

Risk of recurrent venous thromboembolism after a first oestrogen-associated episode

Data from the REVERSE cohort study

Grégoire Le Gal^{1,2}; Michael J. Kovacs³; Marc Carrier^{1,4}; Kimberley Do⁴; Susan R. Kahn^{5,6}; Philip S. Wells^{1,4}; David A. Anderson⁷; Isabelle Chagnon⁸; Susan Solymoss⁵; Mark Crowther⁹; Marc Righini¹⁰; Karine Lacut²; Richard H. White¹¹; Linda Vickers¹²; Marc Rodger^{1,4}

¹Thrombosis Program, Division of Hematology, Department of Medicine, University of Ottawa, Ottawa, Ontario, Canada; ²Department of Internal Medicine and Chest Diseases and EA 3878, Brest University Hospital, Brest, France; ³Division of Hematology, Department of Medicine, University of Western Ontario, London, Ontario, Canada; ⁴Clinical Epidemiology Unit, Ottawa Health Research Institute, The Ottawa Hospital, Ottawa, Ontario, Canada; ⁵Department of Medicine, McGill University, Montreal, Canada; ⁶Centre for Clinical Epidemiology and Community Studies, Jewish General Hospital, Montreal, Canada; ⁷Department of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada; ⁸Department of Medicine, Hôpital du Sacré-Coeur de Montréal, University of Montreal, Montreal, Canada; ⁹Department of Medicine, Michael G. DeGroot School of Medicine, McMaster University, Hamilton, Ontario, Canada; ¹⁰Department of Internal Medicine, Geneva University Hospital, Geneva, Switzerland; ¹¹Department of Medicine, UC Davis School of Medicine, Sacramento, California, USA; ¹²Department of Medicine, St. Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada

Summary

The use of exogenous oestrogen in women with otherwise unprovoked venous thromboembolism (VTE) could be considered sufficient explanation to classify VTE as provoked if the risk of recurrent VTE after 3–6 months of anticoagulant treatment is similar to the risk of recurrent VTE observed after a surgery or prolonged immobilisation. Our objective was to assess the risk of recurrent VTE in women after a first unprovoked episode on oestrogen. The REVERSE study is a cohort study of patients with a first unprovoked VTE treated with anticoagulant treatment for 5–7 months. The risk of recurrent VTE during follow-up was compared between women users and non users of oestrogen at the time of index VTE. Among the 646 patients included, 314 were women, of them 67 were cur-

rent users of oestrogen at the time of their VTE: 49 were on oral contraceptives and 18 on post-menopausal hormone replacement therapy (HRT). No significant association was found between oestrogen exposure, either oral contraceptives or HRT, and a lower risk of recurrent VTE after adjustment for age, or analysis restricted to women in the same age range as oestrogen contraceptives and HRT users, respectively. The risk of recurrent VTE is low in women after a first otherwise unprovoked oestrogen-associated VTE. However, this risk is not significantly lower than in women whose VTE was not related to oestrogen use.

Keywords

Venous thromboembolism, recurrence, cohort study, oestrogens

Correspondence to:

Dr. M. Rodger
Division of Hematology
The Ottawa Hospital, General Campus
501 Smyth Rd, Box 201
Ottawa, Ontario, Canada K1H 8L6
Tel.: +1 613 737 8899 ext 74641, Fax: +1 613 739 6102
E-mail: mrodger@ohri.ca

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Introduction

The American College of Chest Physicians Guidelines on Antithrombotic and Thrombolytic Therapy recommend to discontinue anticoagulation therapy after a three month course for provoked venous thromboembolism (VTE) but to consider prolonging the anticoagulation indefinitely for patients with unprovoked

VTE (1). Therefore, classification of a VTE as a provoked or unprovoked event is of utmost importance.

Whether women who develop VTE while on oestrogen therapy should be classified as having “unprovoked” or “provoked” VTE is controversial. Whereas some studies have classified them as unprovoked events (2–5), others consider oestrogen-associated VTE as provoked events (6–8). In fact, the use of exogenous oestrogen

therapy is associated with an increased risk of VTE in women: three- to four- and a two- to three-fold increased risk on oestrogen oral contraceptive or postmenopausal hormone replacement therapy (HRT), respectively (9, 10). Given the risks and consequences of long-term anticoagulation, it is important to determine whether women developing VTE while on oestrogen therapy need to be managed as patients with unprovoked or provoked VTE.

