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Circulation. 2007;115:840-845

doi: 10.1161/CIRCULATIONAHA.106.642280

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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Hormone Therapy and Venous Thromboembolism Among Postmenopausal Women

Impact of the Route of Estrogen Administration and Progestogens: The ESTHER Study

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Background—Oral estrogen therapy increases the risk of venous thromboembolism (VTE) in postmenopausal women. Transdermal estrogen may be safer. However, currently available data have limited the ability to investigate the wide variety of types of progestogen.

Methods and Results—We performed a multicenter case–control study of VTE among postmenopausal women 45 to 70 years of age between 1999 and 2005 in France. We recruited 271 consecutive cases with a first documented episode of idiopathic VTE (208 hospital cases, 63 outpatient cases) and 610 controls (426 hospital controls, 184 community controls) matched for center, age, and admission date. After adjustment for potential confounding factors, odds ratios (ORs) for VTE in current users of oral and transdermal estrogen compared with nonusers were 4.2 (95% CI, 1.5 to 11.6) and 0.9 (95% CI, 0.4 to 2.1), respectively. There was no significant association of VTE with micronized progesterone and pregnane derivatives (OR, 0.7; 95% CI, 0.3 to 1.9 and OR, 0.9; 95% CI, 0.4 to 2.3, respectively). In contrast, norpregnane derivatives were associated with a 4-fold-increased VTE risk (OR, 3.9; 95% CI, 1.5 to 10.0).

Conclusions—Oral but not transdermal estrogen is associated with an increased VTE risk. In addition, our data suggest that norpregnane derivatives may be thrombogenic, whereas micronized progesterone and pregnane derivatives appear safe with respect to thrombotic risk. If confirmed, these findings could benefit women in the management of their menopausal symptoms with respect to the VTE risk associated with oral estrogen and use of progestogens. (*Circulation*. 2007;115:840-845.)

Key Words: embolism ■ epidemiology ■ estrogens ■ progestogens ■ thrombosis

Since the publication of the Women Health Initiative (WHI) results,¹ medical practices of hormone therapy have been dramatically altered.² Despite a striking decrease in hormone therapy use, many women remain eligible for this treatment to correct postmenopausal climacteric symptoms and to prevent osteoporosis. Cardiovascular disease, including venous thromboembolism (VTE), is an important determinant of the benefit-to-risk profile of hormone therapy.³ Both observational studies^{4–13} and clinical trials^{1,14,15} have shown a significant increase in VTE risk among postmenopausal women using hormone therapy. However, most of these studies were done in women using preferentially oral estrogen alone or combined with a

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specific pregnane derivative (medroxyprogesterone acetate), and these results are not necessary relevant to other hormone regimens. In European countries, especially in France, the transdermal route of estrogen administration is used most often. In addition, many progestogen derivatives are available, and the impact of the different types of progestogens on the VTE risk has not been investigated. Therefore, we designed the Estrogen and Thromboembolism Risk (ESTHER) study, a multicenter case–control study performed in

Received May 26, 2006; accepted November 8, 2006.

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Circulation is available at <http://www.circulationaha.org>

DOI: 10.1161/CIRCULATIONAHA.106.642280

France, to investigate the impact of the route of estrogen administration on VTE risk among postmenopausal women. Early results of our study have shown that oral but not transdermal estrogen increases VTE risk.¹¹ Final analysis of the ESTHER study, based on a more important pool of cases and controls, focuses on the impact of the progestogens on VTE risk.

Methods

The ESTHER study is a multicenter case–control study. It was done in France in 8 hospitals and in the general population between 1999 and 2006. Details of the study design have been described.^{11,16}

Selection of Cases and Controls

We included consecutively 208 hospital cases with a first documented episode of idiopathic VTE and 426 hospital controls. Controls had to have been admitted to the hospital with an a priori diagnosis unrelated to estrogen use. These diagnoses included diseases of eye, ear, skin, respiratory and alimentary tracts, bones and joints, and kidneys; infectious diseases; and diabetes. In addition, we included consecutively 63 outpatient cases from 3 hematology centers matched with 184 community controls selected at random from electoral rolls. About 5% of hospital controls and 10% of community controls refused to participate in this study. Cases and controls were matched for center, 2-year age band, admission date, and area of residence. Each case was matched with 1 to 3 controls.

