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Hormone therapy and recurrence of venous thromboembolism among postmenopausal women

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Abstract

Objectives: The route of estrogen administration is an important determinant of the risk of the first venous thromboembolism (VTE) event in postmenopausal women using hormone therapy (HT). However, the impact of transdermal estrogens on VTE recurrence risk has not been investigated. The aim of our study was to assess the impact of HT by route of estrogen administration on the risk of recurrent VTE.

Methods: A total of 1,023 consecutive postmenopausal women aged 45 to 70 years with a confirmed first VTE were recruited from an outpatient clinic of a hemostasis hospital unit between January 2000 and December 2008 and were followed for an average of 79 months after discontinuation of anticoagulation therapy.

Results: Recurrent VTE occurred in 77 women (1.1% per year). During the follow-up, 130 women used HT (12.7%), including 103 transdermal estrogen users (10.0%) and 10 oral estrogen users (1.0%). After adjustment for potential confounders, there was no significant association between recurrent VTE and use of transdermal estrogens (hazard ratio, 1.0; 95% CI, 0.4-2.4), with the nonusers as a reference group. In contrast, women using oral estrogens had an increased risk of recurrent VTE (hazard ratio, 6.4; 95% CI, 1.5-27.3). Consistently, no subgroup of women had evidence of a risk of recurrent VTE with transdermal HT that significantly differed from that observed for all women.

Conclusions: Oral but not transdermal estrogens are associated with a higher risk of recurrent VTE among postmenopausal women. This result provides further epidemiological evidence that transdermal estrogens may be safe with respect to VTE risk.

Key Words: Hormone therapy – Venous thromboembolism – Transdermal estrogens – Recurrence.

Venous thromboembolism (VTE) is a common disease affecting 1.5 per 1,000 persons every year, with a potential fatal outcome in approximately 5% to 10% of cases.[1,2] Moreover, individuals who experience a first event are at high risk for a recurrent VTE during many years after discontinuation of anticoagulant treatment.[3] Although several clinical risk factors have already been identified as risk factors for recurrent VTE,[4,5] data regarding the influence of hormone use on VTE recurrence are scarce. Despite an important decrease in hormone therapy (HT) use since the publication of the Women Health Initiative trials results,[6,7] many postmenopausal women experiencing severe climacteric symptoms remain eligible for this treatment, which is the most effective for hot flashes. Because oral estrogen therapy is contraindicated in postmenopausal women with a personal history of VTE, it is important to identify a safe therapy to counteract severe climacteric symptoms in women at high risk of recurrent VTE. Although there is evidence that oral estrogen therapy increases the risk of VTE among postmenopausal women,[6,7] recent epidemiological data suggest that transdermal estrogen use does not expose a woman to an excess risk of a first VTE event.[8,9] Transdermal estrogens are widely used in Europe, especially in France, but the impact of this route of administration on the risk of recurrent VTE has not been investigated yet.

In this context, we set up the MEVE (Menopause, Estrogen, and Veins) cohort study aimed to evaluate the safety of transdermal estrogens among postmenopausal women with a personal history of VTE.

METHODS

Participants and study design

Between January 1, 2000, and December 31, 2008, all postmenopausal women aged 45 to 70 who came to the outpatient clinic of the hemostasis unit in the Hotel-Dieu Hospital because of a first objectively confirmed episode of

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VTE were screened and retrospectively included. Eighty-five percent of these women agreed to participate in the study and provided written consent forms. Women were considered as postmenopausal if they had had 12 consecutive months without menstrual periods (unless due to hysterectomy) or had undergone bilateral oophorectomy or had ever used HT. Diagnosis of deep vein thrombosis (DVT) or pulmonary embolism (PE) was established with an imaging procedure. PE was defined as the presence of a positive pulmonary angiogram or a high-probability ventilation/perfusion lung scan. DVT was diagnosed by use of compression ultrasonography or venography. Superficial vein thrombosis, upper extremity DVT, and central retinal vein obstruction were excluded. DVT of the calf vein was considered as distal, and DVT involving the remaining vein segment (popliteal, femoral, or iliac) was considered as proximal. The presence of transient risk factors in the month preceding the first event was recorded. These factors included surgical operation, trauma, plaster, prolonged immobilization (>10 d), oral contraceptive or HT use, pregnancy, venous sclerosis, or air travel. In the absence of one of these mentioned conditions, VTE was considered as idiopathic.

