUSSION

Based on real-world health insurance claims from the MarketScan database, this large retrospective study was conducted to quantify the risk of VTE and hospitalization-related VTE for participants treated with ETS compared with those treated with oral estrogen-only HT regimens. In the period from January 2002 to October 2009, a total of 27,018 ETS users, matched with an equal number of oral estrogen-only HT users, were studied. Both unadjusted and adjusted results

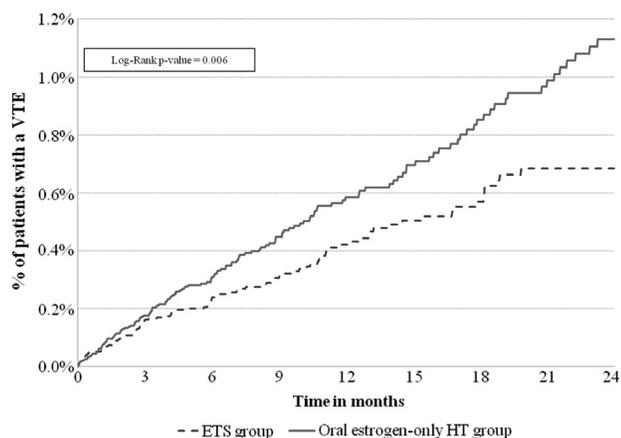


FIG. 2. Kaplan-Meier rates of VTE. ETS, estradiol transdermal system; HT, hormone therapy; VTE, venous thromboembolism.

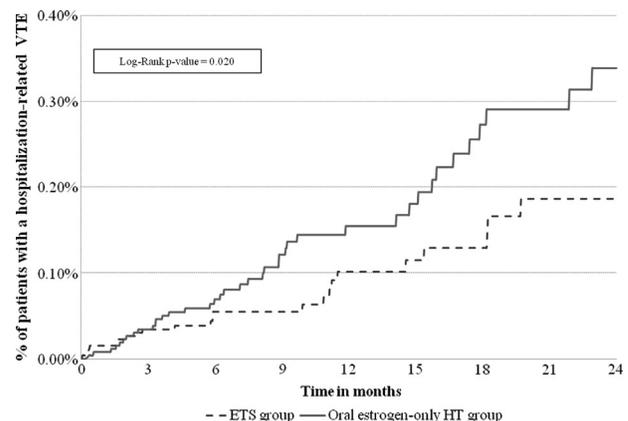


FIG. 3. Kaplan-Meier rates of hospitalization-related VTE. ETS, estradiol transdermal system; HT, hormone therapy; VTE, venous thromboembolism.

TABLE 4. Sensitivity analysis: risk of VTE for postmenopausal women receiving only ETS (*N* = 9,264) compared with women only receiving oral estrogen-only HT (*N* = 9,264)^a

Outcome measure	No. of events ^b		Incidence rate (per 100 participant-y)		Univariate analysis		Multivariate analysis conditional Poisson ^{c,d}	
	ETS	Oral estrogen-only	ETS	Oral estrogen-only	Unadjusted IRR (95% CI)	<i>P</i>	Adjusted IRR (95% CI)	<i>P</i>
VTE								
DVT or PE	29	56	0.36	0.62	0.58 (0.37-0.92)	0.019	0.44 (0.25-0.77)	0.004
DVT	23	43	0.29	0.48	0.60 (0.36-1.00)	0.051	0.49 (0.26-0.92)	0.025
PE	7	14	0.09	0.16	0.57 (0.23-1.40)	0.218	0.55 (0.15-1.98)	0.362
Hospitalization-related VTE								
DVT or PE	5	17	0.06	0.19	0.33 (0.12-0.90)	0.030	0.34 (0.10-1.19)	0.092
DVT	5	11	0.06	0.12	0.51 (0.18-1.48)	0.217	0.57 (0.15-2.22)	0.420
PE	1	7	0.01	0.08	0.16 (0.02-1.31)	0.088	Not estimable	

VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis; ETS, estradiol transdermal system; IRR, incidence rate ratio; HT, hormone therapy.

^aThe analysis was restricted to nonpregnant women 50 y or older not using progestin agents or contraceptive pills during the baseline period. The observation period was censored 1 d before any progestin or other HT dispensings observed during the follow-up period.

^bThe observation period was truncated at the time of the first VTE event.

^cCovariates adjusted for in the multivariate conditional Poisson regression models included baseline healthcare costs and census region.

^dBecause of the rarity of hospitalization-related VTE events and the limited degree of freedom for estimation, the list of covariates for adjustment in the hospitalization-related VTE models was limited to baseline healthcare costs.

consistently indicated that ETS was associated with a significant risk reduction for VTE. After adjustment for confounding factors, ETS was associated with a statistically significant risk reduction for VTE and hospitalization-related VTE by 33% and 62%, respectively, compared with the oral estrogen-only HT cohort. Of note, the risk reduction associated with ETS was more pronounced for PE events, the most serious type of VTE. Furthermore, a sensitivity analysis restricting the study population to postmenopausal women who received only ETS or oral estrogen-only HT during the baseline and follow-up periods corroborated the findings that ETS was associated with a significantly lower risk for VTE events relative to oral estrogen-only HT.