Both hospital and outpatient cases were excluded if they reported a personal history of VTE, had a contraindication for hormone therapy (breast cancer, endometrial cancer, and cardiovascular disease), or had a predisposing factor for VTE (history within the previous month of surgical intervention, trauma with immobilization for >8 days, illness necessitating bed rest for >8 days, known cancer, systemic inflammatory disease). Outpatient cases also were excluded if they were referred to clinical centers for estrogen advice or known thrombophilia.¹⁶ Controls were subjected to the same exclusion criteria as cases.

Ascertainment of Cases

Clinical events had to be diagnosed with an imaging procedure. Pulmonary embolism was defined as the presence of either helicoidal computed tomography showing at least 1 intraluminal defect in 1 segmental pulmonary artery, high-probability ventilation/perfusion scan according to criteria from the Prospective Investigation of Pulmonary Embolism Diagnosis,¹⁷ or pulmonary angiography showing a clot. Deep venous thrombosis was diagnosed by use of compression ultrasonography. Events were adjudicated within each center but also centrally for outpatient cases. Events were validated by investigators blinded to estrogen use.

Data Collection

Cases and controls were identified without knowledge of estrogen use, and they were interviewed at hospital in a standard way with the same questionnaire. Menopause was defined by amenorrhea for >12 months or bilateral ovariectomy or hysterectomy together with an age >52 years. Women were classified as current users if they used estrogen at any time in the past 3 months before the case admission date. Similarly, current smokers were women who had smoked during the 3 months before inclusion. Varicose veins were defined as a reported history of varicose veins or stripping. Familial history of VTE was defined as the occurrence of VTE before 65 years of age in a first degree-relative. Overweight and obesity were defined as body mass index >25 and 30 kg/m², respectively.

The protocol was approved by Inserm and the local ethics committee. Written and informed consent was obtained from all women.

Classification of Hormone Therapy

Identification of hormone therapy was assisted by showing the participants pictures of both available estrogens and progestogens. The questionnaire included details of type, dose, and duration of treatment.

Current users of hormone therapy were classified according to both the route of estrogen administration and the type of progestogens. First, treated women were classified as either oral estrogen users or transdermal estrogen (patch or gel) users. Second, current users of hormone therapy also were categorized according to the progestogen North American Menopause Society classification.¹⁸ Women were classified as users of micronized progesterone or pregnane derivatives, norpregnane derivatives, or nortestosterone derivatives. Pregnane derivatives included dydrogesterone or medrogestone, chlormadinone acetate, cyproterone acetate, or medroxyprogesterone acetate. Norpregnane derivatives included either nomegestrol acetate or promegestone.

Statistical Analysis

Continuous data are expressed as mean and SD; categorical variables are given as absolute values and percentages.

We estimated the odds ratios (ORs) and 95% CIs from conditional logistic regressions. Data were analyzed by classifying the cases and controls according to hormone therapy. Current users were compared with nonusers in a joint model of both route of estrogen administration (either oral or transdermal) and type of progestogens (either micronized progesterone or pregnane or norpregnane derivatives). We excluded the users of oral estrogen combined with nortestosterone derivatives (12 cases, 7 controls), and VTE odds ratio associated with this type of hormone therapy was estimated separately with nonusers as the reference group. ORs were adjusted for obesity status, familial history of VTE, and varicose veins (adjustment 1) and further adjusted for education, age at menopause, hysterectomy, and cigarette smoking (adjustment 2). Interactions between estrogens and progestogens effect were tested by using a multiplicative OR model. Stratified analyses were done to investigate the impact of estrogen dose and duration of treatment on the main findings. Statistical analyses were performed with SAS statistical software (version 8.2, SAS Institute Inc, Cary, NC).

P.-Y.S. had full access to and takes full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

General characteristics of cases and controls are given in Table 1. As expected, the mean age of cases and controls was similar. Mean body mass index and age at menopause were significantly higher among cases than controls. Cases were more likely than controls to have reported familial history of VTE and varicose veins. No significant differences in current smoking, education level, type of menopause, and hysterectomy were found between cases and controls. There was no association between past use of estrogen and VTE risk (OR, 1.1; 95% CI, 0.6 to 1.7). In addition, because recency of treatment was not associated with VTE risk, past users and never users were pooled as nonusers.

