Risk of recurrence after a first venous thromboembolic event in young women

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Acknowledgments: the skilful technical assistance of Laura Ovissi and Silvia Koder is acknowledged. We thank those centers that sent patients for evaluation of thrombosis risk factors: H. Partsch and C. Bialonczyk, Wilhelminenspital, Vienna; E. Minar, Department of Angiology, Medical University Vienna; M. Hirschl, Hanusch-Krankenhaus, Vienna; and C. Stöberl, KA Rudolfstiftung, Vienna.

Manuscript received October 25, 2006.
Manuscript accepted June 27, 2007.

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ABSTRACT

Background and Objectives

Few data are available on the long-term risk of recurrence of venous thromboembolism (VTE) and on the impact of established thrombosis risk factors in young women. We aimed to study the recurrence rate and the predictive value of laboratory and clinical thrombosis risk factors in young women.

Design and Methods

Three-hundred and sixty-one women with a first objectively confirmed VTE under 45 years of age (median age 29.6 years, interquartile range 21.9-36.9) known to our outpatient department were included in this retrospective analysis. These women were re-examined with regard to recurrence of thrombosis and laboratory thrombosis risk factors.

Results

Within a median observation period of 11.3 years, recurrent VTE occurred in 141 patients (39.2%). The cumulative probability of recurrence was 10.9% after 2 years, 29% after 10 years and 56% after 20 years. There were no significant associations between recurrence of VTE and laboratory risk factors such as natural inhibitor deficiency, factor V Leiden, the G20210A prothrombin variation, elevated factor VIII or hyperhomocysteinemia. Even women with more than one risk factor were not found to have a higher risk of recurrent VTE. Among the clinical characteristics only an increased body mass index (p=0.03) was associated with a higher probability of recurrence.

Interpretation and Conclusions

The risk of recurrent VTE in young women is higher than previously expected and remains constant over at least 20 years. Neither clinical features nor laboratory parameters help predict this risk. Thus, also in young women VTE should be regarded as a chronic disease.

Key words: recurrent venous thromboembolism, thrombosis risk factors, venous thromboembolism, young women.

Haematologica 2007; 92:1201-1207. DOI: 10.3324/haematol.10967

Venous thromboembolism (VTE) is a serious clinical condition manifesting as deep venous thrombosis (DVT) and/or pulmonary embolism (PE). Patients with symptomatic VTE have a considerable risk of recurrent VTE that persists for many years.[1] The duration of anticoagulant treatment after a first episode of VTE essentially depends on the estimated risk of recurrence. Two-thirds of first-time episodes of DVT occur in connection with external factors such as surgery, immobilization or trauma.[2] In women, pregnancy, puerperium and oral contraceptives represent further risk factors. In addition, there are known a demographic risk factors for first VTE as well as for recurrent events, such as advanced age,[3,4] obesity,[5] cancer and male sex.[3] Other clinical factors are known to increase the risk of recurrence, e.g. first manifestation as PE.[6]

During the last decade testing for thrombosis risk factors has become common practice. Several abnormalities in the coagulation system have been shown to be associated with an increased risk of thrombosis. Their impact on the recurrence rate has been the focus of several clinical studies. The association of the commonest inherited risk factors for thrombosis, factor V Leiden and the prothrombin G20210A variation, with recurrent VTE is still under discussion.[7-11] Among the deficiencies of natural inhibitors, antithrombin deficiency has been shown to increase the risk for recurrence, whereas the same effect could not be demonstrated for protein C or protein S deficiency.[12] High factor VIII levels[13] and hyperhomocysteinemia[14] have been reported to be associated with an increased risk of recurrence.

A number of studies evaluating the gender-specific risk of recurrence have revealed that women are at lower risk of experiencing a recurrent event than are men.[3,5,12] However, the long-term incidence of recurrence and the role of risk factors have never been evaluated in women who present with a first VTE at an age younger than 45 years. We feel that it is very important to look at young individuals, since the duration of treatment with oral anticoagulants has major implications for their future life. Treatment with vitamin K antagonists increases menstrual bleeding,[15] may cause coumarin embryopathy and increases the rate of spontaneous abortion.

