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6 versus 30 months anticoagulation for recurrent venous thrombosis in patients with high factor VIII

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Abstract Patients with first venous thromboembolism (VTE) and high factor VIII (FVIII) are at increased risk of recurrence. It is unknown whether these patients benefit from prolonged secondary thromboprophylaxis. In a prospective trial patients with first spontaneous VTE and FVIII levels >230 IU/dl were randomized to discontinue vitamin K Antagonist (VKA) after 6 months or to continue VKA for additional 24 months. Patients were excluded if they had a natural inhibitor deficiency, lupus anticoagulant, cancer, were pregnant, required long-term antithrombotic therapy or had acute-phase reaction. Primary study endpoints were symptomatic recurrent VTE or major bleeding within 2 years. Follow-up was continued beyond 2 years. Of 3,219 screened patients 34 met the inclusion criteria. Mean observation time was 37 months. Two of 17 patients allocated to discontinue VKA and two of 17 patients randomized to prolonged anticoagulation had recurrent VTE within 2 years. In the prolonged treatment group, one patient had recurrence during VKA therapy and one patient 4 weeks after voluntary discontinuation of VKA. One major nonfatal bleeding (severe epistaxis) after 10 months of VKA occurred in the prolonged treatment group. Five patients allocated to prolonged anticoagulation had recurrent VTE after discontinuation of VKA. The probability of recurrence at 2 years after discontinuation of VKA was 30% (95% CI 13–46%). Patients with high FVIII are at increased risk of recurrence. Our findings in a small

number of patients indicate that prolonged anticoagulation seems to be effective but that the benefit is not maintained after discontinuation of anticoagulation.

Keywords Anticoagulation · High factor VIII · Recurrence of venous thromboembolism · Interventional trial

Introduction

High levels of factor VIII are associated with an increased risk of venous thrombosis. In the Leiden Thrombophilia Study, factor VIII levels greater than 150 IU/dl conferred an increased risk of first venous thrombosis with an odds ratio of almost 5.0 [1]. In a retrospective study, O'Donnell detected high factor VIII activity in 25% of 260 patients with venous thromboembolism (VTE) [2].

We previously showed that patients with high factor VIII are at increased risk of recurrent VTE. Risk of recurrence was more than sixfold higher among patients with factor VIII levels above the 90th percentile than among those with lower levels [3]. The probability of recurrence 2 years after discontinuation of anticoagulation was 36% among patients with high factor VIII as compared with 5% among patients with lower levels. These data were confirmed by an Italian study in which recurrence risk of patients with idiopathic VTE was more than fivefold higher, if factor VIII levels exceeded the 90th percentile [4]. In contrast, in the Leiden Thrombophilia Study high factor VIII levels were not associated with an increased risk of recurrence [5]. This difference can be explained by inclusion of low-risk patients including those with secondary venous thrombosis and a lower factor VIII cut-off level.

Patients with first idiopathic VTE receive secondary thromboprophylaxis with vitamin K-antagonists for a minimum of 6 months. Patients with a particular high risk

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of recurrence including those with multiple VTE, the lupus anticoagulant, or combined coagulation defects, are candidates for long-term anticoagulation. Anticoagulant treatment almost completely prevents recurrence, but bears a considerable risk of severe bleeding which amounts to about 4% per year [6]. It is therefore unclear if the benefit of prolonged anticoagulation in high risk patients is outweighed by the bleeding risk.

We investigated whether patients with high factor VIII benefit from prolonged anticoagulation and randomized patients with first VTE and high factor VIII levels who had received vitamin K-antagonists for 6 months to either continue or discontinue anticoagulation. We prospectively followed all patients for at least 2 years and recorded episodes of recurrent VTE and major bleeding.

Materials and methods

Patients and study design

The study was conducted as a prospective, open, randomized trial with 13 participating centers (12 centers in Vienna, Austria, one center in Stockholm, Sweden). Patients older than 18 years with a first deep vein thrombosis and/or pulmonary embolism were eligible. Diagnosis of VTE had to be objectified by venography or color-coded duplex ultrasound in case of deep vein thrombosis or perfusion/ventilation lung scan or spiral CT in case of pulmonary embolism. Patients were excluded for the following: VTE provoked by surgery, trauma, prolonged bed rest, pregnancy or puerperium; deficiency of antithrombin, protein C or protein S; antiphospholipid syndrome; active malignancy; poor compliance before study entry (less than 30% of the international normalized ratio (INR) values within the therapeutic range); indication for long-term anticoagulation other than VTE; acute-phase reaction (C-reactive protein >1 mg/dl) at the time of factor VIII measurement; factor VIII levels below 230 IU/dl; or refusal to participate.

