Postmenopausal Hormone Therapy and Risk of Idiopathic Venous Thromboembolism

Results From the E3N Cohort Study

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Objective—Oral estrogen therapy increases venous thromboembolism risk among postmenopausal women. Although recent data showed transdermal estrogens may be safe with respect to thrombotic risk, the impact of the route of estrogen administration and concomitant progestogens is not fully established.

Methods and Results—We used data from the E3N French prospective cohort of women born between 1925 and 1950 and biennially followed by questionnaires from 1990. Study population consisted of 80 308 postmenopausal women (average follow-up: 10.1 years) including 549 documented idiopathic first venous thromboembolism. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated using Cox proportional models. Compared to never-users, past-users of hormone therapy had no increased thrombotic risk (HR=1.1; 95% CI: 0.8 to 1.5). Oral not transdermal estrogens were associated with increased thrombotic risk (HR=1.7; 95% CI: 1.1 to 2.8 and HR=1.1; 95% CI: 0.8 to 1.8; homogeneity: $P=0.01$). The thrombotic risk significantly differed by concomitant progestogens type (homogeneity: $P<0.01$): there was no significant association with progesterone, pregnanes, and nortestosterones (HR=0.9; 95% CI: 0.6 to 1.5, HR=1.3; 95% CI: 0.9 to 2.0 and HR=1.4; 95% CI: 0.7 to 2.4). However, norpregnanes were associated with increased thrombotic risk (HR=1.8; 95% CI: 1.2 to 2.7).

Conclusions—In this large study, we found that route of estrogen administration and concomitant progestogens type are 2 important determinants of thrombotic risk among postmenopausal women using hormone therapy. Transdermal estrogens alone or combined with progesterone might be safe with respect to thrombotic risk. **(*Arterioscler Thromb Vasc Biol*. 2010;30:340-345.)**

Key Words: venous thromboembolism ■ estrogens ■ progestogens ■ hormone therapy ■ postmenopausal women

Despite recent data showing that overall health risks may exceed benefits from postmenopausal hormone therapy (HT),[1,2] many women remain eligible for this treatment to correct menopausal symptoms.[3,4] However, harmful effects of HT may include breast cancer and venous thromboembolism.[1,5,6] Recent guidelines recommend that women be prescribed the lowest effective dose of HT for the shortest possible duration.[7,8] Because the risk of venous thromboembolism is highest during the first year of treatment,[9,10] pulmonary embolism, which already represented one-third of the potentially fatal events attributable to long-term HT,[11] has become one of the major side effects of short-term treatments. Reducing thrombotic risk may therefore have important clinical implications in the management of postmenopausal symptoms. Recent observational data have suggested that transdermal estrogens might be safe with respect to thrombotic risk,[12,13] but the impact of estrogens by route of administration is not fully established. In addition, data on the role of concomitant progestogens are scarce.[13] Therefore, we investigated the impact of estrogens by route of administration as well as the influence of concomitant progestogens on the risk of idiopathic venous thrombosis in a large cohort of French women.

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Methods

E3N Study

The E3N (Etude Epidémiologique de femmes de l'Education Nationale) Study is a prospective cohort study initiated in 1990 among 98 995 women born between 1925 and 1950 and insured by a healthcare plan covering mostly teachers. Participants who gave written informed consent completed biennial self-administered ques-

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tionnaires (sent between 1990 and July 2005) which included items about anthropometric measurements, medical history, menopausal status and a variety of lifestyle habits (eg, contraceptive use, HT use, alcohol consumption, smoking). Details of the E3N design have been described elsewhere.[14,15]