Current etiological concepts describe VTE as a multi-causal disease, in which individuals have a basal thrombosis potential that can rise dramatically and exceed the thrombosis threshold in case of strong precipitants acting on one or more of the Virchow's triad components (11). For example, surgery for leg fracture is associated with a 30–40 fold increase in VTE risk. The thrombosis potential thereafter decreases back to its basal level. Should a thrombosis occur during this high risk period, the risk of subsequent recurrence should be lower in patients with such a strong temporary provoking precipitant than in patients which thrombosis occurred without recent exposure to any provoking precipitant. This has been proven for surgery in which the risk of recurrent VTE is as low as 0% (12). Thus, a practical way to determine if a particular risk factor preceding a VTE allows us classify it as provoked, might be to assess the risk of recurrence in patients whose VTE occurs after exposure to this risk factor.

Therefore, among women included in the REVERSE study – a cohort study designed to derive a clinical decision rule for recurrent VTE in patients who discontinued anticoagulant treatment after 5–7 months for a first unprovoked VTE (13), we assessed the annual risk of recurrent VTE in women on oestrogen therapy at the time of a first otherwise unprovoked VTE, compared with patients with unprovoked VTE.

Material and methods

The REVERSE Study

The REVERSE study was a prospective cohort study designed to derive a clinical decision rule to identify patients at low risk for recurrent VTE after completion of 5–7 months of anticoagulant therapy for a first unprovoked VTE (13). Institutional research ethics board approval was obtained at all participating centers.

Patients

Consecutive unselected patients at 12 tertiary care centers in four countries were asked to participate if they had: i) a first episode of unprovoked objectively proven major VTE 5–7 months prior to enrollment initially treated with >5 days of heparin, followed by 5–7 months of oral anticoagulants (target International Normalised Ratio [INR] 2 to 3); and ii) no recurrent VTE during the treatment period. Objective documentation of proximal deep-vein thrombosis (DVT) required a non-compressible segment on com-

pression leg vein ultrasound imaging in the popliteal vein or a more proximal leg vein. Objectively documented pulmonary embolism (PE) required a high probability V/Q scan or a segmental or larger artery filling defect on computed tomography (CT) scan.

A first unprovoked VTE was defined as VTE occurring in the absence of a leg fracture or lower extremity plaster cast, immobilization for more than three days, or surgery using a general anesthetic in the three months prior to the index VTE event, and without diagnosis of malignancy in the prior five years at the time of enrollment.

Patients were excluded if they were unable or unwilling to consent, were under the age of 18 years, had already discontinued anticoagulant therapy, required ongoing anticoagulation for reasons other than VTE, were geographically inaccessible for follow-up, were being treated for a recurrent unprovoked VTE or a previously known high-risk thrombophilia (defined as known deficiency of protein S, protein C or antithrombin, known persistently positive anticardiolipin antibodies [> 30 U/ml], a known persistently positive lupus anticoagulant, or who had two or more known thrombophilic defects [e.g. homozygous for factor V Leiden or prothrombin gene mutation, or compound heterozygous for factor V Leiden and prothrombin gene mutation]).

After obtaining written informed consent, all patients underwent standardised data collection about demographic characteristics, risk factors for VTE at the time of index event (pregnancy or post-partum period, current medications, history of myocardial infarction, stroke or heart failure, varicose veins, obesity, family history of VTE, history of previous secondary VTE, IVC filter insertion), patient-reported post-thrombotic symptoms, concomitant medications, results of thrombophilia testing, and imaging reports confirming the index VTE. The use of any postmenopausal HRT or oral contraceptives during the year preceding the index VTE was systematically recorded including the medication name and the exact period of use.