Women's characteristics were extracted from medical records using a standardized questionnaire. Baseline data included information on the first VTE event; medical history; reproductive factors; cardiovascular risk factors like height, weight, smoking status, diabetes, dyslipidemia, and hypertension (physician reported and/or treatment); and the use of exogenous hormones.

Laboratory analysis

After the first event of VTE, women were screened for acquired and hereditary thrombophilia at the visit in the outpatient clinic. Tests included prothrombin time, activated partial thromboplastin time, anticardiolipin antibodies, antithrombin (AT) heparin cofactor activity (chromogenic method), protein C (PC; chromogenic activity), protein S (chronometric activity and free antigen), activated PC resistance (modified method with factor V [FV]–deficient plasma), FV Leiden mutation, and factor II G20210A mutation after DNA extraction and polymerase chain reaction analysis. Oral and written information was provided, and written consent forms were obtained for genetic analyses. All tests were performed at the Hotel-Dieu Hospital laboratory. Women were considered as having biological thrombophilia if they presented at least one of the following laboratory abnormalities: mutation of the FV Leiden or prothrombin G20210A mutation or hereditary deficiency in natural anticoagulant PC, protein S, or AT or antiphospholipid syndrome. Diagnosis of thrombophilia was confirmed on a second blood sampling.

Follow-up and study outcome

The endpoint of the study was a documented recurrent VTE event. Self-reported recurrent VTE was identified by a subsequent visit at the outpatient clinic and/or a follow-up questionnaire sent to all participants. Detailed information on the potential recurrent event, diseases, treatments, and hormone use (estrogen by route of administration, progestogen, dose, regimen, duration, etc) was updated. Participants who indicated that they had a recurrent VTE event were asked to complete a specific questionnaire and to provide medical documentation related to the thrombotic event. Recurrent events were adjudicated within a medical committee blinded to HT use using the same validation criteria as for the first event.

The follow-up started at the time of the discontinuation of anticoagulation therapy and finished either at the time of first thrombotic event recurrence or at the date of the follow-up questionnaire.

HT classification

Women were classified as users if they had used HT at any time during the 3 months before the date of recurrent VTE; otherwise, they were considered as nonusers. Current users of HT were classified according to the route of estrogen administration (oral or transdermal) and to the type of concomitant progestogen. Pregnane derivatives included dydrogesterone, medrogestone, chlormadinone acetate, cyproterone acetate, and medroxyprogesterone acetate. Norpregnane derivatives included nomegestrol acetate and promegestone.

Statistical analysis

Baseline characteristics are presented as mean ± SD for continuous variables and proportions for categorical variables. Differences between groups were tested with the Student's t test for continuous variables and the χ^2 test for categorical variables.

Cumulative incidence of recurrent VTE was estimated by the Kaplan-Meier survival method, censoring at the time of thrombotic event recurrence or the end of the study.

Univariate and multivariate Cox proportional hazard models were used to estimate the risk of recurrent VTE associated with potential risk factors. Age was used as the basic time scale. Exposition to HT was used as a time-dependent variable. Data were analyzed by classifying women according to HT by route of estrogen administration. Current users of oral estrogen and transdermal estrogens were compared separately with nonusers. The difference between the two routes of administration was tested with a χ^2 of homogeneity. Analyses were adjusted for all risk factors for recurrent VTE found in this study (age, overweight, obesity, and characteristics of first event [idiopathic vs secondary]) or identified in the literature (FV Leiden and factor II G20210A mutations).