The aim of our study was to evaluate the long-term recurrence rate in women who suffered a first venous thromboembolic event at a young age, as well as the predictive value of risk factors of thrombosis in regard to their impact on recurrence.

Design and Methods

Patients

All consecutive women who presented to our outpatient clinic between January 1985 and December 1998 for thrombophilia screening because of a history of VTE (first or recurrent event) and a first manifestation from an age of 13 up to 45 years were eligible for the current investigation. In all women the first VTE had been documented by objective methods (phlebography, plethysmography, duplex ultrasonography, perfusion ventilation lung scan or computed tomography, as appropriate). In 1999/2000, this group of women was invited for a re-investigation of thrombosis risk factors and an evaluation of recurrent thrombotic episodes. A recurrent VTE was regarded as such if confirmed by appropriate objective methods and/or followed by the implementation of a new course of anticoagulation. Those women who were retrieved and accepted our invitation for re-investigation were recruited in the current study, provided that they had discontinued anticoagulation and had not developed recurrent events while on anticoagulation. After informed consent had been obtained, a blood sample for thrombophilia screening was drawn, patients were asked about their history of thrombosis by means of a standardized interview and underwent a clinical examination including calculation of body mass index (BMI), and the date of occurrence and site of the thrombotic event(s). Clinical situations predisposing them to recurrent VTE such as surgery, trauma, pregnancy or immobility and the onset and duration of oral contraceptive use were recorded. Furthermore, the dates of hospital admission, duration of hospitalization and anticoagulant treatment were documented. Women in whom no recurrent event had been documented until 2000 were again contacted in 2002 and interviewed on whether a recurrent event had occurred. The study was approved by the Ethics Committee of the Medical University of Vienna.

Laboratory analysis

Plasma samples were obtained from the patients after overnight fasting and centrifuged at 2000g for 20 minutes. Coagulation tests (lupus anticoagulant, factor VIII) were performed within 3 hours of blood sampling. For determination of natural coagulation inhibitors plasma was frozen at –20° C until analysis. For determination of homocysteine the samples were immediately cooled at 4° C and centrifuged within 30 minutes of sampling, snap frozen and stored at – 70° C. The diagnosis of the lupus anticoagulant was made according to the criteria of the International Society of Thrombosis and Haemostasis[16] using two different screening tests (activated partial thromboplastin time and diluted Russels viper venom time) and confirmatory tests as described elsewhere.[17] Antithrombin- and protein C activities were determined on the STA analyzer. Free protein S antigen was determined by an enzyme-linked immunosorbent assay (ELISA). Factor VIII clotting activity (95th percentile of 307 healthy individuals - 248% used as cut-off) was determined by a one step clotting assay on a KC 10 coagulometer (Amelung, Lieme, Germany). Total homocysteine concentration (normal range for women < 13.6 μmol/L) was determined using a high performance liquid chromatography kit from Immunodiagnostic, Bensheim, Germany as

described previously.[18] The factor V:R506Q and the prothrombin G20210GA genotypes were analyzed by multiplex polymerase chain reaction (PCR) following the general principle of mutagenically separated PCR.[19] An individual heterozygous for both mutations was included as a positive control in each experiment.

Statistical methods

To evaluate the time span up to the first recurrent event, we started the observation period after cessation of the anticoagulant treatment following the first VTE and concluded it at the first recurrence. If no anticoagulant treatment had been administered or anticoagulation treatment had been given for a short period only, the observation period started 3 months after the first event. The observation period for patients who did not experience a recurrent VTE ended at the time of the last follow-up. Probabilities of recurrence-free times were estimated by the Kaplan-Meier method[20] and differences were tested using the log-rank test. Univariate and multiple Cox regression models[21] were used to describe the unadjusted and adjusted effects of potential prognostic factors on the length of time up to the first recurrent event. The following prognostic factors were considered in the multiple regression model: deficiency of a natural inhibitor (yes/no), presence of factor V Leiden (yes, including heterozygous and homozygous individuals/no), presence of the prothrombin G20210A variation (yes, including heterozygous and homozygous individuals/no), hyperhomocysteinemia (yes/no), and factor VIII levels (as a continuous variable). Due to sporadically missing laboratory values, data from 327 (not all 361) women were used for the multiple Cox regression model. The strength of the prognostic factors is described by the estimate of the relative risk (with 95% confidence interval). *p*-values smaller than 0.05 were considered statistically significant.

