

Differential association of oral and transdermal oestrogen-replacement therapy with venous thromboembolism risk

Pierre-Yves Scarabin, Emmanuel Oger, Geneviève Plu-Bureau, on behalf of the EStrogen and THromboEmbolism Risk (ESTHER) Study Group

Summary

Background Oral oestrogen-replacement therapy (ERT) activates blood coagulation and increases the risk of venous thromboembolism (VTE) in postmenopausal women. Transdermal ERT has little effect on haemostasis, but data assessing its effect on thrombotic processes are scarce. We aimed to examine the effect of the route of oestrogen administration on VTE risk.

Methods We did a multicentre hospital-based case-control study of postmenopausal women in France. During 1999–2002, we recruited 155 consecutive cases with a first documented episode of idiopathic VTE (92 with pulmonary embolisms and 63 with deep venous thrombosis), and 381 controls matched for centre, age, and time of recruitment.

Findings Overall, 32 (21%) cases and 27 (7%) controls were current users of oral ERT, whereas 30 (19%) cases and 93 (24%) controls were current users of transdermal ERT. After adjustment for potential confounding variables, the odds ratio for VTE in current users of oral and transdermal ERT compared with non-users was 3.5 (95% CI 1.8–6.8) and 0.9 (0.5–1.6), respectively. Estimated risk for VTE in current users of oral ERT compared with transdermal ERT users was 4.0 (1.9–8.3).

Interpretation Oral but not transdermal ERT is associated with risk of VTE in postmenopausal women. These data suggest that transdermal ERT might be safer than oral ERT with respect to thrombotic risk.

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INSERM Cardiovascular Epidemiology Unit U258, Villejuif, France (Pierre-Yves Scarabin MD, Geneviève Plu-Bureau MD), and **Department of Internal Medicine, Hôpital de la Cavale Blanche, Brest** (Emmanuel Oger MD)

Correspondence to: Dr Pierre-Yves Scarabin, INSERM Cardiovascular and Metabolic Epidemiology U258, Avenue Paul Vaillant Couturier 94807 Villejuif Cedex, France (e-mail: scarabin@vjf.inserm.fr)

Introduction

Postmenopausal women are often prescribed oestrogen-replacement therapy (ERT) to treat menopausal symptoms and to prevent osteoporosis. Harmful effects of ERT include breast cancer¹ and VTE. ERT might also increase the risk of coronary heart disease and stroke.¹

Despite evidence that oral oestrogen activates blood coagulation in postmenopausal women² and might be thrombogenic,³ ERT has long been believed to have little effect on the risk of VTE.⁴ Early studies of VTE risk in ERT users provided inconclusive results.⁴ However, results of recent observational studies showed consistent associations between current use of ERT and increased risk of VTE in postmenopausal women.^{5–10} These findings have been confirmed by randomised clinical trials.¹¹

Most previous studies of VTE risk in ERT users were done in women using oral oestrogen.¹² Transdermal oestrogen is widely used in European countries, especially in France, and has little or no effect on haemostasis.¹³ Clinical data assessing the effect of transdermal ERT on thrombotic processes are scarce. Therefore, we did a case-control study to investigate the effect of the route of oestrogen administration on VTE risk.

Methods

Selection and ascertainment of cases and controls

During 1999–2002, we recruited 155 consecutive cases with a first documented episode of idiopathic VTE at seven teaching hospitals in France. Eligible cases were postmenopausal women aged 45–70 years and living in the vicinity of the recruiting hospitals. Women were excluded if they reported a previous episode of VTE; had a contraindication for ERT (history of breast cancer, VTE, valvular cardiopathy, coronary heart disease, or stroke); or had a predisposing factor for VTE (history within the previous month of surgical intervention, trauma with immobilisation for longer than 8 days, illness necessitating bed rest for longer than 8 days, known cancer, systemic inflammatory disease).¹⁴

Women diagnosed with pulmonary embolism (n=92) were included if they had one of the following: high probability ventilation or perfusion scan according to criteria from the Prospective Investigation of Pulmonary Embolism Diagnosis,¹⁵ helicoidal CT scan showing a clot in one of the pulmonary arteries, or pulmonary angiography showing a clot. Women with the diagnosis of deep venous thrombosis alone, either proximal (popliteal, femoral, or iliac veins) (n=47) or distal (calf veins) (n=16), were included if they had positive ultrasonography. Cases were identified, without knowledge of ERT exposure, through daily screening of all relevant wards. Within each centre, medical data were reviewed by a senior clinician with a special interest in thromboembolism.