Overall, 26.0% of cases and 29.9% of controls used transdermal estrogen therapy (OR, 0.9; 95% CI, 0.4 to 2.1), and 17.4% of cases and 6.5% of controls were treated by oral estrogen therapy (OR, 4.0; 95% CI, 1.4 to 11.4) (Table 2). Adjustment for potential confounding factors made little changes to the results. Most current users of estrogen therapy received 17 β -estradiol. No controls and only 2 cases used conjugated equine estrogens. The most common dose for transdermal estrogen use was \leq 50 μ g/d. Approximately 15% of transdermal estrogen users received preparations delivering >50 μ g/d. In current users of oral estrogen therapy, the mean dose of estradiol was 1.5 mg/d, ranging from 0.5 to 2 mg daily.

Table 2 gives the VTE OR associated with the types of progestogen after exclusion of 12 cases and 7 controls who used oral estrogen combined with nortestosterone derivatives (OR, 6.7; 95% CI, 2.1 to 21.9). There was no significant interaction between estrogens by route of administration and progestogens.

TABLE 1. Characteristics of Cases and Controls

Variables	Cases (n=271)	Controls (n=610)	P*
Age, y	61.6±6.7	61.5±6.6	0.33
Body mass index,† kg/m ²	27.0±5.7	24.5±4.8	<0.0001
Obesity (body mass index >30 kg/m ²),† n (%)	56 (20.7)	75 (12.3)	0.001
Familial history of VTE, n (%)	83 (30.6)	125 (20.5)	0.0019
Personal history of varicose veins, n (%)	149 (55.8)	273 (44.8)	0.0014
Current smokers,‡ n (%)	33 (12.4)	78 (12.8)	0.773
Education level beyond secondary, n (%)	44 (17.1)	119 (19.8)	0.385
Age at menopause,§ y	49.6±4.6	48.6±5.1	0.004
Hysterectomy, n (%)	42 (17.1)	113 (19.2)	0.6302
Type of menopause, n (%)			0.6074
Natural	203 (82.5)	474 (80.6)	
Surgical	43 (17.5)	114 (19.4)	
Estrogen therapy use,¶ n (%)			<0.0001
Never use	106 (39.3)	286 (46.9)	
Past use	40 (14.8)	98 (16.1)	
Current use of transdermal estrogen	67 (24.8)	180 (29.5)	
Current use of oral estrogen	57 (21.1)	46 (7.5)	

Data are mean±SD when appropriate.

*Probability values are derived from conditional logistic regression.

†Data for 1 case and 1 control are missing.

‡Data for 4 cases are missing.

§Data for 22 cases and 19 controls are missing.

||Data for 25 cases and 22 controls are missing.

¶Data for 1 case are missing.

Overall, only 5.4% of cases and 6.7% of controls were treated by estrogen alone. Micronized progesterone was used by 7.4% of cases and 10.4% of controls (OR, 0.7; 95% CI, 0.3 to 2.0). Mean dose of micronized progesterone was 100 mg/d. Pregnanes were used by 15.1% of cases and 13.1% of controls (OR, 0.9; 95% CI, 0.4 to 2.4). Pregnane derivatives included dydrogesterone, medrogestone, chlormadinone acetate, cyproterone acetate, and medroxyprogesterone acetate. Finally, norpregnane derivatives, either nomegestrol acetate or promegestone, were used by

15.5% of cases and 6.1% of controls. Twenty-two cases received nomegestrol acetate; 18 received promegestone. The usual daily dose of nomegestrol acetate was 5 mg and of promegestone was 0.250 mg. The risk of VTE increased significantly (>3 times) among users of norpregnane derivatives compared with nonusers (OR, 3.9; 95% CI, 1.5 to 10.2). In addition, ORs of VTE in current users of nomegestrol acetate and current users of promegestone were similar and significantly differed from 1 (data not shown).