Cox models for subgroup analyses were stratified according to risk factors of recurrent VTE estimated in this study, and interactions of transdermal estrogens with VTE recurrence risk factors on VTE recurrence were tested using a multiplicative model.

Because the basic time scale in the Cox models was age, we used a simple logistic regression to assess the risk of recurrence associated with age at the first event. Nine women were excluded from the Cox models because of an ongoing anticoagulant therapy or because the date of first event was not available.

TABLE 1. *Clinical characteristics of the 1,023 women*[a]

Characteristics	All (n = 1,023)	Nonusers of HT (n = 893)[b]	Users of HT (n = 130)[b]	P[c]
Age at inclusion, mean (SD), y	57.9 (6.2)	58.3 (5.4)	55.4 (5.5)	<0.001
Age at first venous thromboembolism, mean (SD), y	54.0 (9.5)	54.7 (9.2)	49.4 (10.1)	<0.001
Age at recurrence, mean (SD), y	62.0 (6.6)	62.2 (6.8)	60.5 (5.0)	0.44
BMI, mean (SD), kg/m^2	25.0 (4.5)	25.2 (4.5)	23.7 (4.1)	<0.001
Overweight (25 kg/m^2 ≤ BMI < 30 kg/m^2)	297 (29.9)	267 (30.9)	30 (23.4)	0.09
Obese (BMI ≥30 kg/m^2)	125 (12.6)	114 (13.2)	11 (8.6)	0.14
Duration of anticoagulant therapy, mean (SD), mo	7.3 (11.2)	7.5 (13.9)	6.0 (8.2)	0.4
Duration of the follow-up, mean (SD), mo	79.0 (82.9)	75.2 (78.6)	105 (104.7)	<0.001
Family history of VTE	456 (47.2)	406 (48.2)	50 (40.3)	0.1
Idiopathic first event	227 (22.4)	212 (24.0)	15 (11.7)	0.002
Initial location of first event (proximal DVT or/and PE)	441 (43.3)	405 (45.6)	36 (27.7)	<0.001
Thrombophilia[d]	266 (26.0)	246 (27.6)	20 (15.4)	0.003
FV Leiden	147 (14.4)	132 (14.8)	15 (11.6)	0.34
Prothrombin G20210A	83 (8.1)	80 (9.0)	3 (2.3)	0.01
Natural anticoagulant deficiency	33 (3.2)	33 (3.7)	3 (2.3)	0.43

HT, hormone therapy; BMI, body mass index; DVT, deep vein thrombosis; PE, pulmonary embolism; FV Leiden, factor V Leiden.
[a]Data are given as n (%) unless otherwise stated.
[b]After the first event.
[c]P value comparing nonusers and users of HT.
[d]Thrombophilia: mutation of the FV Leiden or prothrombin G20210A mutation or deficiency in natural anticoagulant protein C, protein S, or antithrombin or antiphospholipid syndrome.

Analyses were performed using SAS software version 9.1 (SAS Institute, Cary, NC).

The study was approved by an ethics committee.

RESULTS

Study population

A total of 1,023 consecutive postmenopausal women aged 45 to 70 years with a first confirmed VTE were recruited. Table 1 shows the clinical characteristics of the women included in our cohort study for all women and separately according to the use of HT since the first event. Among 1,023 women, 130 used HT after the first event and 893 did not use any HT during the follow-up. Users of HT were, on average, younger than nonusers at first event (49.4 vs 54.7 y; $P < 0.001$), had a longer duration of follow-up (105.0 vs 75.2 mo; $P < 0.001$), were thinner than nonusers (body mass index, 23.7 vs 25.2 kg/m^2; $P < 0.001$), and presented less thrombophilia (27.6% vs 15.4%; $P = 0.003$). In addition, there were less proximal localization of the first event (45.6% vs 27.7%; $P < 0.001$) and less idiopathic first event (24.0 vs 11.7; $P = 0.002$) in the users group than in the nonusers. In contrast, there were no significant differences between users and nonusers of HT regarding age at recurrence (62.2 vs 60.5 y; $P = 0.44$), duration of anticoagulation therapy (7.5 vs 6.0 mo; $P = 0.40$), and family history of VTE (40.3% vs 48.2%; $P = 0.10$).