381 hospital controls (one to three controls for each case) were recruited during the same period. Cases and

	Cases (n=155)	Controls (n=381)	p
Age (years)	62.1 (6.8)	62.0 (6.8)	0.18
Body-mass index (kg/m ²)	26.4 (5.3)	24.5 (5.1)	0.0003
Body-mass index >30 kg/m ² ,	29 (18.7%)	50 (13.1%)	0.09
Family history of VTE	41 (26.5%)	71 (18.6%)	0.05
Current smokers	17 (11.0%)	49 (12.9%)	0.52
Educational level beyond secondary*	30 (19.4%)	62 (16.3%)	0.42
Personal history			
Hypertension	25 (16.1%)	47 (12.3%)	0.24
Diabetes mellitus	2 (1.3%)	26 (6.8%)	0.01
Varicose veins	85 (54.8%)	167 (43.8%)	0.02
At least one risk factor†	44 (28.4%)	99 (26.0%)	0.80

Data are number (%) or mean (SD). *Data for one case missing. †Hypertension, obesity, or diabetes.

Table 1: Characteristics of cases with VTE and controls

controls were matched by centre, 2-year age band, date of admission, and area of residence. Cases with high blood pressure, obesity, or diabetes were also matched to controls with one of these vascular risk factors. Controls had to have been admitted with a diagnosis judged to have no association with ERT, including diseases of the eye, ear, skin, respiratory and alimentary tracts, bones and joints, kidneys; infectious diseases; and diabetes. Controls were identified without knowledge of ERT exposure by screening selected patients in wards at random. Controls were subject to the same exclusion criteria as were cases.

Assessment of ERT status

Cases and controls were interviewed in a standard way with the same questionnaire. Few women (less than 1%) refused participation. Two cases died before interview. The protocol was approved by INSERM and the local ethics committee. Written and informed consent was obtained from all women. While in hospital, participants were interviewed by specially trained research assistants. Identification of hormone type was assisted by showing pictures of available ERT and progestagen packets. Questionnaire included details of type, dose, and duration of oestrogen use, as well as information on progestagens.

Menopause was defined by amenorrhoea for more than 12 months, bilateral ovariectomy, or hysterectomy and age older than 52 years. Women were classified as current users if they had used ERT at any time in the past 3 months before the admission date. Hypertension was defined as self-reported systolic pressure greater than 140 mm Hg, diastolic pressure more than 90 mm Hg, or use of antihypertensives. Diabetes mellitus was defined as a self-reported history of physician-diagnosed diabetes, or use of antidiabetics, or both; varicose veins were defined as a self-reported history of varicose veins or stripping; and obesity as body-mass index greater than 30 kg/m². Women were classified as current smokers if they had smoked during the 3 months before admission. They were judged at high risk if they had obesity, hypertension, or diabetes.

	n	Ever use of ERT*	Current use of ERT	Current oral ERT	Current transdermal ERT
Cases	155	84 (54%)	62 (40%)	32 (21%)	30 (19%)
Control diagnostic group					
Alimentary tract diseases	86	43 (50%)	26 (30%)	4 (5%)	22 (26%)
Respiratory diseases	88	36 (41%)	26 (30%)	6 (7%)	20 (23%)
Bone and joint disorders	79	32 (41%)	23 (29%)	7 (9%)	16 (20%)
Eye and ear diseases	37	15 (41%)	11 (30%)	1 (3%)	10 (27%)
Other diseases†	91	47 (52%)	34 (37%)	9 (10%)	25 (28%)
All controls	381	173 (45%)	120 (32%)	27 (7%)	93 (24%)

Data are numbers (%). *Ever use includes past and current use. †Renal diseases, infectious diseases, diabetes, and ill defined causes of morbidity.

Table 2: ERT use in cases and control diagnostic groups

Statistical analysis

We did conditional logistic regression analyses of matched data. Body-mass index, family history of VTE, history of varicose veins, and education level were considered a priori as potential confounding variables. and they were included in a multivariate analysis.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Table 1 shows the characteristics of the study population. Mean body-mass index was higher in cases than in controls. Cases were more likely than controls to have reported family history of VTE and history of varicose veins. 24 diabetic controls were matched to cases with either hypertension or obesity and, therefore, a higher proportion of controls than cases reported diabetes. However, the proportion of women at high risk was similar among cases and controls (28% and 26%, respectively).

Overall, about a fifth of cases and under 10% of controls were current users of oral ERT, and about a fifth of cases and a quarter of controls were current users of transdermal ERT (table 2). There was no association between past use of ERT and VTE risk. Odds ratios for VTE were increased in current users of oral but not transdermal ERT (table 3), with non-users as a reference. Odds ratio for VTE were also increased in current users of oral ERT compared with transdermal ERT users. Adjustment for potential confounders slightly increased these ratios. Further adjustment for smoking and other risk factors did not change the results.