Ascertainment of Venous Thromboembolism Cases

Nonfatal venous thromboembolism events were initially self-reported by women in the questionnaires. Participants who declared to have had either a thrombosis or a pulmonary embolism were then asked to complete a specific questionnaire and to send medical documentation related to the thrombotic event. In addition, a questionnaire including information on potential predisposing factors for thrombosis and characteristics of the event was sent to the medical doctors reported by the women. To be validated, clinical events had to be diagnosed using an imaging procedure. Pulmonary embolism was defined as the presence of either a positive pulmonary angiography or a positive helicoidal computed tomography or a high-probability ventilation/perfusion lung scan. Deep venous thrombosis had to be diagnosed by use of compression ultrasonography or venography. Events were centrally validated by a medical committee blinded to HT use. Cases of fatal pulmonary embolism were identified from death certificates from the National Service on Causes of Deaths (Inserm) using International Classification of Diseases (ICD) 9 (codes 4151 and 4539) and ICD-10 (codes I26.0 and I26.9). In the present analysis, the main clinical outcome was a first documented incident episode of pulmonary embolism or lower-extremity deep vein thrombosis having occurred without any of the following predisposing factors (ie, cancer, surgery, immobilization, or trauma).

Among the 98 995 women included in the E3N Study, 2142 episodes of venous thromboembolism were self-reported during the overall follow-up. Among those, 1696 nonfatal thrombotic events were further validated and 446 were not considered as venous thromboembolism episode because they were not thrombotic events (n=149) or no information could be obtained (n=297). Superficial vein thrombosis (n=216), upper-extremity thrombosis (n=23), central retinal vein obstruction (n=2), and recurrent events (n=80) were also treated as nonevents which resulted in a total of 1375 incident cases of nonfatal deep vein thrombosis or pulmonary embolism. In addition, 68 cases of fatal pulmonary embolism were identified by death certificates. Overall, 1443 incident thrombotic cases (including 68 deaths) were eligible for inclusion in the present study.

Study Sample and Follow-Up

The present investigation was limited to postmenopausal women. Information on menopausal status was updated at each follow-up questionnaire. Women were considered postmenopausal if they had had 12 consecutive months without menstrual periods (unless attributable to hysterectomy), had undergone bilateral oophorectomy, had ever used HT, or self-reported that they were postmenopausal. Age at menopause was defined as age at last menstrual period (if cessation of menstruation did not occur after hysterectomy); age at bilateral oophorectomy; or, in decreasing order of priority, self-reported age at menopause, age at HT initiation, age at first occurrence of menopausal symptoms. If no information was available, age at menopause was assigned at 47 years if menopause was artificial, and at 51 years otherwise, because these ages corresponded to the respective median ages for artificial and natural menopause in the cohort.

Follow-up started on the return date of the first questionnaire where women declared to be menopausal. Participants contributed person-years of follow-up until the date of death for fatal cases and, for other subjects, until the date of a venous thromboembolism event, the date of cancer diagnosis (other than basal cell skin cancer), the date of the last completed questionnaire or July 2005, whichever occurred first.

From the full cohort, 12 471 women including 219 cases were excluded because they were not menopausal or had had a thrombotic event before the start of follow-up. Of the remaining 86 524 women, 5822 were excluded from the analyses because of personal history of cancer other than basal cell carcinoma (n=213 cases including 30 fatal events) or a nonidiopathic thrombotic event (n=329) or an event without information on predisposing factors (n=65 including 38 fatal pulmonary embolisms). In addition, 68 women with a validated thrombotic event were censored at the date of cancer diagnosis because of a validated cancer predating the thrombotic event.

The final analysis was therefore performed on 80 308 postmenopausal women without personal history of thrombotic events or cancer before the start of follow-up. The study population included 549 incident events of first documented idiopathic venous thromboembolism (134 pulmonary embolisms and 415 deep vein thromboses).

Classification of HT

The 1992 questionnaire inquired about lifetime use of HT. It was accompanied by a booklet and photos of available estrogens and progestogens mailed to all participants. For each treatment episode, women were asked to report information on brand name, age at first use, and duration of treatment. Information on HT was updated from each of the subsequent questionnaires.