All patients then underwent baseline imaging: a) CUS of the leg(s) if the patient had DVT signs or symptoms at the time of the index event, and/or b) V/Q scan if the patient had PE signs or symptoms at the time of index event. After baseline imaging was obtained, patients were instructed to stop their anticoagulant treatment, and to contact study personnel if they developed symptoms of recurrent VTE during follow-up. They were also seen in clinic at least every six months and asked about signs and symptoms of recurrent VTE. A case report form was completed for all suspected recurrent VTE during follow-up. Patients with suspected recurrent VTE underwent a standardised diagnostic strategy based on the comparison of imaging tests with baseline imaging (14). Briefly, recurrent DVT was diagnosed if there was a new non compressible site or if the diameter of a clot had increased by at least 4 mm from a previous measurement. A PE was diagnosed if the V/Q scan showed a new mismatched segmental or greater perfusion defect. All documents related to suspected recurrent VTE (clinical notes, laboratory results and imaging tests) were collected and sent along with the local decision to the coordinating center. All suspected symptomatic VTE events and deaths during follow-up were independently adjudicated by two physicians.

Data analysis

Participants were withdrawn and censored at the time they withdrew consent, were started on anticoagulants for a reason other than VTE or were lost to follow-up. Observation time was defined at the time at risk from the end of the anticoagulant treatment for the index VTE to the first recurrent VTE or withdrawal date. Incidence rates of recurrent VTE were calculated as the number of recurrent VTE over the number of person-years of follow-up. The Cox proportional hazards model was used to compare risks between groups. Several sets of analyses were conducted: 1) univariate analysis comparing users and non users (i.e. men and women) of oestrogen treatment at the time of the index event; 2) stratified analysis: in women, univariate analysis comparing users and non users of oestrogen treatment at the time of the index event, with subgroup analyses for contraceptives and HRT users vs. non oestrogen users; 3) multivariate analysis in women with adjustment on age; 4) comparison of the risk of recurrent VTE in oestrogen users with the risk observed in non users of the same age range, for contraceptives and HRT users, respectively; 5) Finally, we assessed whether or not the clinical decision rule that was derived in the REVERSE study performs similarly in women users and non users of oestrogen therapy at the time of their index VTE. The rule, named "Men continue and HER DOO2", reads as follows. Men, and women with 2 or more of the following are classified as having a high risk of recurrent VTE: 1) Post-thrombotic signs (any Hyperpigmentation, Edema or Redness in either leg); 2) VIDAS® D-dimer level ≥ 250 $\mu\text{g/l}$; 3) Obesity as defined by a body mass index ≥ 30 kg/m^2 ; 4) Older age 65 years or more. All men, and women with two or more of these criteria are classified as having a high risk of recurrent VTE (13).

Results

Between October 2001 and March 2006, we enrolled 665 participants, of them 646 completed at least one follow-up visit. Among these 646 patients, 314 (49%) were women. General characteristics

Table 1: General characteristics of included women.

| Characteristics | n (%), or mean (SD) |
|--|---------------------|
| Age, years | 50 (19.2) |
| Caucasian | 290 (92%) |
| Body mass index, kg/m^2 | 28.8 (7.8) |
| Initial VTE site | |
| ● Isolated PE | 111 (35%) |
| ● Isolated proximal DVT | 145 (46%) |
| ● DVT and PE | 58 (19%) |
| D-dimer ≥ 250 $\mu\text{g/l}$ | 121 (39.8%) |
| Hyperpigmentation, oedema or redness in either leg | 96 (36.9%) |
| n, number; SD, standard deviation. | |

of included women are shown in ► Table 1. During a mean follow-up interval of 24 months (range: 1 to 54), 72/332 men (21.4%), and 30/314 (9.6%) women had an objectively documented symptomatic recurrent VTE. None of the 14 deaths during follow-up were adjudicated as being caused by recurrent VTE. The annual risk of recurrent VTE was higher in men than in women: 12.5% (95% confidence interval [CI] 9.6%-15.4%) vs. 4.7% (95% CI 3.0%-6.4%), respectively; hazard ratio 2.6 (95%CI 1.6 to 3.9).

At the time of the index event, 67 women (21.3%) were on oestrogen therapy: 49 women on an oestrogen-containing oral contraceptive (1,433 person-months of subsequent follow-up) and 18 on an oestrogen-containing HRT (469 person-months of subsequent follow-up). Oestrogen therapy was started less than six months before the index VTE in 15 (31%) and one (6%) women taking oral contraceptive and HRT, respectively. Among oestrogen contraceptive users, the progestin used in combination with the oestrogen was a first-generation progestin in six (12%) (norethindrone or ethynodiol), a second-generation in 15 (31%) (levonorgestrel or norgestrel), a third-generation in 18 (37%) (gestodene, desogestrel or norgestimate), cyproterone acetate in seven (14%), and was not specified in three (6%). Of the 18 oestrogen HRT users, 15 (83%) women were on conjugated equine oestrogens (CEE), one (6%) on 17 beta-estradiol, and the type of oestrogen was not specified in two (11%). All women current oestrogen users at the time of the diagnosis of VTE discontinued this treatment during the six months anticoagulant treatment period, and none restarted OCP or HRT after enrolment in the REVERSE study.