Analysis by diagnosis of VTE showed that adjusted odds ratios for VTE associated with current use of oral and transdermal ERT were 3.8 (1.6–9.0) and 0.8 (0.4–1.7), respectively, for pulmonary embolism, and 3.2 (1.1–9.5) and 0.9 (0.4–2.4), respectively, for deep venous thrombosis. When analysis was restricted to women with or without cardiovascular risk factors, the prevalence of current use of ERT was significantly lower in controls at high risk than in those at low risk (23% vs 34%, respectively, $p < 0.05$). However, there was no significant change in the proportion of women who used transdermal ERT among current users of ERT (20 [87%] vs 72 [75%], respectively, $p = 0.70$). Adjusted risk estimates for VTE associated with oral and transdermal ERT were 2.9 (1.4–5.8) and 0.9 (0.5–1.7), respectively, in women at low risk (111 cases and 282 controls), and 11.5 (1.8–73.2) and 1.1 (0.3–4.0), respectively, in women at high risk (44 cases and 99 controls).

Table 4 shows estimated odds ratios in relation to characteristics of ERT. Most current users of ERT received 17 β -oestradiol. No controls and only two cases

	Cases (n=155)	Controls (n=381)	Matched odds ratio (95% CI)	
			Non-adjusted	Adjusted*
Relative to never-users				
Never use	71	208	1.0	1.0
Past use	22	53	1.3 (0.8–2.5)	1.3 (0.8–2.5)
Current oral ERT use	32	27	3.7 (1.9–7.1)	3.9 (2.0–7.6)
Current transdermal ERT use	30	93	1.0 (0.5–1.7)	1.0 (0.5–1.7)
Relative to non-users†				
Non-use	93	261	1.0	1.0
Current oral ERT use	32	27	3.4 (1.8–6.4)	3.5 (1.8–6.8)
Current transdermal ERT use	30	93	0.9 (0.5–1.5)	0.9 (0.5–1.6)
Relative to current users of transdermal ERT				
Current transdermal ERT use	30	93	1.0	1.0
Current oral ERT use	32	27	3.9 (2.0–7.7)	4.0 (1.9–8.3)

*Adjusted for body-mass index, familial history of VTE, history of varicose veins, and educational level. †Non-users include never and past users.

Table 3: Odds ratio of VTE in relation to ERT use

used conjugated equine oestrogens. Transdermal oestrogen was given in the form of gel or patch (69 [56%] vs 54 [44%] of current users, respectively). Most current users of transdermal ERT (81 [66%]) received preparations delivering 50 µg per day or less. Only seven (6%) of transdermal ERT users received preparations delivering 100 µg per day or more. In current users of oral ERT, the mean dose of oestradiol was 1.5 mg per day, ranging from 0.5 mg to 2 mg daily. There was some evidence that the logarithms of odds ratios decreased

	Cases (n=155)	Controls (n=381)	Matched odds ratio (95% CI)	
			Non-adjusted	Adjusted*
Non-users	93	261	1.0	1.0
Duration of oral ERT (months)				
1–12	5	1	10.1 (1.1–91.7)	8.1 (0.9–74.4)
13–30	8	5	5.7 (1.4–23.3)	5.0 (1.2–20.4)
31–48	8	5	5.0 (1.4–17.9)	4.0 (1.1–14.7)
>48	11	16	2.0 (0.8–4.7)†	2.5 (1.0–6.3)‡
Duration of transdermal ERT (months)				
1–12	3	7	1.9 (0.4–8.7)	1.5 (0.3–6.9)
13–30	5	17	0.6 (0.2–1.8)	0.6 (0.2–1.9)
31–48	4	13	1.0 (0.3–3.3)	1.3 (0.4–4.3)
>48	18	56	0.9 (0.5–1.7)	0.9 (0.4–1.7)
Dose of oral ERT§				
Low-dose oestrogen	12	9	4.8 (1.7–13.8)	4.3 (1.5–12.4)
High-dose oestrogen	19	18	2.9 (1.4–6.1)	3.1 (1.4–6.5)
Unknown dose	1	0
Dose of transdermal ERT¶				
Low-dose oestrogen	17	47	1.0 (0.5–1.9)	1.2 (0.6–2.2)
High-dose oestrogen	10	38	0.8 (0.4–1.7)	0.7 (0.3–1.5)
Unknown dose	3	8	0.8 (0.2–3.2)	0.9 (0.2–3.9)
Oral ERT regimen				
Oestrogen only	1	2	1.3 (0.1–18.8)	1.5 (0.1–23.3)
Oestrogen plus progestagen	31	25	3.5 (1.9–6.8)	3.6 (1.9–7.0)
Transdermal ERT regimen				
Oestrogen only	5	13	0.8 (0.3–2.5)	1.0 (0.3–3.3)
Oestrogen plus progestagen	25	80	0.9 (0.5–1.6)	0.9 (0.5–1.6)