Women were classified as current users if they had used HT at any time during the 3 months before the date of completion of the questionnaire, otherwise they were considered as past users or never users. Current users of HT were classified according to estrogens by route of administration and to the type of concomitant progestogen. Route of estrogen administration included oral, transdermal (patch or gel). Other treatments included tibolone, vaginal treatments, injectable treatments, HT without any information regarding the route of estrogen administration, and estrogens combined with androgens. Most current users of oral and transdermal estrogens received 17β-estradiol. Progestogens were categorized according to the progestogen North American Menopause Society (NAMS) classification.[16] Women were classified as users of either micronised progesterone, pregnane derivatives, norpregnane derivatives, or nortestosterone derivatives. Pregnane derivatives included dydrogesterone, medrogestone, chlormadinone acetate, cyproterone acetate, and medroxyprogesterone acetate. Norpregnane derivatives included nomegestrol acetate and promegestone. Nortestosterone derivatives were norethisterone acetate.

Statistical Analysis

HT exposure was taken into account as a time-dependent variable. To preserve the prospective nature of the study, exposure status declared at the completion of each questionnaire was maintained during the entire interval until completion of the following questionnaire (or until the end of follow-up). Because data on exposure were available from the 1992 questionnaire onward, exposure between 1990 and 1992 was considered as "unknown" for all women. Cox proportional hazards models with age as the time-scale were used to estimate the hazard ratios (HR) and 95% confidence intervals (CI) for venous thromboembolism associated with HT. The HRs were adjusted for body-mass index (as a continuous variable), parity (total number of stillborn and live births as a continuous variable), education level (6 ordered categories as continuous variable), and time-period (before or after 2003 to take into account the changes in HT use after the publication of the Women's Health Initiative trial results). These potential confounders were chosen because they have been related to thrombotic risk (eg, body-mass index and parity[17]) or because they have been linked to HT exposure and might have an impact on thrombotic risk (eg, education level and time-period). Women with missing data for a covariate were excluded from analyses including that covariate.

Data were analyzed by classifying women according to HT use. The main effects of past use, current use of estrogens by route of administration (either oral, transdermal, or other), and current use of concomitant progestogens (either micronized progesterone, pregnanes, norpregnanes, or nortestosterones) were estimated in the same model with never use of HT as the reference group. Homogeneity of estimated HRs was tested among different pharmacological classes of concomitant progestogen and between molecules within the

Table 1. General Characteristics of the Study Population at the Beginning of Follow-Up: The E3N Cohort

Characteristics	Population (n=80 308)
Age at entry, y	54.0 (4.3)
Follow-up, y	10.1 (4.6)
Body-mass index, kg/m^2	22.6 (3.2)
Overweight, 25≤BMI<30 kg/m^2	11 808 (14.6)
Obesity, BMI ≥30 kg/m^2	2483 (3.1)
Current smokers	7095 (9.9)
High school graduate	66 002 (83.1)
Age at menopause, y	50.2 (3.8)
Hysterectomy	16 257 (20.2)
Parity	2.2 (0.9)
Past use of oral contraceptives	46 387 (57.8)

Values are mean (SD) or No. (%).

groups of pregnane and norpregnane derivatives. Interactions between the effects of estrogens and concomitant progestogens were tested by using a multiplicative HR model.

Stratified analyses were conducted by type of diagnosis (deep vein thrombosis or pulmonary embolism) and mortality.

Statistical analyses were performed using SAS statistical software (version 9.1, SAS Institute Inc).

Results

Table 1 shows the general characteristics of the study population. Mean age at the beginning of follow-up was 54.0 years, and women were followed for an average of 10.1 years. At the beginning of follow-up, mean body-mass index was 22.6 kg/m^2, and nearly 18% of the women were overweight or obese.