Previous case-control studies of VTE among postmenopausal women have assessed the impact of HT using oral versus transdermal estrogen alone or combinations with progestogen compared with nonusers. For example, the Estrogen and Thromboembolism Risk (ESTHER) study evaluated the impact of the route of estrogen administration and progestogens on the risk of developing VTE.¹¹

ESTHER was a multicenter VTE case-control study that recruited 271 consecutive cases with a first documented episode of idiopathic VTE (208 hospital cases and 63 outpatient cases) and 610 matched controls (426 hospital controls and 184 community controls) from 1999 to 2005 in France. The authors of this study reported that, after adjustment for potential confounding factors, the odds ratios for VTE in postmenopausal women treated with oral and transdermal estrogen compared with nonusers were 4.2 (95% CI, 1.5-11.6) and 0.9 (95% CI, 0.4-2.1), respectively, concluding that oral, but not transdermal, estrogen was associated with an increased risk of VTE.

More recently, Renoux et al¹² reported the findings of a large population-based case-control study of 23,505 postmenopausal VTE cases matched with 231,562 controls selected from the United Kingdom's General Practice Research Database

between 1987 and 2008. The authors found that the risk of VTE was not increased through the current use of transdermal estrogen alone (relative risk [RR] = 1.01; 95% CI, 0.89-1.16) or combined with a progestogen (RR = 0.96; 95% CI, 0.77-1.20), compared with nonuse, whereas the risk was higher for users of oral estrogen (RR = 1.49; 95% CI, 1.37-1.63) and oral estrogen-progestogen (RR = 1.54; 95% CI, 1.44-1.65).¹² Canonico et al¹³ also showed, based on 80,308 postmenopausal women followed for an average of 10.1 years, that transdermal estrogens were not associated with an increased VTE risk (hazard ratio = 1.1; 95% CI, 0.8-1.8), relative to nonuse, whereas they found a higher risk for oral estrogen (hazard ratio = 1.7; 95% CI, 1.1-2.8). The results of these studies corroborate the assumption that a transdermal estrogen formulation may be safer than oral estrogen with respect to thrombotic risk.

To our knowledge, the current study is the first to quantify the magnitude of risk reduction for VTE events associated with ETS relative to oral estrogen-only HT agents using a matched-cohort design. Our findings that ETS is associated with statistically significant risk reductions for VTE and hospitalization-related VTE events relative to oral estrogen-only HT are consistent with results from ESTHER, Renoux et al,¹² and Canonico et al.¹³ Furthermore, a systematic review and meta-analysis of eight observational studies and nine randomized controlled trials on HT that reported VTE concluded that oral estrogen increases the risk of VTE especially during the first year of treatment and that transdermal estrogen may be safer with respect to thrombotic risk.¹⁶ More recently, the meta-analysis was updated with observational studies conducted since 2008, and it still concluded that oral, but not transdermal, estrogen was associated with a higher risk of VTE.¹⁹

The route of administration may suggest a biological explanation for the lower risk of VTE with ETS compared with oral estrogen-only HT. The first-pass metabolism of oral estrogen-only HT may lead to hemostasis complications related to the activated protein C, a natural anticoagulant.¹⁹ Oral

therapy has been associated with an increased resistance to activated protein C when compared with the transdermal formulation.^{17,18} Experimental and mathematical model studies have found that blood coagulation results from a delicate equilibrium and that even minor disturbances like small increases in clotting factors or small decreases of coagulation inhibitors may lead to significant thrombin generation that could potentially cause thrombosis.^{20,21}

This study was subject to limitations associated with data constraints. First, MarketScan data do not include detailed participant information, such as weight or body mass index (BMI). The presence of VTE risk factors such as overweight and obesity elevates the risk of thrombotic events among postmenopausal women taking estrogen hormone therapy. The ESTHER study found that, compared with nonusers with normal weight, overweight and obese oral estrogen users further increased VTE risk 10-fold (odds ratio, 10.2; 95% CI, 3.5-30.2) and 20-fold (odds ratio, 20.6; 95% CI, 4.8-88.1), respectively.²² However, ETS users with BMI in the overweight and obesity categories had a threefold to fivefold increased risk of VTE, which was similar to nonusers with increased BMI.²² In the current study, even if it was not possible to benefit from the detailed BMI information, we controlled for obesity identified using ICD-9 diagnosis codes. Second, claims databases may contain inaccuracies or omissions in coded procedures, diagnoses, or pharmacy claims. However, it would be improbable that these inaccuracies have significantly affected our results, considering the large sample size and the matched-cohort design approach. Third, the use of the conditional Poisson regression models accounting for matched pairs did not permit us to update the covariates over time (ie, time-varying analysis). It is possible that this may lead to residual confounding during the observation period. Lastly, the observational design was susceptible to various biases such as information or classification bias (eg, identification of false-positive VTE events). It is also possible that VTE events were undercoded (ie, false-negative). However, well-designed observational studies with appropriate statistical techniques adjusting for potential confounding factors through matching techniques provide valuable information with real-life scenarios and high generalizability. Despite these limitations, the current research has several advantages including relying on the real-world utilization of these agents, having a relatively large sample size, and using multivariate adjustments to control for any remaining baseline imbalances after matching.