In the univariate analysis among the 646 study participants, current use of oestrogen at the time of the index VTE was significantly associated with a lower risk of recurrent VTE: annual risk 3.8% (95%CI 0.8%-6.8%) in users, and 9.1% (95%CI: 7.3%-10.9%) in non users (both men and women), respectively, hazard ratio 0.4 (95%CI 0.2 to 1.0, $p=0.05$).

In the female gender subgroup, the risk of recurrent VTE was not significantly different between women on or off oestrogen therapy at the time of the index event (► Table 2). Overall six out of 67 women on oestrogen therapy recurred (two contraceptive and four HRT users) compared to 24 out of 247 of the remainders; annual risk 3.8% (95%CI: 0.8 to 6.8%) vs. 5.0% (95%CI: 3.0 to 7.0%) respectively; hazard ratio 0.8 (95%CI: 0.3 to 1.9), $p=0.59$. Among women on oral contraceptives, the annual risk of recurrent VTE was not lower in the 15 women who recently started oestrogen therapy (less than six months): annual risk 2.9% (95%CI: 0.0 to 8.7%). Of the two women on an oestrogen oral contraceptive at the time of the index VTE event and who recurred during follow-up, one used a second-generation progestin pill, and the other a combination with cyproterone acetate. Adjustment for age did not alter the results (Table 2).

The age range for women on oestrogen oral contraceptives was between 18 and 51 years old. In the subgroup of all women aged 18 to 51 years old in the REVERSE study, the risk of recurrent VTE was 2/49 (4%) and 7/114 (6%) in women on and off oestrogen oral contraceptives at the time of the index event, respectively. The annual risk of recurrent VTE was 1.7% (95% CI 0.0 to 4.0) vs. 3.1%

Table 2: Risk of recurrent VTE in oestrogen users and non users.

| | N | Number of recurrent VTE/Number of person-months of follow-up | Annual risk (95%CI) | HR (95% CI), P-value | Adjusted HR* (95% CI), P-value |
|---------------------------------|-----|--|---------------------|------------------------|--------------------------------|
| Current oestrogen use | | | | | |
| Yes | 67 | 6/1,902 | 3.8 (0.8 to 6.8) | 0.8 (0.3 to 1.9), 0.59 | 1.2 (0.5 to 3.1), 0.71 |
| No | 247 | 24/5,736 | 5.0 (3.0 to 7.0) | | |
| Oestrogen contraceptives | | | | | |
| Current use | 49 | 2/1,433 | 1.7 (0.0 to 4.0) | 0.3 (0.1 to 1.4), 0.09 | 0.6 (0.1 to 2.8), 0.51 |
| No oestrogen use | 247 | 24/5,736 | 5.0 (3.0 to 7.0) | | |
| Oestrogen HRT | | | | | |
| Current use | 18 | 4/469 | 10.2 (0.2 to 20.3) | 2.1 (0.7 to 6.1), 0.21 | 1.8 (0.6 to 5.2), 0.29 |
| No oestrogen use | 247 | 24/5,736 | 5.0 (3.0 to 7.0) | | |

* Adjusted on age; current was defined as a regular use of oestrogen in the month preceding VTE

Table 3: Risk stratification by the "Men and HER DOO 2" clinical decision rule.