All patients had been treated with unfractionated or low molecular weight heparin at therapeutic dosages and subsequently received vitamin K-antagonists for 6 months.

The study was approved by the ethics committees of the Vienna University Hospital, Austria, and of the Karolinska University Hospital, Sweden, and the patients provided written informed consent before inclusion.

Study procedures

Three months after acute VTE factor VIII levels were measured in the local laboratories of the participating centers. Austrian patients with factor VIII levels above

230 IU/dl were referred to the study center (Department of Internal Medicine I, Medical University of Vienna, Austria), where determination of factor VIII level was repeated. In Swedish patients, factor VIII levels were determined at the Coagulation Unit of the Karolinska University Hospital, Stockholm. Diagnosis of high factor VIII was made when the factor VIII activity determined 5 months after the acute VTE in the central laboratory of the respective study center exceeded 230 IU/dl. This procedure ensured that factor VIII levels were not influenced by the acute VTE and that interlaboratory variations were kept at a minimum.

After 6 months patients were randomized to either continue vitamin K-antagonists for two additional years (INR 2.0–3.0) or to discontinue anticoagulation. All randomized patients formed the intention-to-treat population.

Patients who stopped vitamin K-antagonists did not receive any other thromboprophylaxis beyond 6 months except in high risk situations such as surgery, trauma, immobilization longer than 3 days, or long distance flights. All patients were advised to refrain from platelet function inhibitor intake.

Patients were seen 1 month after randomization for a clinical follow-up and documentation of INR and then at 6-month intervals. At the end of follow-up, all patients consented to continue clinical visits until the last patient had completed the 2 years observation period. They received written information on symptoms of VTE and bleeding, and were instructed to report in case of symptoms.

Laboratory analysis

Factor VIII activity was measured in plasma by a one-step clotting assay (Dade Actin FS Activated PTT Reagent, Dade Behring, Germany). Determination of antithrombin, protein C, or protein S and evaluation of the presence of antiphospholipid antibodies were performed at the time of VTE and 5 months thereafter as reported [3]. Plasma and whole blood samples were obtained after randomization, and were stored at -70°C for future testing.

Study endpoints

The endpoint of the study was recurrent symptomatic deep vein thrombosis and/or pulmonary embolism and major hemorrhagic complications.

Recurrent VTE was established by venography, color-duplex sonography, ventilation-perfusion scanning, and/or spiral computer tomography. Deep vein thrombosis was considered to have recurred if the patient had a thrombus in the leg not affected by the previous event; a thrombus in another deep vein in the leg affected by the previous event; or a thrombus in the same venous system affected in the previous event with proximal extension of at least 5 cm if the upper limit of the original thrombus had been visualized

or a constant filling defect surrounded by contrast medium (if the original thrombus had not been visible).

A major hemorrhage was defined as a bleeding that resulted in death, hospitalization, chronic sequelae, or transfusion with blood, plasma, or coagulation factors.

The diagnosis of endpoint events was established by an adjudication committee consisting of independent clinicians and radiologists unaware of the factor VIII levels.

Statistical analyses

Calculation of the number of study patients was based on our previous study in which risk of recurrent VTE in patients with high factor VIII levels was 36% at 24 months after discontinuation of vitamin K-antagonists as opposed to 5% in patients with lower levels [3]. Calculations were further based on the results of several trials in which the risk of recurrence in patients with VTE who continued vitamin K-antagonists at INR 2.0–2.85 beyond 6 months was 1% [6, 7, 8] and the risk of major hemorrhage during 2 years was approximately 4% [9, 10]. We wanted to show that the risk of the endpoints recurrence and major hemorrhage was 6% in patients with high factor VIII and prolonged anticoagulation. To keep an alpha of 0.05 and 90% power, 40 patients in each treatment group would have been needed.

For numerical operations SPSS 12.0 software (SPSS Inc. Headquarters, Chicago, IL, USA) was used. To test for homogeneity between strata we applied the log-rank and the generalized Wilcoxon test. Categorical data were checked for homogeneity using contingency-table analyses (by the chi-squared test), and continuous data (presented as mean±SD) were compared using Mann–Whitney *U* test. Time to recurrence (possibly censored) was analyzed according to survival methods. Probability of recurrence was estimated according to Kaplan and Meier [11].

In January 2005, when 3,219 patients with VTE had been screened, an interim analysis was performed after 17 patients had been randomized into each group because of low recruiting rate.