TABLE 2. Impact of Hormone Therapy on VTE Risk by Route of Estrogen Administration and Type of Progestogens

	Cases (n=259)	Controls (n=603)	Matched OR (95% CI)		
			Crude	Adjustment 1	Adjustment 2
Nonuse	146	384	1	1	1
Oral estrogen use	45	39	3.6 (1.5–8.8)	4.0 (1.6–10.1)	4.2 (1.5–11.6)
Transdermal estrogen use	67	180	0.8 (0.4–1.6)	0.8 (0.4–1.8)	0.9 (0.4–2.1)
No progestogens	14	40
Micronized progesterone	19	63	1.0 (0.4–2.3)	0.9 (0.4–2.2)	0.7 (0.3–1.9)
Pregnane derivatives	39	79	1.0 (0.4–2.3)	0.9 (0.4–2.2)	0.9 (0.4–2.3)
Norpregnane derivatives	40*	37†	3.8 (1.6–8.7)	4.0 (1.7–9.4)	3.9 (1.5–10.0)

Users of oral estrogen combined with nortestosterone derivatives (12 cases, 7 controls) were excluded (OR, 6.7; 95% CI, 2.1 to 21.9 vs nonusers). Estrogen-by-progestogen interaction terms were not significant. Adjustment 1: adjustment for obesity status, familial history of VTE, and history of varicose veins. Adjustment 2: adjustment for obesity status, familial history of VTE, history of varicose veins, education, age at menopause, hysterectomy, and cigarette smoking.

*Twenty-two cases received nomegestrol acetate, and 18 cases received promegestone.

†Nineteen controls received nomegestrol acetate, and 18 controls received promegestone.

To ensure that our findings were not influenced by estrogen dose and time of hormone exposure, stratified analyses were done. Using the median of the distribution of exposure time (5 years) as a cutoff point, we obtained consistent results in the corresponding subgroups. When the analysis was restricted to women using the more common doses of estrogens ($\leq 50 \mu\text{g/d}$ for transdermal estrogen and $\leq 1.5 \text{ mg/d}$ for oral estrogen), risk estimates were similar to those observed in the whole population.

With regard to the potential determinants of the route of estrogen administration and type of progestogens, transdermal estrogen users were older and used estrogen longer than oral estrogen users. There was no significant difference in other characteristics between oral and transdermal estrogen users. No significant correlates of type of progestogens were found, except for the estrogen dose. The proportion of women using high- or low-dose estrogen was lower in the pregnane subgroup without any change in the mean dosage.

Discussion

Our data confirm that oral but not transdermal estrogen increases VTE risk among postmenopausal women. In addition, these data show that micronized progesterone and pregnane derivatives may be safe with respect to thrombotic risk. Furthermore, our results suggest that norpregnane derivatives are thrombogenic.

Progestagen is added to estrogen therapy among postmenopausal women with an intact uterus to prevent the elevated risk of estrogen-induced endometrial hyperplasia and adenocarcinoma. Unlike medical practices in the United States where medroxyprogesterone acetate is the almost exclusively prescribed progestogen among postmenopausal women, a wide variety of progestogens is used in European countries, especially in France. Progestogens include both progesterone and synthetic progestins derived from progesterone (pregnanes and 19-norpregnanes) or from testosterone (19-nortestosterones). Progestins have different pharmacological properties depending on the parent molecule from which they are derived. Very small structural changes in the parent molecule may induce considerable differences in the progestin activity.¹⁹ The effects of progestins are related to interactions not only with progesterone receptors but also with other steroid hormone receptors. Norpregnane derivatives, including nomegestrol acetate and promegestone, appear to have a very high progestational activity, and unlike nortestosterone derivatives, they do not possess androgenic, estrogenic, or glucocorticoid activity.²⁰ Norpregnane derivatives bind almost exclusively to the progesterone receptor and do not interfere with the other steroid receptors. Their affinity for the progesterone receptor is higher than the progesterone one. In addition, these progestins have both antiestrogenic and antigonadotropic actions.^{21,22} Therefore, in some countries, including France, norpregnane derivatives often are used in premenopausal women with hyperestrogenic symptoms such as mastodynia and/or benign breast disease, as well as in hormone-treated postmenopausal women with intolerance to exogenous estrogen.^{21,23}