| Risk stratification (CDR) | N | Number of recurrent VTE/Number of person-months of follow-up | Annual risk (95%CI) | HR (95% CI), P-value |
|---------------------------------|-----|--|---------------------|--------------------------|
| All women | | | | |
| Low risk | 177 | 5/4,780 | 1.3 (0.2 to 2.4) | 7.8 (3.0 to 20.5), <0.01 |
| High risk | 134 | 24/2,780 | 10.4 (6.2 to 14.5) | |
| All oestrogen users | | | | |
| Low risk | 50 | 2/1,481 | 1.6 (0.0 to 3.9) | 5.0 (0.9 to 30.1), 0.07 |
| High risk | 16 | 3/400 | 9.0 (0.0 to 19.2) | |
| Oestrogen contraceptives | | | | |
| Low risk | 38 | 0/1,120 | 0.0 (0.0 to 3.2) | + 8 , p=0.66 |
| High risk | 10 | 1/292 | 4.1 (0.0 to 12.2) | |
| Oestrogen HRT | | | | |
| Low risk | 12 | 2/361 | 6.6 (0.0 to 15.9) | 3.1 (0.4 to 23.6), 0.27 |
| High risk | 6 | 2/108 | 22.2 (0.0 to 53.0) | |
| Non oestrogen users | | | | |
| Low risk | 127 | | 1.1 (0.0 to 2.3) | 9.1 (2.7 to 30.6), <0.01 |
| High risk | 118 | | 10.6 (6.1 to 15.1) | |

(95%CI: 0.8 to 5.4) in users and non users within the 18 to 51 subgroup, respectively: hazard ratio 0.6 (95% CI: 0.1 to 2.7), $p=0.47$. The age range of women on oestrogen HRT was between 44 and 81 years old. In the group of all women aged 44 to 81 years in the REVERSE study, the risk of recurrent VTE was 4/18 (22%) and 19/158 (12%) in women on and off HRT within the 44 to 81 subgroup at the time of the index event, respectively. The annual risk of VTE was 10.2% (95% CI: 0.2 to 20.3) vs. 6.1% (95% CI: 3.4 to 8.9) in users and non users, respectively: hazard ratio 1.7 (95% CI: 0.6 to 5.0), $p=0.33$.

Among the 314 women, 87 (27.7%) were over 65 years old, 114 (36.4%) had a BMI of 30 kg/m² or more (one missing value, 0.3%), 121 (39.8%) had a VIDAS® D-Dimer ≥ 250 $\mu\text{g/l}$ (10 missing values, 3.2%), and 96 (36.9%) had hyperpigmentation, edema or redness

of either leg (54 missing values, 17.2%). Overall, 134 (43.1%) women met at least two of these criteria and were therefore classified by the clinical decision rule at high risk of recurrent VTE, whereas 177 had none or one of these criteria. Three women could not be classified because of missing values. Risks of recurrent VTE according to the clinical decision rule are shown in ► Table 3.

Discussion

The risk of recurrent VTE after 5–7 months of anticoagulant therapy for a first unprovoked VTE is not significantly different between women on or off oestrogen-containing birth control pill or

HRT. The “Men and HER DOO2” clinical decision rule could help in identifying women at low and high risk of recurrent VTE in both oestrogen users and non users. Finally, the lower risk of recurrent VTE in exogenous oestrogen associated otherwise unprovoked VTE is likely an as yet unexplained gender effect rather than an exogenous oestrogen provoking effect.

Our findings are consistent with previously published literature. In the landmark study by Baglin et al. (12), the risk of recurrence was null in patients after a fracture-related VTE, high (cumulative risk at two years 19.4%) in patients without identified VTE risk factors, and intermediate in a group patients which VTE occurred after a fracture or plaster cast, immobilisation, non-specific transient illness, or a history of recent travel. The latter group also included women taking oestrogen-containing oral contraceptives. In a subsequent analysis of this cohort, the risk of recurrence was found to be similar in the 37 women on oestrogen (29 on birth control pill, and eight on HRT) at the time of the index event, as in the other women included in the group with non-surgical risk factors: cumulative rate at two years 8.7% in both groups (15). This 8.7% two-year risk is in line with the 3.8% annual risk we observed in the REVERSE study. Even if analyses in the paper by Baglin et al. did not take age into account, and formal comparison was not provided, this risk seemed lower than in women with no identified risk factor. On the other hand, it was clearly higher than the 0% risk observed in patients with a post-surgical VTE. Finally, separate results for oral contraceptives and HRT were not provided (15). The Austrian Study on Recurrent Venous Thromboembolism showed no difference in the risk of recurrence between women who were taking oral contraceptives and women in the same age groups in whom the first event was unprovoked (5). The Leiden Thrombophilia Study included both provoked and unprovoked consecutive VTE patients in the Netherlands. In this population, the risk of recurrent VTE was 9.7 (95% CI: 4.3–21.5) per 1,000 patient-years in women who were oestrogen users at the time of their VTE episode, as compared with 16.2 (95% CI: 8.7–30.2) in women who had never used an oral contraceptive (8). Finally, in a post-hoc analysis of the PREVENT trial, no statistically significant difference in risk of recurrent VTE was found between women with and without hormone related events. However, the risk of recurrent VTE in women with hormone-related events was statistically significantly lower than in men (16).