Table 2 shows the HRs of venous thromboembolism by type of HT. Women who had never taken any HT were used as the reference group (n=181 cases). Past users of HT had similar thrombotic risk as never users (adjusted HR=1.1; 95% CI: 0.8 to 1.5). There was no significant interaction between the route of estrogen administration (either oral or transdermal) and concomitant progestogens (either micronized progesterone, pregnane derivatives, norpregnane derivatives, or nortestosterone derivatives; *P* for interaction=0.62). After adjustment for potential confounders, oral but not transdermal estrogen use was associated with an increased risk of thrombosis (HR=1.7; 95% CI: 1.1 to 2.8 and HR=1.1; 95% CI: 0.8 to 1.8, respectively). In addition, among users, the hazard ratio was significantly increased in oral estrogen users as compared to transdermal estrogen users (HR=1.5; 95% CI: 1.1 to 2.0). Regarding the impact of concomitant progestogens, the test for homogeneity among pharmacological subgroups was statistically significant (*P*<0.01). However, no significant heterogeneity was found between molecules within the groups of pregnane and norpregnane derivatives (*P*=0.07 and *P*=0.17, respectively). There was no significant association of venous thrombosis with micronized progesterone and pregnane derivatives (HR=0.9; 95% CI: 0.6 to 1.5 and HR=1.3; 95% CI: 0.9 to 2.0, respectively). In addition, nortestosterone derivatives were not significantly associated with thrombotic risk (HR=1.3; 95% CI: 0.7 to 2.4). By contrast, norpregnane derivatives were associated with an increased thrombotic risk (HR=1.8; 95% CI: 1.2 to 2.7).

Stratified analyses by type of diagnosis showed no striking differences in thrombotic risk associated with HT use between deep vein thrombosis and pulmonary embolism (data not shown).

In the principal analysis, 65 of the validated cases were excluded because no information on predisposing factors was available. These cases included fatal pulmonary embolisms identified from death certificates which did not contain such information (n=38). Thus, additional analyses were per-

Table 2. Hazard Ratios of Idiopathic Venous Thromboembolism in Relation to Both Estroges by Route of Administration and Concomitant Progestogens

Treatment	Cases n=549	Person-Years 811 643	Hazard Ratios (95% Confidence Intervals) Age-Adjusted	Multivariable Adjusted*
Never use	181	291399	1 [reference]	1 [reference]
Past use	66	100943	1.0 (0.7–1.3)	1.1 (0.8–1.5)
Current use of oral estrogens	81	93211	1.5 (0.9–2.3)	1.7 (1.1–2.8)
Current use of transdermal estrogens	174	268481	1.1 (0.7–1.6)	1.1 (0.8–1.8)
No progestogens use	26	46163	…	…
Current use of micronized progesterone	47	87959	0.9 (0.6–1.4)	0.9 (0.6–1.5)
Current use of pregnane derivatives	91	125804	1.3 (0.8–1.9)	1.3 (0.9–2.0)
Current use of norpregnane derivatives	69	78855	1.7 (1.1–2.6)	1.8 (1.2–2.7)
Current use of nortestosterone derivatives	22	22911	1.4 (0.8–2.5)	1.4 (0.7–2.4)
Current use of other treatment	30	47693	1.0 (0.7–1.5)	1.1 (0.7–1.8)
Unknown	17	9916	2.0 (0.5–3.9)	2.0 (0.5–3.9)

*Adjusted for age, body-mass index, parity, education level, and time-period.

Data for adjustment missing for 19 cases and for 843 non-cases.

P for homogeneity between current use of oral estrogens vs current use of transdermal estrogens is significant (*P*=0.01).

P for homogeneity between progestogen subgroups is significant (*P*<0.01).

formed with pooled idiopathic cases and cases without any information on predisposing factors (n=614). The inclusion of these cases did not substantially modify the results. Indeed, the hazard ratios of venous thromboembolism for oral and transdermal estrogens were respectively 1.6 (95% CI 1.0 to 2.4) and 1.1 (95% CI 0.8 to 1.6). Using this same study sample, an additional analysis restricted to nonfatal events (n=576) led to similar results (data not shown).