Cumulative incidence of VTE recurrence

During the follow-up period, 110 recurrent events were self-declared by women. Thirty-three of these recurrent events were excluded because of superficial thrombosis (n = 15), undocumented recurrent VTE (n = 11), or DVT of the upper extremity or other (n = 7). A total of 77 women experienced a documented recurrent VTE. Among them, 36 were proximal

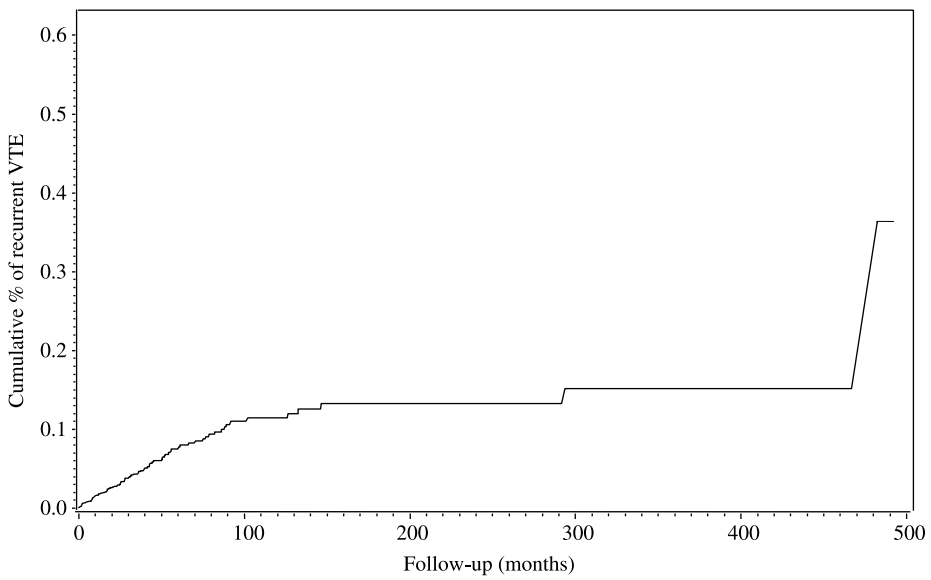

FIG. 1. Kaplan-Meier estimation of the cumulative incidence of recurrent VTE during follow-up. VTE, venous thromboembolism.

TABLE 2. *Univariate and multivariate HRs of recurrent venous event*

Hormone therapy	Cases (n = 76)	Person-years (n = 6,667)	Univariate HR (95% CI)	*P*	Multivariate HR (95% CI)[a]	*P*
Nonusers	68	6,064	1.0 (reference)		1.0 (reference)	
Oral estrogens[b]	2	50	5.7 (1.4-24.0)	0.02	6.4 (1.5-27.3)	0.01
Transdermal estrogens[b]	6	458	0.9 (0.4-2.1)	0.80	1.0 (0.4-2.4)	0.98
Estrogen alone	1	99	0.9 (0.1-6.3)	0.90	1.1 (0.2-8.1)	0.90
+Micronized progesterone	3	231	0.9 (0.3-2.8)	0.80	1.0 (0.3-3.2)	0.90
+Pregnane derivatives	0	94	NA		NA	
+Norpregnane derivatives	2	34	4.0 (0.9-16.5)	0.06	4.7 (1.1-20.0)	0.03
Unknown	0	86	NA		NA	

P for homogeneity between current use of oral estrogens versus current use of transdermal estrogens is significant ($P = 0.03$). *P* for homogeneity between progestogens subgroups among transdermal estrogen users is not significant ($P = 0.22$). Data for adjustment are missing for 32 patients. One case of use of tibolone was excluded from the analysis.
HR, hazard ratio; NA, not applicable.
[a]Multivariate model included age, overweight, obesity, and characteristics of first event (idiopathic/secondary).
[b]At the time of the recurrent event.