*Adjusted for obesity, familial history of VTE, history of varicose vein, and educational level. Test for linear trend †p=0.04. ‡p=0.07. §Low-dose preparation containing 0.625 mg conjugated equine oestrogens, 1 mg oestradiol or 1 mg oestradiol valerate; high-dose preparation containing 1.25 mg conjugated equine oestrogens, or 1.5 mg and 2 mg oestradiol or 2 mg oestradiol valerate. ¶Low-dose preparations delivering less than 50 µg oestradiol per 24 h; high-dose preparations delivering 50 µg and 100 µg oestradiol per 24 h.

Table 4: Odds ratio of VTE by duration of current episode of use, oestrogen dose, and ERT regimen

linearly with the duration of current oral ERT use (p=0.04 for the unadjusted likelihood ratio test). Risk did not change with time in current users of transdermal ERT. Estimated risks were not related to the dose of oestrogen among current users of oral and transdermal ERT. There was no difference in VTE risk between unopposed oestrogen and combined oestrogen-progestagen.

Discussion

Our data show an increased risk of VTE in current users of oral ERT compared with non-users. Current users of oral ERT seem to be at higher risk of VTE than users of transdermal ERT. There was no association between VTE risk and use of transdermal ERT.

Our results for current users of oral ERT are consistent with previous data. Observational studies reported a greatly increased risk of VTE in current users of oral ERT.⁴ This finding is in accord with those in recent randomised trials,¹¹ and quantitative assessments of these studies gave pooled risks of VTE ranging from 2 to 3.^{11,12} Our odds ratios of VTE associated with use of oral ERT were somewhat higher than those previously reported. In our study, all diagnoses of deep venous thrombosis and pulmonary embolism required confirmation by imaging methods, and assessment of ERT exposure was rigorous. Therefore, misclassification should have been rare, and risk estimates might be more valid than in previous investigations. We noted that VTE risk was highest in the first year of oral ERT, which is consistent with previous data.^{4,12}

In most previous studies, workers investigated the risk of VTE in postmenopausal women who used conjugated equine oestrogen. Investigators in two case-control studies^{6,8} reported no difference in VTE risk between users of oral and transdermal ERT. However, these results were based on five and seven cases of VTE who used transdermal ERT.^{6,8} Others have assessed the risk of VTE in women who predominantly used transdermal ERT, but the odds ratios were based on only six cases who used ERT, and results by route of ERT administration were not shown.⁹

Conjugated equine extracts and 17β-oestradiol are the two most widely used forms of oestrogen in postmenopausal women. Oestrogens are usually given orally, but such a delivery route has drawbacks, including intestinal and hepatic first-pass effects.¹⁶ Oral, but not transdermal, oestrogen administration leads to high hormone concentrations in the liver and promotes hepatic protein synthesis.¹⁶ Data for the pharmacokinetics of oral and transdermal oestradiol showed dose-dependent increase in serum oestradiol exposure.^{17,18} However, oral ERT results in a substantial increase in plasma oestrone concentration leading to non-physiological ratio of oestrone to oestradiol close to 5.¹⁸ By contrast, transdermal ERT leads to plasma oestrone to oestradiol ratios close to 1, which is similar to that in menstruating women.^{16–18} In our investigation, transdermal oestradiol delivering 50 µg per day and oral oestradiol 1.5 mg were the most common preparations, and led to similar expected ranges of plasma oestradiol concentrations.^{17–18} However, a large within-person and between-person variation in plasma oestradiol has been consistently reported in ERT users,^{13,16,18} and whether this variation is relevant to clinical outcomes warrants further investigations.

Biological evidence lends support to the difference in VTE risk between oral and transdermal ERT. Oral, not transdermal, ERT increases plasma concentrations of prothrombin fragment 1+2,¹³ which is a marker for in-vivo

thrombin generation, and increases the fibrinolytic potential in postmenopausal women.^{13,19} A lower antithrombin concentration has also been shown in women on oral but not transdermal ERT.²⁰ Furthermore, an acquired resistance to activated protein C has been noted in users of oral ERT,²¹ but a randomised trial recently indicated that these results did not apply to users of transdermal ERT.²² Thus, oral ERT might impair the balance between procoagulant factors and antithrombotic mechanisms, whereas transdermal ERT seems to have little or no effect on haemostasis.