It has also emerged over the last five years that men are at higher risk of recurrent VTE than women (5, 13, 17), introducing the possibility that gender and exogenous oestrogen use confounds their individual associations with the risk of recurrent VTE. Our stratified analyses in the female gender subgroup suggest that exogenous oestrogen use may not influence the risk of recurrent VTE compared to all patients with unprovoked VTE. That is, it is likely that the lower risk observed in exogenous oestrogen-associated VTE is a gender effect. To corroborate this finding, when we conducted a multivariate analysis of recurrent VTE with gender and exogenous oestrogen use as dependent variables, exogenous oestrogen use was no longer a significant risk factor.

The REVERSE study has a number of strengths. To date, this is the largest and most comprehensive clinical study that has evaluated risk factors for recurrent VTE in patients with unprovoked

proximal DVT or PE. We prospectively collected all data in a standardised fashion. Our study included a representative sample of patients from multiple centres and countries. These patients were consecutively enrolled without bias. The clinically relevant primary outcome of recurrent VTE was clearly defined and independently adjudicated. As regards our analysis is that the use of oestrogen was systematically recorded at inclusion in all patients, along with the drug name and the date it was started. This also allowed us to examine the relationship between the timing of initiation of oestrogenic medications in relation to the index VTE, and recurrent VTE. The list of current medications was reviewed and recorded at each follow-up visit, allowing us to ascertain that no woman with oestrogen-associated VTE resumed oestrogenic medications during follow-up. The main limitation of our study is the low number of women on oestrogen therapy at the time of their index event. This impeded us to provide precise estimates of the risk of recurrence for each type or duration of oestrogen therapy, and possibly to detect significant differences between subgroups. Nevertheless, the risk of recurrent VTE may not be low enough in women users of oestrogen therapy at the time of their index VTE to safely discontinue anticoagulants on the basis of this criterion alone. In other words, our results suggest that exogenous oestrogen-related VTE should potentially not be considered in the category of provoked VTE and safely treated with short term anticoagulants. The “Men and HER DOO 2” clinical decision rule could be informative in determining whether to continue anticoagulants in women with exogenous oestrogen VTE. As shown in Table 3, it allowed the identification among women on oestrogen of a large subgroup (50/66, 76%) with a low risk of recurrent VTE. When the rule identified women on oestrogen as having a high risk of recurrence, the risk was higher. However, confidence intervals around estimates for the risks of recurrent VTE are too wide to draw any firm conclusion. Moreover, since the rule was derived from patients included in the REVERSE study, these results need to be confirmed in a larger prospective validation study.

These findings may have important clinical implications. Whereas anticoagulant treatment can be safely discontinued after a few months in patients with a first provoked VTE because the risk of recurrence in such patients is low and outweighed by the risk of bleeding, a prolonged or even indefinite anticoagulant treatment is recommended in patients with unprovoked VTE (1). Most phys-

What is known about this topic?

- Oestrogen use increases the risk of venous thromboembolism (VTE).
- The risk of recurrence after a first oestrogen-associated VTE is unknown.

What does this paper add?

- The risk of recurrent VTE is low in women after a first otherwise unprovoked oestrogen-associated VTE.
- This risk is not significantly lower than in women whose VTE was not related to oestrogen use.

icians would likely agree that it is safe to discontinue anticoagulant therapy in patients with a risk of recurrence lower than 3% per year, given that the estimated case fatality rate of such a recurrence is 5% to 15% (18, 19), whereas continuing on anticoagulant therapy exposes the patient to a risk of major bleeding of approximately 1.0 to 7.2% per year (6, 20), with a case fatality rate of 13% (20). Our results suggest that the risk of recurrence in women who were users of oestrogen at the time of their VTE may not be low enough to consider them as having provoked events: the upper limit of the 95% CIs were 6.8%, 4.0% and 20.3%, i.e. all higher than 3%, for oestrogen, oestrogen contraceptives and oestrogen HRT use, respectively. This stresses the need for a validated risk stratification tool that would allow identification of a low risk group among patients with unprovoked VTE, and in particular in young women, given the inconvenience and potential cumulative risks of prolonged anticoagulant therapy in this young group.