Data on the impact of progestogens by the route of estrogen administration on VTE risk among postmenopausal women are scarce. Previous studies reported estimates of VTE risk among users of transdermal estrogen,^{4,8,10} but the results were based on

a few cases who used transdermal estrogen, and each study was inconclusive. Pooling all these data, along with the results of the ESTHER study, gives an overall VTE risk close to 1 (OR, 1.1; 95% CI, 0.7 to 1.9) among current users of transdermal estrogen compared with nonusers.²⁴ With regard to the impact of progestogens, Smith et al¹² have compared the VTE risk among users of different estrogen types with or without progestogen and among nonusers. The results have shown that concomitant progestogen use was associated with an increased VTE risk compared with the use of estrogen alone. However, women received oral estrogen alone or combined exclusively with medroxyprogesterone acetate, and none used transdermal estrogen. Recently, Douketis et al¹³ have studied the differential VTE risk in users of opposed estrogen by route of estrogen administration and in users of oral estrogen alone. Data showed that the VTE risk was higher in users of opposed oral estrogen than in users of oral estrogen alone. However, the OR of VTE in relation to transdermal estrogen was not assessed. In both WHI trials, the VTE risk was studied in relation to opposed estrogen and to estrogen alone.^{1,15} Despite differences in the general characteristics of women included in these 2 trials, the results suggest that the use of opposed estrogen results in a higher VTE risk than the use of estrogen alone. In our study, the VTE risk estimates associated with oral estrogen are higher than those observed in these trials. However, VTE cases with predisposing factors were excluded in the ESTHER study, and only idiopathic events were assessed. In contrast, secondary VTE was analyzed in the WHI trials, and ORs for procedure-related events were lower. In addition, compliance to hormone therapy was not optimal in WHI trials, and this might have led to a substantial underestimation of the true effect of oral estrogen on VTE risk.

Progestogens are also prescribed to premenopausal women for their antigonadotrophic activity. Some data on the impact of contraceptive progestogens on VTE risk have been published.²⁵⁻²⁷ In these studies, women who received either cyproterone acetate or nortestosterone had an elevated VTE risk. However, these results are not relevant to norpregnane derivatives.

The mechanisms underlying the increased VTE risk among users of oral estrogen or transdermal estrogen combined with norpregnane derivatives include a prothrombotic state, a decreased blood flow, and/or an alteration in the vessel wall.²⁸ Few data on the effect of progestogens by route of estrogen administration on hemostatic variables have been reported. However, we have previously reported that transdermal estrogen combined with micronized progesterone had little or no effect on blood coagulation activation as shown by the absence of significant variation in plasma concentration of prothrombin fragment 1+2.²⁹ In addition, 2 randomized controlled trials have shown that oral but not transdermal estrogen, both combined with micronized progesterone, induced an activated protein C resistance.^{30,31} Thus, hemostatic data, together with the results of the ESTHER study, suggest that transdermal estrogen combined with micronized progesterone is safe with respect to VTE risk. Similarly, recent data showing that chlormadinone acetate, a pregnane derivative, has little or no effect on blood coagulation and fibrinolysis³² are consistent with the absence of increased VTE risk among postmenopausal women using transdermal estrogen combined with pregnane derivatives. With regard to the

norpregnane derivatives, one randomized trial failed to show any changes in hemostatic variables among women receiving oral estrogen combined with norgestrel acetate.³³ Among women recruited from the Project Aging Women, van Baal et al³⁴ and Post et al³⁵ have studied the effect of trimegestone (a norpregnane derivative), dydrogesterone, or both combined with oral estrogen therapy on hemostatic variables. Deleterious effects of oral estrogen therapy on coagulation without significant differences between all progestogen subgroups were found. These results are consistent with our clinical findings about oral estrogen use but are not relevant to transdermal estrogen therapy. Thus, whether norpregnane derivatives have prothrombotic effects among postmenopausal women requires further investigation.

Elevated VTE risk among postmenopausal women using some hormone regimens also could be mediated through changes in venous structure and function.²⁸ The occurrence of venous stasis during luteal phase or pregnancy, together with the presence of estrogen and progesterone receptors in the venous wall,³⁶ suggests that venous blood flow may be directly modulated by steroid hormones. Therefore, norpregnane derivatives, which have a high progestational activity, might increase the VTE risk through venous stasis via a progesterone receptor-mediated pathway. The role of progestogens in the alteration of vessels blood flow and in the development of varicose veins warrants further study.³⁶