DVTs and/or PEs and 41 were distal DVTs. The rate of recurrence was 7.5%, with an average of 1.1% per year. The cumulative incidence of recurrent VTE was 1.8% (95% CI, 1.2-2.9) after 12 months, 7.5% (95% CI, 5.8-9.7) after 60 months, 11.0% (95% CI, 8.6-14.1) after 96 months, and 36.4% (95% CI, 12.1-79.6) after 482 months of follow-up (Fig. 1).

HT and VTE recurrence

Table 2 shows the hazard ratios (HRs) of recurrent venous thrombosis by type of HT. Transdermal estrogen use after a first VTE event did not expose women to an excess risk of recurrence (univariate HR, 0.9; 95% CI, 0.4-2.1). After adjustment for age, characteristics of first event (idiopathic or secondary), overweight, and obesity, the risk of recurrence was 1.0 (95% CI, 0.4-2.4) among women using transdermal estrogens. In contrast, oral estrogens increased significantly the risk of recurrent VTE (adjusted HR, 6.4; 95% CI, 1.5-27.3). The test for homogeneity among the two different routes of estrogen administration was statistically significant ($P = 0.03$). Further adjustment for cancer at inclusion did not change the results.

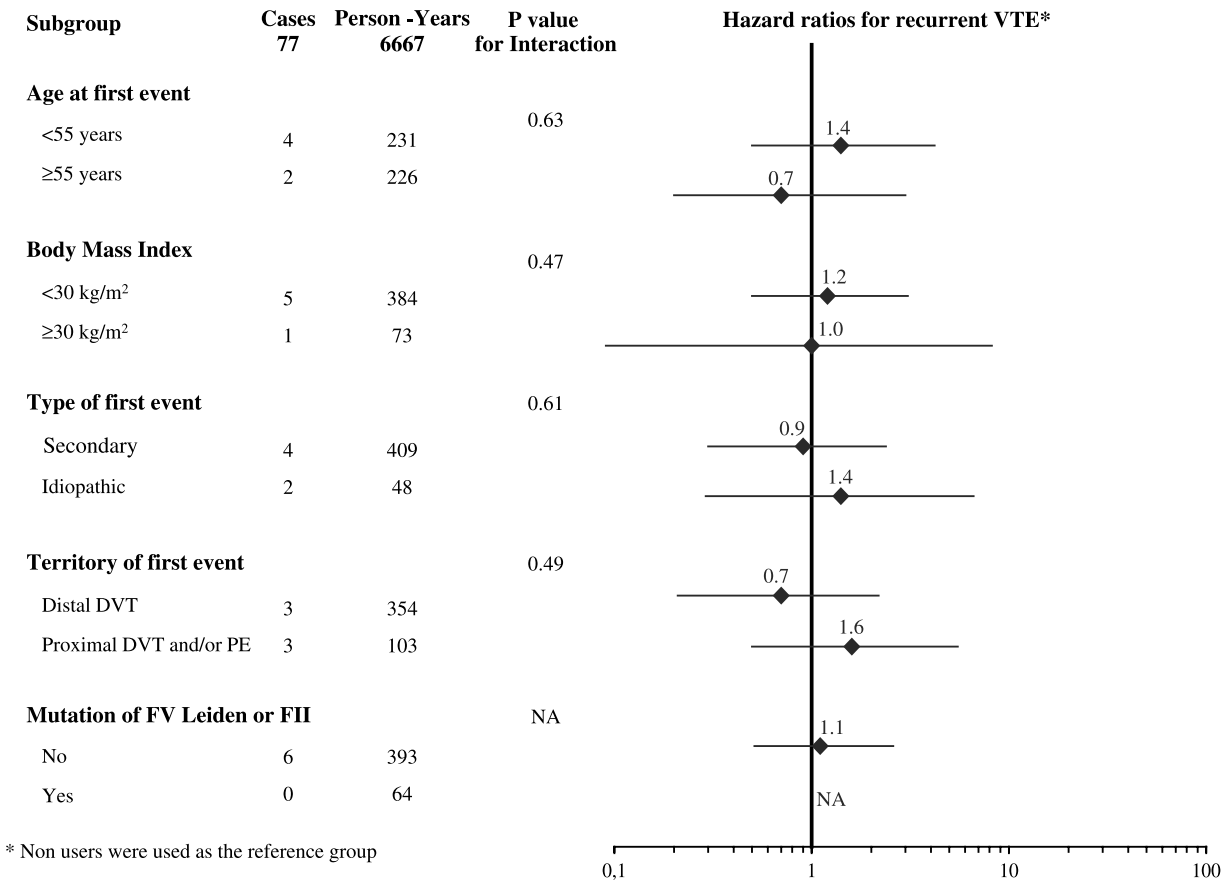

FIG. 2. Transdermal estrogen therapy and the risk of VTE recurrence by subgroup characteristics. VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; FV, factor V Leiden mutation; FII, G20210A prothrombin gene mutation; NA, not applicable.