To summarise, the risk of recurrent VTE is low in women after a first otherwise unprovoked oestrogen-associated VTE. However, this risk does not seem to be significantly lower than in women whose VTE was not related to oestrogen use. Hence, these results suggest that oestrogen-related VTE should not be considered as provoked events, and other risk factors of recurrence should be considered to tailor length of anticoagulant therapy. Risk stratification tools could help to resolve this issue.

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References

1. Kearon C, Kahn SR, Agnelli G, et al. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; 133: 454S-545S.
2. Oger E, Lacut K, Le Gal G, et al. Hyperhomocysteinemia and low B vitamin levels are independently associated with venous thromboembolism: results from the EDITH study: a hospital-based case-control study. *J Thromb Haemost* 2006; 4: 793-799.
3. Kearon C, Gent M, Hirsh J, et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. *N Engl J Med* 1999; 340: 901-907.
4. Palareti G, Cosmi B, Legnani C, et al. D-dimer testing to determine the duration of anticoagulation therapy. *N Engl J Med* 2006; 355: 1780-1789.
5. Kyrle PA, Minar E, Bialonczyk C, et al. The risk of recurrent venous thromboembolism in men and women. *N Engl J Med* 2004; 350: 2558-2563.
6. Agnelli G, Prandoni P, Santamaria MG, et al., the Warfarin Optimal Duration Italian Trial Investigators. Three Months versus One Year of Oral Anticoagulant Therapy for Idiopathic Deep Venous Thrombosis. *N Engl J Med* 2001; 345: 165-169.
7. Piccioli A, Lensing AWA, Prins MH, et al., for the SOMIT investigators group. Extensive screening for occult malignant disease in idiopathic venous thromboembolism: a prospective randomized clinical trial. *J Thromb Haemost* 2004; 2: 884-889.
8. Christiansen SC, Cannegieter SC, Koster T, et al. Thrombophilia, clinical factors, and recurrent venous thrombotic events. *J Am Med Assoc* 2005; 293: 2352-2361.
9. Petitti DB. Clinical practice. Combination estrogen-progestin oral contraceptives. *N Engl J Med* 2003; 349: 1443-1450.
10. Canonico M, Plu-Bureau G, Lowe GD, et al. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. *Br Med J* 2008; 336: 1227-1231.
11. Rosendaal F. Venous thrombosis: a multicausal disease. *Lancet* 1999; 353: 1167-1173.
12. Baglin T, Luddington R, Brown K, et al. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. *Lancet* 2003; 362: 523-526.
13. Rodger MA, Kahn SR, Wells PS, et al. Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. *CMA J* 2008; 179: 417-426.
14. Le Gal G, Kovacs MJ, Carrier M, et al. Validation of a diagnostic approach to exclude recurrent venous thromboembolism. *J Thromb Haemost* 2009; 7: 752-759.
15. Baglin T, Luddington R, Brown K, et al. High risk of recurrent venous thromboembolism in men. *J Thromb Haemost* 2004; 2: 2152-2155.
16. Cushman M, Glynn RJ, Goldhaber SZ, et al. Hormonal factors and risk of recurrent venous thrombosis: the prevention of recurrent venous thromboembolism trial. *J Thromb Haemost* 2006; 4: 2199-2203.
17. McRae S, Tran H, Schulman S, et al. Effect of patient's sex on risk of recurrent venous thromboembolism: a meta-analysis. *Lancet* 2006; 368: 371-378.
18. Douketis JD, Kearon C, Bates S, et al. Risk of fatal pulmonary embolism in patients with treated venous thromboembolism. *J Am Med Assoc* 1998; 279: 458-462.
19. Columbus investigators. Low-molecular-weight heparin in the treatment of patients with venous thromboembolism. The Columbus Investigators. *N Engl J Med* 1997; 337: 657-662.
20. Linkins LA, Choi PT, Douketis JD. Clinical impact of bleeding in patients taking oral anticoagulant therapy for venous thromboembolism: a meta-analysis. *Ann Intern Med* 2003; 139: 893-900.