One potential limitation of our study is that observational studies are subject to bias. The validity of the ESTHER study has been discussed.^{11,16} To minimize the effects of bias on interpretation, both cases and controls were recruited using a number of selection criteria.³⁷ Elevated levels of VTE risk factors, including age, obesity, familial history of VTE, varicose veins, and prothrombotic mutations,¹⁶ could explain our findings related to the route of estrogen administration and progestogens. However, the proportion of women at high risk for VTE was similar across all the estrogen and progestogen subgroups. In addition, adjustment for these potential confounders and other relevant covariates³⁸ made few changes to the results. On the other hand, stratified analyses by characteristics of hormone therapy, including estrogen dose and duration of treatment,³⁸ showed consistent results. Another selection bias could be related to the differential prescription of progestogens according to the estrogen status of women using hormone therapy. Norpregnane derivatives are more likely to be prescribed to women with hyperestrogenic symptoms. Because there is evidence that lifetime estrogen exposure is positively related to VTE risk in postmenopausal women,³⁹ such prescription bias could explain in part the high VTE risk among women using transdermal estrogen combined with norpregnane derivatives. Another limitation of our study is related to the small number of subjects within progestogen subgroups, especially among users of oral estrogen. Among transdermal estrogen users, the upper 95% confidence bounds for the adjusted odds ratios show that the data only rule out increases in the odds ratios of VTE >80%, 20%, and 60% for estrogen alone, estrogen combined with micronized progesterone, and estrogen combined with pregnane derivatives, respectively.

In the WHI trials, pulmonary embolism accounts for about one third of the excess incidence of potentially fatal events

resulting from oral estrogen.³ Therefore, our findings may be of great clinical relevance in minimizing the VTE risk among women who require hormone therapy. Our data emphasize the importance of the route of estrogen administration and the choice of progestogen in determining of the benefit-to-risk profile of hormone therapy. The effect of transdermal estrogen combined with different progestogen types on health outcomes should be investigated in randomized trials.

Acknowledgments

Clinical centers: Département de Médecine Interne, Hôpital de la Cavale Blanche, Brest (E. Oger, D. Mottier); Service d'Exploration Fonctionnelle, Centre Hospitalier de Caen (M.T. Barrellier); Unité Hémostase-Thrombose, Hôtel-Dieu, Paris (J. Conard, G. Plu-Bureau); Service de Médecine Interne et Médecine Générale, Service d'Hématologie Biologique, Centre Hospitalier et Universitaire de Nancy (D. Wahl, T. Lecomte, E. de Maistre, M.C. Laprevote-Heully); Département de Pneumologie, Hôpital Européen Georges Pompidou, Paris (G. Meyer, M.T. Guillauneuf); Laboratoire d'Hématologie, Hôpital Cardiologique, Département de Médecine Interne, Centre Hospitalier de Rouen (H. Lévesque, N. Cailleux); and Département de Médecine Vasculaire, Hôpital Purpan, Toulouse (P. Léger, A. Elias). Coordinating center: Inserm U780 (E. Oger, G. Plu-Bureau, L. Carcaillon, M. Canonico, and P.Y. Scarabin).

Sources of Funding

The study was supported by the Fondation de France, by the Fondation pour la Recherche Médicale and Institut National de la Santé et de la Recherche Médicale (Inserm), and by grants from Aventis, Besins International, Sanofi, and Servier Institute.

Disclosures

None.

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CLINICAL PERSPECTIVE

Since the results of the Women's Health Initiative trials, hormone therapy use dramatically decreased among postmenopausal women. However, many women remain eligible for this treatment. Venous thromboembolism is a serious side effect of hormone therapy, and pulmonary embolism accounts for about one third of the excess incidence of potentially fatal events resulting from hormone therapy. So far, most studies assessing the effect of hormone therapy on clinical outcomes have been done in women using preferentially oral estrogen, alone or combined with medroxyprogesterone acetate. In European countries, many women use transdermal estrogen, alone or combined with a large variety of progestogens. The Estrogen and Thromboembolism Risk study, a French case–control study, was the first to provide evidence for a differential association of oral and transdermal estrogen with venous thromboembolism risk. Final analysis of this study confirms that oral but not transdermal estrogen increases venous thromboembolism risk. In addition, these data suggest that norepregnane derivatives may be thrombogenic, whereas micronized progesterone and pregnane derivatives appear safe with respect to thrombotic risk. Although these findings have to be confirmed by randomized clinical trials, they suggest that the route of estrogen administration and the type of progestogen may be important determinants of the benefit-to-risk profile of hormone therapy, especially in women at high venous thromboembolism risk.