Discussion

These findings suggest that the route of estrogen administration and the type of concomitant progestogen are both important determinants of thrombotic risk among postmenopausal women who use HT. Transdermal estrogens may be safe when they are administrated alone or along with micronized progesterone but not with norpregnane derivatives. By contrast, oral estrogens are associated with an increased thrombotic risk irrespective of the presence of concomitant progestogens.

Our results regarding oral estrogen therapy are in agreement with those from both observational studies and clinical trials which have shown that oral estrogens were thrombogenic.[9,18] Thus far, only 4 studies have investigated the impact of transdermal estrogens on the risk of venous thrombosis.[12,19–21] A combined analysis of these studies yielded an overall odds ratio close to one in transdermal estrogen users compared to nonusers.[9] Our results showing no increased thrombotic risk among women who use transdermal estrogens alone are consistent with this previous report.

Although some previous studies have focused on the estrogens by route of administration, few data are available regarding the impact of concomitant progestogens by pharmacological classes on the risk of venous thromboembolism. On one hand, some observational studies[19–23] and one clinical trial[24] have compared the risk of venous thromboembolism between users of estrogens alone and users of estrogens combined with progestogens. Overall, these results showed that oral estrogens combined with progestogens could be more thrombogenic than oral estrogens alone.[9] In addition, a comparison of both Women's Health Initiative trials also suggested that the risk of thrombosis was higher among users of opposed estrogens than among users of estrogens alone.[1,2,5,6] On the other hand, the ESTHER case–control study recently investigated the impact of concomitant progestogens by pharmacological classes.[13] In this study, micronized progesterone and pregnane derivatives were not significantly associated with an increased risk of venous thromboembolism, whereas norpregnane derivatives were thrombogenic compared to nonuse. The present findings regarding micronized progesterone and norpregnane derivatives are consistent with these previous results. Finally, to our knowledge, the E3N study is the first to assess thrombotic risk in relation to nortestosterone derivatives used in HT, and only few data are available on the effect of nortestosterones used alone. Although not statistically significant, the increased thrombotic risk associated with combined use of nortestosterones and estrogens in the E3N study can be paralleled with the elevated thrombotic risk observed in premenopausal women who received nortestosterone derivatives alone.[25] However, the limited number of cases exposed to nortestosterone derivatives in our study did not allow assessing the effect estimates with sufficient statistical power.

The potential mechanisms underlying the increase in thrombotic risk among users of specific treatments include a prothrombotic state, a decrease in blood flow, or an alteration of the vessel wall.[26,27] Since 1997, several studies have shown that oral but not transdermal estrogens activate blood coagulation and induce an activated protein C resistance, providing biological evidence to support the difference in thrombotic risk by route of estrogen administration.[28–33] In some of the studies, oral and transdermal estrogens were both combined with micronized progesterone. These hemostatic data, together with the results of both the ESTHER[13] and the E3N studies, support the potential safety of transdermal estrogens combined with micronized progesterone. Data on the effect of progestogens on hemostasis are scarce, and results remain inconsistent. One study has shown that a pregnane derivative had little to no effect on hemostasis.[34] Moreover, several trials have failed to show any changes in levels of hemostatic parameters between progestogen subgroups.[35–38] Nevertheless, recent data suggested that trimegestone, a norpregnane derivative, had a stronger effect on fibrinolysis inhibition as compared to dydrogesterone.[39] Thus, whether or not progestogens have differential effects on hemostasis requires further investigation.

The increase in thrombotic risk among postmenopausal women using some progestins could also be mediated by changes in venous structure and function.[27] The occurrence of venous stasis, especially observed during pregnancy and the luteal phase, could be modulated by steroid sex hormones via progesterone receptors which are present in the venous wall.[40] Therefore, an increase in progestational activity of progestins, especially norpregnanes, compared to micronized progesterone might further alter blood flow and increase thrombotic risk.