Results

Of the 750 eligible women, 396 were retrieved and accepted our invitation for re-investigation. Of these, 35 were excluded because they either had not discontinued anticoagulation (n=30) or had developed recurrent events while on anticoagulation (n=5). Tables 1a, 1b and 2 report the demographic and clinical characteristics, including the frequency of hereditary risk factors of the 361 patients who qualified for the current investigation. The median age of the overall study population at first VTE was 29.6 years. Of these women 51.8% were using oral contraceptives when they experienced their first VTE. Since these women represent a large subgroup, we have put special emphasis on this group, characterizing them in a separate table (1b). Almost 40% of women had one risk factor, 17% had two or more risk factors (Table 1a). The sites of the first thrombotic event are listed in Table 2. One third of women had PE with or without DVT as their first event. Surgery was the most frequent trigger of the first VTE, followed by pregnancy and the puerperium as a second important triggering condition (Table 2).

Table 1a. Descriptive and laboratory risk factors for recurrent VTE in 361 women.

Charactaristics and laboratory risk factors	*Patient number / Total patient number*	*Percentage*
Median age (years, IQR) at first VTE	29.6 (21.9-36.9)	
BMI≥25	182/348	52.3%
OC at first VTE	186/359	51.8%
PE as first VTE	121/359	33.5%
Unprovoked first VTE	179/361	49.6%
Factor V Leiden	118/360	32.8%
Homozygous	11/360	3.1%
Heterozygous	107/360	29.7%
Prothrombin G20210A	36/354	10.2%
Antithrombin deficiency	8/361	2.2%
Deficiency of protein C	11/361	3.1%
Deficiency of protein S	8/361	2.2%
Elevated factor VIII	36/342	10.5%
Hyperhomocysteinemia	60/341	17.6%
No laboratory risk factor	143/327	43.7%
One laboratory risk factor	127/327	38.8%
Two or more laboratory risk factors	57/327	17.4%

Prothrombin variation – all heterozygous; IQR: interquartile range; BMI: body mass index; OC: oral contraceptives; PE: pulmonary embolism; VTE: venous thromboembolism

Table 1b. Descriptive and laboratory risk factors in women who were taking oral contraceptives when the had their first VTE.

Charactaristics and laboratory risk factors	*Patient number/total patient number*	*Percentage*
Median age (years, IQR) at first VTE	26.4 (20.5-35.2)	
BMI≥25	102/179	57.0%
PE as first VTE	59/186	68.3%
Unprovoked first VTE	120/186	64.5%
Factor V Leiden	73/186	60.8%
Prothrombin G20210A	17/183	9.3%
Deficiency of a natural inhibitor	13/186	7.0%
Elevated factor VIII	16/174	9.2%
Hyperhomocysteinemia	26/173	15.0%
Two or more laboratory risk factors	28/165	17.0%

Prothrombin variation – all heterozygous; IQR: interquartile range; BMI: body mass index; OC: oral contraceptives; PE: pulmonary embolism; VTE: venous thromboembolism

Recurrent venous thromboembolism

The median observation period was 11.3 years. Of the 361 women, 141 (39.1%) had suffered a recurrent event: in 122 this had been confirmed by objective methods, and in the remaining 19 (13.5%) on clinical grounds. The cumulative probability for recurrence was 29% after 10 years and 56% after 20 years (Figure 1), and remained nearly constant over the whole period, being only slightly higher within the first 2 years (5% after 1 year and 10.6% after 2 years).