CONCLUSIONS

This large population-based study of over 50,000 participants based on real-world data indicates that women receiving ETS (Vivelle-Dot) have a significantly lower incidence of VTE and hospitalization-related VTE than do women receiving oral estrogen-only HT. Future prospective studies are warranted to evaluate the impact of the route of estrogen administration on the risk of developing VTE.

REFERENCES

1. The North American Menopause Society (NAMS) Position Statement. Estrogen and progestogen use in postmenopausal women: 2010 position statement of The North American Menopause Society. *Menopause* 2010;17:242-255.
2. Umland EM. Treatment strategies for reducing the burden of menopause-associated vasomotor symptoms. *J Manag Care Pharm* 2008;14:S14-S19.
3. Kopper NW, Gudeman J, Thompson DJ. Transdermal hormone therapy in postmenopausal women: a review of metabolic effects and drug delivery technologies. *Drug Des Devel Ther* 2008;2:193-202.
4. Bachmann GA. Menopausal vasomotor symptoms: a review of causes, effects, and evidence-based treatment options. *J Reprod Med* 2005;50:155-165.
5. Daly E, Vessey MP, Hawkins MM, et al. Risk of venous thromboembolism in users of hormone replacement therapy. *Lancet* 1996;348:977-980.
6. Perez Gutthann S, Garcia Rodriguez LA, Castellsague J, et al. Hormone replacement therapy and risk of venous thromboembolism: population-based case-control study. *BMJ* 1997;314:796-800.
7. Høibraaten E, Qvigstad E, Amesen H, et al. Increased risk of recurrent venous thromboembolism during hormone replacement therapy—results of the randomized, double-blind, placebo-controlled estrogen in venous thromboembolism trial (EVTET). *Thromb Haemost* 2000;84:961-967.
8. Scarabin PY, Oger E, Plu-Bureau G. Differential association of oral and transdermal oestrogen replacement therapy with venous thromboembolism risk. *Lancet* 2003;362:428-432.
9. Cushman M, Kuller LH, Prentice R, et al. Estrogen plus progestin and risk of venous thrombosis. *JAMA* 2004;292:1573-1580.
10. Curb JD, Prentice RL, Bray PF, et al. Venous thrombosis and conjugated equine estrogen in women without a uterus. *Arch Intern Med* 2006;166:772-780.
11. Canonico M, Oger E, Plu-Bureau G, et al. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER Study. *Circulation* 2007;115:840-845.
12. Renoux C, Dell'aniello S, Suissa S. Hormone replacement therapy and the risk of venous thromboembolism: a population-based study. *J Thromb Haemost* 2010;8:979-986.
13. Canonico M, Fournier A, Carcaillon L, et al. Postmenopausal hormone therapy and risk of idiopathic venous thromboembolism. Results from the E3N cohort study. *Arterioscler Thromb Vasc Biol* 2010;30:340-345.
14. Gomes MPV, Deitcher SR. Risk of venous thromboembolic disease associated with hormonal contraceptives and hormone replacement therapy. *Arch Intern Med* 2004;164:1965-1976.
15. Lowe GD, Upton MN, Rumley A, et al. Different effects of oral and transdermal hormone replacement therapies on factor IX, APC resistance, t-PA, PAI and C-reactive protein—a cross-sectional population survey. *Thromb Haemost* 2001;86:550-556.
16. Canonico M, Plu-Bureau G, Lowe GDO, Scarabin PY. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. *BMJ* 2008;336:1227-1231.
17. Post MS, Christella M, Thomassen LGD, et al. Effect of oral and transdermal estrogen replacement therapy on hemostatic variables associated with venous thrombosis. A randomized, placebo-controlled study in postmenopausal women. *Arterioscler Thromb Vasc Biol* 2003;23:1116-1121.
18. Oger E, Alhenc-Gelas M, Lacut K, et al. Differential effects of oral and transdermal estrogen/progesterone regimens on sensitivity to activated protein C among postmenopausal women: a randomized trial. *Arterioscler Thromb Vasc Biol* 2003;23:1671-1676.
19. Olié V, Canonico M, Scarabin PY. Risk of venous thrombosis with oral versus transdermal estrogen therapy among postmenopausal women. *Curr Opin Hematol* 2010;17:457-463.
20. Sandset PM, Høibraaten E, Eilertsen AL, Dahm A. Mechanisms of thrombosis related to hormone therapy. *Thromb Res* 2009;123:S70-S73.
21. Mann KG. Biochemistry and physiology of blood coagulation. *Thromb Haemost* 1999;82:165-174.
22. Canonico M, Oger E, Conard J, et al. Obesity and risk of venous thromboembolism among postmenopausal women: differential impact of hormone therapy by route of estrogen administration. The ESTHER Study. *J Thromb Haemost* 2006;4:1259-1265.