One potential limitation of the E3N prospective cohort study is that, as an observational study, it is subject to bias. Several types of bias have already been discussed.[14,15] In the present analysis, potential limitations include how selected the population was, why women were prescribed a specific treatment, misclassification regarding diagnosis, or exposure and potential confounders in the statistical analysis. First, women recruited in the E3N study were mostly teachers and could represent a health-conscious population which might be at lesser risk than the general population. However, it is unlikely that this nondifferential selection of healthy subjects could affect the comparison between users and nonusers of HT.

Second, an indication bias might have occurred due to differential prescription of concomitant progestogens according to the estrogenic status of women using HT. Norpregnane derivatives are potent progestogens with antiestrogenic activity. Women with moderate to severe hyperestrogenic symptoms, such as breast tenderness or endometrial diseases, may be more likely to be prescribed these types of progestogen.[41,42] Because there is evidence that lifetime estrogen exposure is positively related to venous thromboembolism in postmenopausal women,[17] this prescription bias could partly

explain the increase in thrombotic risk among women using such antiestrogenic progestogens.

Another limitation of our cohort study is that HT use was self-reported and nondifferential misclassifications regarding exposure might have occurred during follow-up. The effect of such errors is to decrease the strength of the observed associations toward the null. This limitation could explain the lower relative risks observed in our study compared to previous findings.[9] We also cannot rule out a potential nondetected relationship between some treatments which appear safe and thrombotic risk. Another possible dilution of risk estimates may result from our definition of exposure. We used hormonal exposure declared at the beginning of each follow-up interval for the entire interval until the following subsequent questionnaire. This strategy allowed preserving the prospective nature of the study and avoiding differential recall bias between cases and noncases. However, such exposure classification might lead to an incomplete capture of exposed cases, especially for those who started their treatment just after the date of questionnaire completion. Further, potential confounders including elevated levels of thrombotic risk factors could explain our findings related to the effects of estrogens by route of administration and concomitant progestogens. Although some thrombotic risk factors, such as prothrombotic mutations or family history of venous thromboembolism, were not measured in this study, adjustment for other predisposing factors for thrombosis, such as body-mass index or parity, did not appreciably change the results. The unavailable information on estrogens doses was also a limitation of our study. Although increasing doses of estrogens may increase the coagulation activation,[43] observational studies have suggested no significant difference in thrombotic risk by estrogen dose.[12,19,20,22,23] However, studies with high level of evidence comparing estrogen doses effect on thrombotic risk are still lacking.

Finally, our analysis was restricted to idiopathic venous thromboembolism because inclusion of cases with predisposing factors might have attenuated the associations between hormone use and thrombotic risk. In addition, it is likely that the presence of predisposing factors for venous thromboembolism could modify hormone exposure. Therefore, analysis restricted to idiopathic cases provides more accurate estimates of thrombotic risk. Nonetheless, this selection criterion did not allow extrapolating our results to secondary events.

The E3N cohort study also has several strengths including its prospective population-based design as well as its large number of participants. In addition, follow-up questionnaires sent biennially starting from 1990 allow for the frequent update of information on menopausal status and HT use. In the present ancillary study, a further strength is the large number of well documented incident cases of venous thromboembolism.

Our findings regarding the impact of estrogens by route of administration and concomitant progestogens on thrombotic risk may have important clinical implications. Because pulmonary embolism has become a major determinant of the benefit/risk ratio of short-term oral estrogen therapy, reducing the risk of venous thromboembolism could substantially improve the benefit/risk profile of HT. Therefore, short-term use of transdermal estrogens alone or combined with progesterone could be a good option in the management of postmenopausal symptoms. However, further data are needed, and the present results should be confirmed with randomized controlled trials.

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Disclosures

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