Results

Patients and treatment groups

Figure 1 shows a flow diagram according to the revised CONSORT Statement [12]. Between July 2001 and November 2004, 3,219 patients with a first VTE were screened; 3,174 were excluded because of one of the exclusion criteria; 11 patients refused to participate. Thus, the study population consisted of 34 patients. Seventeen patients were randomized to stop vitamin K-antagonists after 6 months and 17 to continue treatment for additional 2 years. Baseline characteristics of the two groups are shown in Table 1. They were well-balanced regarding clinical and thrombophilic characteristics.

Among patients allocated to stop vitamin K-antagonists, anticoagulation was continued in one patient due to his preference, and was resumed in another patient after 9 months because of a stroke as a complication of new-onset atrial fibrillation. Two patients assigned to prolonged anticoagulation declined to continue anticoagulation immediately after randomization and one patient decided to stop anticoagulation 10 months after study entry. These patients consented to follow-up visits and their data were analyzed according to the intention-to-treat-principle.

Recurrent venous thromboembolism and major bleeding

Two of 17 patients allocated to stop anticoagulation had recurrent VTE within the following 24 months. Two of 17

Fig. 1 Flow diagram of study patients according to CONSORT [12]

Table 1 Patients characteristics

	6 months VKA (<i>n</i> =17)	Prolonged VKA (<i>n</i> =17)	<i>p</i> value
Sex			
Male— <i>n</i> (%)	6 (35)	5 (29)	0.7
Female— <i>n</i> (%)	11 (65)	12 (71)	
Age (years)			
Mean±SD	54±16	53±18	0.7
Localization of VTE			
DVT only— <i>n</i> (%)	11 (65)	9 (53)	0.5
PE±DVT— <i>n</i> (%)	6 (35)	8 (47)	
Months of VKA before randomization			
Mean±SD	6.2±0.3	6.3±0.6	0.3
FVIII (IU/dl)			
Mean±SD	276±39	298±49	0.3
CRP (mg/dl)			
Mean±SD	0.5±0.08	0.5±0.03	0.9
BMI (kg/m ²)			
Mean±SD	26.4±3.3	29.2±5.1	0.2
Faktor V Leiden— <i>n</i> (%)	2 (12)	3 (18)	0.8
Faktor II G20210A— <i>n</i> (%)	0	1 (6)	0.3

VTE Venous thromboembolism, PE pulmonary embolism, DVT deep vein thrombosis, VKA vitamin K antagonists, SD standard deviation

patients randomized to continue anticoagulation developed recurrent VTE within 24 months. One patient had recurrence during vitamin K-antagonist treatment (with no documented INR at recurrence) and one patient stopped vitamin K-antagonists 10 months after randomization for personal reasons and had recurrence 4 weeks later.

One patient in the prolonged treatment arm experienced severe epistaxis requiring transfusion of 2 U of packed red blood cells after 10 months of vitamin K-antagonists, and anticoagulation was terminated. No bleedings during follow-up were seen among patients allocated to stop anticoagulation after 6 months.

Prolonged follow-up

All patients in the prolonged treatment arm stopped vitamin K-antagonists 24 months after randomization. Two of these patients wished to continue treatment. Clinical visits were continued until the last randomized patient completed the 24-months follow-up. Mean observation time for all patients was 37 months (range 4–64 months).

Five patients allocated to prolong anticoagulation had recurrence after vitamin K-antagonists had been stopped at 24 months. Thus, in total nine of 34 patients had recurrent VTE; their characteristics are shown in Table 2. No

Table 2 Characteristics of patients with recurrent VTE

Treatment group	Sex	Age (years)	Localization of 1st event	FVIII (IU/dl)	Time until recurrence (months after VKA)	Localizaton of recurrent VTE
6 months	F	62	PE	340	4.1	PE
6 months	M	47	DVT	364	6.1	PE
Prolonged	F	68	PE	275	10.3	PE
Prolonged	F	45	DVT+PE	339	24.1	DVT
Prolonged	M	76	PE	243	0.7	PE
Prolonged	F	69	DVT	234	6.0	DVT
Prolonged	F	69	DVT	277	1.1	PE
Prolonged	F	38	PE	400	Recurrence during VKA	PE
Prolonged	F	38	DVT+PE	332	13.3	DVT+PE
Mean±SD		57±15		311±57	8.2±7.2	

PE Pulmonary embolism, DVT deep vein thrombosis, VKA vitamin K antagonists, SD standard deviation

bleeding complications occurred during prolonged follow-up. According to Kaplan–Meier analysis, in patients with first unprovoked VTE and high factor VIII probability of recurrence at 2 years after discontinuation of vitamin K-antagonists was 30% (95% CI 13–46%) (Fig. 2).