Clinical characteristics

We differentiated patients with regard to various clinical characteristics and investigated the impact of these characteristics on recurrence of VTE. Hazard ratios and 95% confidence intervals are given in Table 3. If the age at occurrence of the first VTE was above or below the median age of the study population (29.6 years), this had no impact on recurrence. Women with a BMI equal to or higher than 25 had a significantly higher risk of recurrence. Oral contraceptive intake at the time of the first thrombotic event had no impact on recurrence. When analyzing the impact of site of the first VTE, we found no significant difference in the recurrence risk when the first VTE included PE. Moreover, we could not detect a significant difference in recurrence rates, depending on whether the first event had been unprovoked or had occurred in association with a triggering event.

Laboratory risk factors

Hazard ratios and 95% confidence intervals for recurrent VTE with regard to established laboratory risk factors are shown in Table 4. We did not find any statistically significant associations between recurrence of VTE and deficiencies of protein C, protein S or antithrombin, the presence of the prothrombin G20210A variation, elevated factor VIII or hyperhomocysteinemia. Women who were homozygous for factor V Leiden did not have a higher risk of recurrence, possibly due to the low number of such women in this group. Women who were heterozygous for factor V Leiden had a recurrence rate that was comparable to that of women with wild type factor V. When women with no or one risk factor were compared to those with at least two risk factors, again no higher risk of recurrence was observed.

We performed a multivariate analysis of the data from those women for whom all laboratory parameters were available (n=327). The results are shown in Table 4. None of the parameters was shown to serve as an independent statistically significant risk factor for recurrent VTE. The results did not change when clinical characteristics were included in the analysis (*data not shown*). When performing multivariate analysis on data from women with an unprovoked first VTE, again none of the parameters was found to be a significant risk factor. These results are shown in Table 4.

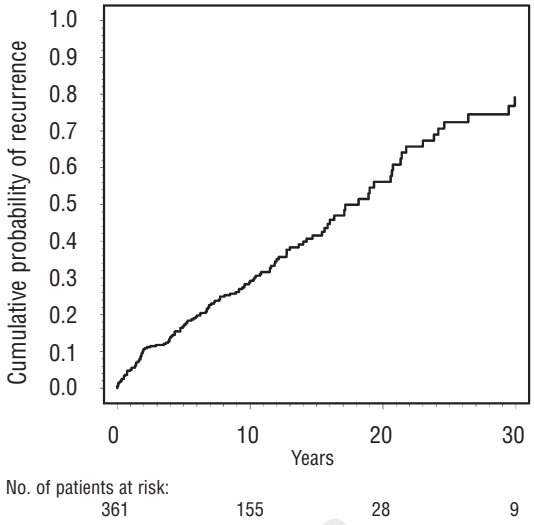

Figure 1. Cumulative probability of recurrence after cessation of anticoagulation.

Table 2. Site of first VTE in all women (n=361) and triggering factors in women with provoked first VTE (n=182).

Site of thrombosis	*Number of patients (n = 361)*	*Percentage*
DVT leg	214	59.3%
DVT arm	14	3.9%
Isolated caval thrombosis	2	0.6%
PE and DVT	64	17.7%
PE without detectable DVT	57	15.8%
Others	10	2.8%

Triggering Event	*Number of patients (n = 182)*	*Percentage*
Surgery	53	29.1%
Trauma	32	17.6%
Pregnancy	15	8.2%
Puerperium	24	13.2%
Cesarean section	11	6.0%
Abortion	2	1.1%
Immobilization	28	15.4%
Others	17	9.3%

VTE: venous thromboembolism; DVT: deep venous thrombosis; PE: pulmonary embolism

Discussion

The present study was performed in a cohort of young female patients with a history of VTE. The study population included women under 45 years of age at the time of their first VTE and who were not affected by malignant or chronic disease. The observation period covered a median of more than 11 years. The data from our study cohort of young women demonstrate that the risk of recurrence persists over at least 20 years. Estimation of the cumulative probability of recurrent VTE revealed recurrence in at least one quarter of patients after 10 years and half of the patients after 20 years, with the rate of recurrence being remarkably constant throughout the whole period.