Among transdermal estrogen users, there was no significant association between micronized progesterone or estrogen alone use and the risk of VTE recurrence (adjusted HR, 1.0 [95% CI, 0.3-3.2] and 1.1 [0.2-8.1], respectively), with nonusers as the reference group. In contrast, using norpregnane derivatives was associated with a significantly increased risk of recurrent VTE (adjusted HR, 4.7; 95% CI, 1.1-20.0) compared with nonusers. Nevertheless, the heterogeneity between progestogen subgroups among transdermal estrogen users was not significant ($P = 0.22$).

Subgroup analyses

Because obesity, an idiopathic first event, a proximal DVT and/or PE, and age at first event were independent risk factors for VTE recurrence (adjusted HR, 2.2 [95% CI, 1.2-4.1], 2.1 [1.3-3.4], 1.6 [1.0-2.6], and 1.9 [1.1-3.1], respectively), we determined high-risk and low-risk subgroups for VTE recurrence.

Figure 2 shows the HRs for VTE recurrence among transdermal estrogen users in the different subgroups compared with nonusers. The HRs for recurrent VTE in women using transdermal estrogens did not differ significantly according to different VTE risk factors. No significant interaction of transdermal estrogens with age at first event, obesity, type of first event, and localization of first event on recurrent VTE was found.

DISCUSSION

In this cohort study including 1,023 postmenopausal women, the cumulative incidence of recurrence increased from 7.5% after 5 years to 11.0% after 8 years of follow-up. In a multivariate survival analysis, oral but not transdermal estrogen therapy was associated with a higher risk of recurrence in postmenopausal women. In addition, postmenopausal women who were in the high risk of recurrent VTE subgroup did not have a significantly greater excess risk of recurrent VTE using transdermal estrogens than did women without these risk factors.