In a post hoc analysis we looked for differences in clinical and thrombophilic characteristics between patients with and without recurrence. The two groups did not significantly differ with regard to age (mean $\pm$ SD, 57 $\pm$ 15 vs. 53 $\pm$ 18 years, $p=0.7$), sex (female 77.8% vs. 64.0%), factor VIII levels (mean $\pm$ SD, 312 $\pm$ 57 vs. 278 $\pm$ 37 IU/dl, $p=0.2$), proportion of carriers of factor V Leiden (0% vs. 27.8%) or prothrombin G20210A (14.3% vs. 0%), body mass index (mean $\pm$ SD, 30.6 $\pm$ 5.5 vs. 26.8 $\pm$ 3.7 kg/m², $p=0.1$). The proportion of patients with pulmonary embolism as first event was higher among those with recurrence as compared with those with initial isolated deep vein thrombosis (88.9% vs. 11.1%, $p=0.08$).

Discussion

Our study is the first to investigate efficacy and safety of prolonged secondary thromboprophylaxis in patients with first spontaneous VTE and high factor VIII levels. The results show that treatment with vitamin K-antagonists extended beyond 6 months is effective in preventing recurrent VTE. Among patients randomized to prolong anticoagulation, only one had recurrence during treatment. INR at recurrence had not been documented and it is thus unknown whether anticoagulation was adequate at this time. A second patient randomized to prolonged anticoagulation suffered recurrence after he had stopped treatment voluntarily. The only bleeding episode observed in the prolonged treatment group was epistaxis sufficiently severe to require red blood cell transfusion.

Fig. 2 Kaplan–Meier estimates of the probability of recurrence in patients with first VTE and high factor VIII

Patients receiving prolonged treatment discontinued vitamin K-antagonists after 2 years, but continued clinical visits for a mean of 19 months. During this time, five patients had recurrent VTE. While recurrence was effectively prevented during treatment, this benefit was not maintained after discontinuation of anticoagulation. This phenomenon has already been observed in other interventional trials. In the Warfarin Optimal Duration Italian trial, 3 months of vitamin K-antagonists were compared with 1 year of anticoagulation in patients with deep vein thrombosis [13]. Recurrence rates were significantly lower in the prolonged treatment group, but after 1 year returned to rates that were comparable to those of patients who stopped treatment earlier.

Two of 17 (12%) patients randomized to stop vitamin K-antagonists had spontaneous recurrent VTE after 4 and 6 months, respectively. This number was lower than expected and cannot be readily explained. The two study groups were well-balanced regarding clinical and thrombophilic characteristics and the low rate of recurrence can probably be considered a chance finding. However, 23 of 34 (68%) patients were women. When our trial was initiated, the higher risk of recurrence in men as compared with women was unknown, and we did not stratify our study population according to sex [14]. The larger proportion of women could therefore have resulted in an overall lower recurrence rate.

Our study confirms the increased risk of recurrence in patients with high factor VIII levels. Nine of the 34 patients developed recurrent VTE. Two years after withdrawal of vitamin K-antagonists, probability of recurrence was 30%, which was somewhat lower than the 37% seen in our previous study [3]. This difference could be explained by the large proportion of women in the present study with a known lower risk of recurrence. In five of six patients who had pulmonary embolism as a first event, VTE recurred as pulmonary embolism. This finding is in line with results from other studies that an initial diagnosis of pulmonary embolism predicts recurrence as pulmonary embolism [15–17].

The results of our study are limited by the small number of patients. In our previous study, 10% of patients had high factor VIII levels. However, for unknown reasons prevalence of high factor VIII among patients eligible for the present study was considerably lower. Moreover, 11 of 45 patients eligible for inclusion refused to participate because of personal preference to either continue or discontinue anticoagulation. The study was terminated early because of slow recruitment. The open design can be regarded as another limitation. Our study was purely academic and non-sponsored and a double-dummy design would have been beyond our resources. We excluded patients with VTE provoked by surgery, trauma, or pregnancy, as well as those

with previous recurrences. The decision on the duration of anticoagulation in these patients is usually based on the low recurrence risk in the former and the high risk in the latter group. We also excluded patients with high CRP-levels to avoid influence of acute phase reactions, as the relevance of high factor VIII with regard to thrombotic risk of patients with acute phase reactions is unknown.

In conclusion, the ultimate question whether patients with VTE and high factor VIII levels benefit from prolonged anticoagulant cannot be answered on the basis of our study because of the limited number of patients. Our trial shows that patients with unprovoked VTE and high factor VIII are at increased risk of recurrence and that prolonged anticoagulation may be considered in these patients already after the first VTE. Larger interventional trials are needed to evaluate the optimal secondary thromboprophylaxis in these patients.

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