A meta-analysis of the main findings from randomised trials on the long-term effects of oral ERT showed that pulmonary embolism accounted for an excess of about a third of potentially fatal events in healthy postmenopausal women using ERT over 5 years.¹¹ Therefore, use of transdermal ERT could substantially improve the risk-benefit profile among ERT users. The clinical relevance of our findings might be even more important for women at high risk of VTE who need short-term ERT for severe menopausal symptoms.

One potential limitation of our study is that observational studies are subject to bias. Preferential referral and diagnosis of exposed cases as well as recall bias can occur in case-control studies. However, such selection bias would have to have occurred differentially according to the route of oestrogen administration to affect the comparison between oral and transdermal ERT users. Women with recurrent thromboembolism were excluded since a previous episode of VTE would contraindicate ERT. Similarly, predisposing factors for VTE could determine ERT use or dilute any oestrogen-induced effect, and, therefore, such cases were excluded.¹⁴

Bias could also have arisen in selection of controls. We used hospital controls with a range of pre-defined diagnoses because they provide information in a similar way and have similar access to hospital as the cases. Analysis of the prevalence of ERT use, according to diagnosis on admission for hospital controls, showed no systematic differences between groups. Additionally, the prevalence of ERT use in controls in our investigation was close to that in healthy women attending for breast screening in France during a similar period.²³ Furthermore, the proportion of women on ERT who used transdermal oestrogens was consistent with present French practices.²⁴

Differential prescription of oral or transdermal ERT according to known risk factors for VTE or arterial disease could confound the associations between ERT use and VTE. However, we excluded women with personal history of VTE or predisposing factors for VTE, and adjustment for multiple risk factors did not change the results. Additionally, similar results were noted in women with or without cardiovascular risk factors. Furthermore, the effect of such prescription bias would be to increase the estimated risk of VTE associated with transdermal ERT use.

We did not detect correlates of the route of oestrogen administration in ERT users. More women using transdermal ERT were in cardiovascular high-risk groups, but this finding was not significant. We now need to assess the determinants of transdermal ERT use. Thus, oral but not transdermal ERT is associated with risk of VTE among postmenopausal women. This pattern of association is biologically plausible. Our finding could be important in assessment of the risk-benefit profile of ERT. The effects of transdermal ERT on health outcomes should be assessed in randomised trials.

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Coordinating centre—INSERM U258 (G Plu-Bureau, E Oger, MT Guillauneuf, S Guillonnet, and PY Scarabin).

Contributors

P Y Scarabin was the principal investigator and took the lead role in writing the report. E Oger wrote the protocol. All authors contributed to study design, data collection, analysis and interpretation of data, and writing of the manuscript.

Conflict of interest statement

None declared.

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Uses of error

Expect the unexpected—twice!

John Bache, Paul Knowles

Our flying squad was called out to a road traffic collision involving two cars and a lorry. One car driver, a 49-year-old male, was initially trapped in his car, but was freed within 5 min. At the scene, his injuries appeared to be confined to the limbs. He was fully alert with a Glasgow coma scale score of 15. He was rapidly transported to hospital. There were major open fractures of the right femur and the left tibia and fibula and these fractures were thought to be limb-threatening. There was also an open fracture of the right ulna with displacement of the radial head. He informed us that he was normally fit and well and was not taking any medication.

He was transfused with crystalloid until cross-matched blood was available. He remained haemodynamically stable and his vital signs were well maintained. His oxygen saturation was 100% on high flow oxygen via a face mask. While being measured for a Thomas's splint prior to log rolling, he suddenly had a grand mal fit.

Following this he went into cardiac arrest (pulseless electrical activity). The carotid and the femoral pulses were absent and no heart sounds were heard at the apex. He was successfully resuscitated and the major pulses reappeared, but again no heart sounds were heard at the apex.

His relatives then arrived and informed us that he suffered from epilepsy but often failed to take his medication, and he was "a mirror baby". A spiral CT scan of the head, chest and abdomen confirmed dextrocardia and situs inversus totalis, but there was no significant injury. He was taken to theatre for internal fixation of his fractures and is now progressing well.

It is always advisable to expect the unexpected. We had assumed that the fit was due to a head injury, as we did not expect a patient with uncontrolled epilepsy to be driving a car. His apex beat was not heard on the left as he had situs inversus totalis.

Accident and Emergency Department (J Bache FRCS, P Knowles FRCS), **Leighton Hospital, Crewe, Cheshire CW1 4QJ, UK**