In general, only a limited number of studies on recurrent VTE have long observation periods. In Table 5 we have listed eight studies with a median observation period exceeding 2 years. None of these studies covered a period of more than 20 years, a time-span that is unique to our study. It has to be mentioned that the studies dif-

Table 3. Hazard ratios for the risk of recurrence according to laboratory risk factors and clinical characteristics.

Risk Factor	*Hazard Ratio (95% confidence interval)*	*p Value*
Deficiency of natural inhibitor	1.12 (0.64-1.95)	0.69
Hyperhomocysteinemia	1.18 (0.78-1.79)	0.46
Elevated factor VIII	1.0 (1.0-1.0)	0.33
Prothrombin G20210A	1.17 (0.67-2.03)	0.59
Factor V Leiden	1.14 (0.81-1.61)	0.46
> 1 risk factor	1.45 (0.96-2.18)	0.1
Age ≥ 29.6 years	1.11 (0.80-1.55)	0.54
BMI ≥ 25	1.48 (1.04-2.11)	0.03
OC use at time of first VTE	0.85 (0.60-1.21)	0.36
PE as first VTE	1.38 (0.98-1.95)	0.07
Unprovoked first VTE	1.0 (0.71-1.39)	0.97

BMI: body mass index; OC: oral contraceptives; VTE: venous thromboembolism; PE: pulmonary embolism.

Table 4. Multivariate analysis of established laboratory risk factors in the whole group of women and in those with unprovoked VTE .

All women (n=327)

Risk Factor	*Hazard Ratio (95% confidence interval)*	*p Value*
Deficiency of natural inhibitors	1.37 (0.77-2.44)	0.28
Hyperhomocysteinemia	1.10 (0.71-1.70)	0.68
Elevated factor VIII	1.00 (0.1-1.0)	0.47
Prothrombin G20210A	1.31 (0.73-2.35)	0.36
Factor V Leiden	1.03 (0.71-1.50)	0.88

Women with unprovoked VTE (n=159)

Risk Factor	*Hazard Ratio (95% confidence Interval)*	*p Value*
Deficiency of natural inhibitors	1.12 (0.44-2.83)	0.81
Hyperhomocysteinemia	1.20 (0.58-2.48)	0.62
Elevated factor VIII	1.00 (1.0-1.0)	0.68
Prothrombin G20210A	1.05 (0.32-3.43)	0.94
Factor V Leiden	0.93 (0.53-1.63)	0.80

VTE: venous thromboembolism

fer remarkably with regard to inclusion criteria. Whereas one study included only patients with spontaneous thrombosis,[3] some also included patients with provoked events[4,5,12,22,23] and even patients with malignancy.[24,25] The mean age at onset of the thrombotic disease also varied significantly, ranging between 32 and 66 years. Recurrence rates varied remarkably. After 2 years recurrence rates ranged between 8 and 12% and after 10 years between 18 and 40%. The highest recurrence rate after 10 years of observation was found by Prandoni *et al.*,[23] who recently reported on one of the largest cohort of patients ever prospectively observed, a group of 1626 individuals. In this study the cumulative risk of recur-

Table 5. Recurrence rates in studies with a median observation period > 2 years.

Author	*N*	*Age*	*Observervation period (years)*	*Specific characteristics*	*Recurrence rate (yrs, %)*				*Predictive parameters*		
					2	*5*	*8*	*10*	*Sex*	*Age*	*Thrombophilia*
Hansson, 2000[23]	738	66 (17-95)	3.7-8.8	Cancer included	12	22	–	–	No	No	–
Heit, 2000[24]	1719	61.7 +/-20.4	7.4	Cancer included	8	12	–	18	Yes	Yes	–
Kyrle, 2004[3]	826	45 +/-18	2.1	Women	–	9	–	–	Yes	Yes	–
Christiansen, 2005[21]	474	45 +/-13.7	7.3 +/-2.7	–	–	12	–	–	Yes	–	No
Vossen, 2005[11]	180	32	5.6 (1-7)	all TP	12	–	–	–	Yes	–	–
Garcia-Fuster, 2005[5]	98	32 +9.2	9.8 (0.9-13.8)	–	10	–	34	–	Yes	–	Yes
Schulman, 2006[4]	545	60.6 +15.4	10	–		–	–	29	Yes	No	–
Prandoni, 2007[22]	1626	66 (16-96)	4.2	–	–	29	–	40	No	Yes	Yes
Present Study	361	29.6 (21.9-36.9)	11.3 (1-22)	Women	11	17	25	29	–	No	No