The rate of recurrence reported in the present study seems to be lower than those reported in other investigations. Indeed, previous studies have reported approximately 25% higher recurrence rates after 5 years of follow-up.[10-12] However, these recurrence rates were estimated irrespective of the sex of the participants, and a meta-analysis[13] showed that men had a 50% higher risk of recurrent VTE than do women after stopping anticoagulation therapy. Rates of recurrent VTE found in two studies among women only were similar to those in the present study.[14,15] Regarding VTE risk among estrogen users, there is no available randomized controlled trial comparing routes of administration (oral vs transdermal). However, several observational studies consistently showed that transdermal estrogens did not expose women to an excess risk of first VTE.[16] Although the route of estrogen administration is an important determinant of first VTE event risk,[8,16] data regarding the influence of hormone use on VTE recurrence are scarce.[7,17] The present study investigated for the first time the association between transdermal estrogens and the risk of recurrent VTE and provided further data about oral estrogens and the risk of recurrent VTE. Thus, women using oral estrogen therapy had a 6.4-fold increased risk of recurrent VTE compared with nonusers. Similarly, the Estrogen in Venous Thromboembolism Trial and the Women's Health Initiative randomized trial found an excess risk of VTE recurrence in women using oral estrogen therapy, although these results were not significant.[7,17] In contrast, in our study, transdermal estrogens were not associated with the risk of VTE recurrence and seemed to be safer than oral estrogens. Moreover, no subgroup of women had evidence for a risk of recurrent VTE with transdermal HT that differed significantly from that observed for all women. In addition, although we cannot detect any significant association between micronized progesterone and the risk of VTE recurrence, there was a significant increase in recurrent VTE risk among users of norpregnane derivatives compared with nonusers. These results are consistent with our previous data on the risk of first VTE event in women using HT.[18] However, the limited number of exposed cases in the different subgroups did not allow comparing progestogen types with sufficient statistical power.

The increase in first VTE risk among users of oral estrogens is supported by biological data. Oral estrogen administration results in a hepatic first-pass effect, which may be responsible for an activation of the coagulation cascade with an increase in the plasma concentration of procoagulant factors.[19,20] Furthermore, oral estrogens can induce a decrease in antithrombotic mechanisms.[21] Thus, a lower AT concentration and an acquired resistance to activated PC have been demonstrated in users of oral estrogens.[19,20] In contrast, transdermal estrogens seem to have little or no effect on hemostasis.[19,20,22,23] Therefore, changes in hemostatic variables could also be relevant to the difference in risk of recurrent VTE by route of estrogen administration and could explain the lack of association between transdermal estrogens and the risk of recurrent VTE.

One potential limitation of our study is that observational studies are subject to bias. First, because our cohort study was retrospective, the identification of HT exposure after inclusion in the cohort was based on women's memory or records of their physicians. In addition, exposure to HT during the follow-up period was self-reported. For these reasons, misclassifications regarding HT exposure might have occurred and could partly explain the absence of association between transdermal estrogens and the risk of recurrent VTE. Nevertheless, we found a positive association between oral estrogen use and recurrent VTE risk, and there is no reason for differential misclassifications in HT exposure by route of estrogen administration. Another limitation may be the small number of recurrence cases and, more particularly, for the progestogen subgroup analysis and for oral estrogen users. Regarding the characteristics of HT, the mean dose of transdermal estrogens was 50 μg daily. There was no significant association between the dose of transdermal estrogens and the risk of recurrent VTE. However, about 50% of the data regarding the dose of

estrogens taken were missing, and this is a limitation of our study. Finally, an indication bias might have occurred because of differential prescription of HT according to the clinical characteristics of the women (presence of thrombophilia, high body mass index, familial history of VTE, etc) and the severity of the first event (idiopathic and/or proximal localization). Women in the subgroup at low risk of recurrence may be more likely to be prescribed HT. This prescription bias could partly explain the lack of association between transdermal estrogens and VTE recurrence. However, adjustment for all these potential cofounders did not significantly change the results.

CONCLUSIONS

In conclusion, our results provide the first evidence supporting the safety of transdermal estrogen's route of administration with respect to VTE recurrence risk. These data add to the current epidemiological evidence that transdermal estrogens may be safe with respect to VTE risk in general. If confirmed, these data could have important clinical implications among women at high VTE risk who require HT for severe postmenopausal symptoms. Reducing VTE risk by using transdermal estrogens could substantially improve the benefits-risks profile of HT among postmenopausal women with a personal history of VTE.

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