rence amounted to 40% after 10 years, thus being considerably higher than that in our cohort. It must to be mentioned that the patients in the Italian study had a relatively high median age of 66 years, which in part might explain the high recurrence rate that was found.

The results on gender as a risk predictor for recurrence are inconsistent. Whereas most studies found a higher risk in men,[3-5,12,22,25] there are two studies [23,24] which did not confirm this. The same is true for thrombophilia as a risk factor, which was evaluated by four investigators. Two studies, including the present one, did not find thrombophilia to be predictive for recurrence,[22] while the two other studies did find it to be so.[5, 23]

There is one important aspect that is rather unique to our patient population, namely that the presence of a triggering event at onset was not predictive for recurrence. One explanation for this result might be that we included only young women with VTE. In the general population the overall risk of thrombosis at this age is very low,[25] so it can be speculated that in young patients with VTE an underlying thrombophilia is much more likely than in older patients, which consequently leads to a higher basic risk of thrombosis in these young patients and also to a higher recurrence rate. Indeed, when the rate of patients with established thrombophilia was compared among the different studies, the number of patients with an established thrombosis risk factor was highest in our study (56%) and much lower in other studies, e.g. that of Prandoni (24%)[23] or of Garcia-Fuster (36%).[5] Furthermore, it can be hypothesized that in a considerable number of young patients with VTE a yet unrecognized risk factor for thrombosis is present. The low number of women free of recurrence after a long period of time is most probably due to the persisting risk for developing thrombosis, which does not decline after a certain time period, as previously suggested by other authors.[4, 26] Recently described laboratory parameters, such as D-dimer testing[27] or the endogenous thrombin potential[28] might better reflect the basic risk of thrombosis of an individual than thrombophilia testing.

Our study has some limitations. First of all, the design was not prospective, which may have led to an inclusion bias regarding women who had already suffered a recurrent VTE and were more willing to participate in the study than those who had remained free of thrombosis. The confirmation of recurrent VTE could represent another limitation. We decided to accept all patients, including the small number with not-objectively confirmed events, in the analysis if their symptoms had led to therapeutic anticoagulation. Exclusion of these probable events would not have changed the results considerably, as in the majority of patients (88%) the recurrent events were documented by objective methods as described above. We cannot provide data on mortality in our study population. However, as has been shown previously the mortality from recurrent VTE is low.[4, 29] Since our patients were not formally included in a prospective study, their prophylactic anticoagulation in risk situations may well have differed from that of subjects participating in prospective studies with regular visits. The situation in our study might better reflect daily practice and shows the constant risk of recurrence.

In summary, VTE must be regarded as a chronic disease, as convincingly demonstrated in our study. The risk of recurrence remains constant over at least 20 years and is, therefore, never negligible. In this respect, the question of long-term, even life-long anticoagulation treatment arises. In our study of a population of young women neither clinical features nor common laboratory risk factors nor the presence of known risk factors enabled us to identify patients at higher risk of suffering a recurrent VTE. These parameters do not help decisions on the duration of oral anticoagulant treatment.

Authors' contributions

CL: analyzing and interpretation of the data, writing the first draft, HG: contribution to study design, management of patient recruitment, collection of the data; AK: statistical analysis, PQ: managment of thrombophilia screening; RS: analysis and interpretation of data; CM: management of genetic investigations; KL: contribution to conception of the study, interpretation of data; IP: principal investigator, conception of the study and interpretation of data.

Conflict of Interest

The authors reported no potential conflicts of interest.

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