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Recurrent thrombosis and survival after a first venous thrombosis of the upper extremity

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Summary

Little is known about the consequences of a first venous thrombosis in the upper extremity. We studied the incidence of, survival, and risk factors for recurrence in a follow-up study. We followed up 224 patients 18 to 70 years of age after a first venous thrombosis of the arm. Information was collected through anticoagulation clinics, the national death registry, discharge letters, and questionnaires. The median follow-up was 3 years, during which time 30 patients experienced a recurrent event, yielding an incidence rate of 43.2 per 1000 person-years. Survival was reduced: 55 out of 224 patients died, which was 5.4-fold higher than age- and sex-adjusted population rates (standardized mortality ratio 5.4; 95% CI 4.2-7.0). The risk of recurrence was 2-fold higher in women than in men (hazard ratio 1.8; CI 95% 0.9-3.9). A central venous catheter at the time of first thrombosis was associated with a reduced risk of recurrence. A body mass index ≥ 25 kg/m² and a first non-subclavian thrombosis appeared to increase the risk of a recurrent event. Prothrombotic mutation carriers did not appear to have an increased recurrence risk. The risk of recurrence was high, with women, patients with body mass index ≥ 25 kg/m², and patients with a first non-subclavian vein thrombosis having a higher risk of recurrence. Patients with a first venous thrombosis of the arm have a poor vital prognosis.

Introduction

The incidence of venous thrombosis varies between 1 per 10 000 in young adults and 1 per 100 persons per year in the very old, with a population average of 1 to 3 per 1000 persons per year^{2,3}. About 4% of all cases of venous thrombosis are located in the upper extremities^{41,51}. Because of its rarity, thrombosis of the arm has not been investigated as extensively as deep venous thrombosis of the leg or pulmonary embolism. However, the incidence of upper extremity venous thrombosis increases over time^{90,122,123}. This is mainly due to the increasing use of central venous catheters (CVCs) which, combined with malignancy, is the strongest determinant of upper extremity venous thrombosis, with >1000-fold increased risk compared with patients without a CVC and malignancy^{44,86}. Besides foreign objects such as CVCs and pacemaker leads, the main known causes of arm thrombosis are a hypercoagulable state, as induced by malignancy or coagulation abnormalities, and stasis in veins. The latter can be caused by a variety of related syndromes, ie, trauma of the arm, effort-related compression of the deep veins of the upper extremity (Paget-Schrötter syndrome), and compression caused by the thoracic outlet syndrome^{41,46,68,86,90,91,124}. A few of the major coagulation abnormalities appear to enhance the risk of arm thrombosis as they do for venous thrombosis of the lower extremities^{41,68}. Factor V Leiden, Protein C and S deficiency, anticardiolipin antibodies and lupus anticoagulants are frequent among patients with a venous thrombosis of the upper extremity^{87–89,91}.

Because of the low incidence, few studies have investigated recurrent venous thrombosis of the arm and its risk factors^{90,103,106,108}. In these studies, the cumulative incidence of recurrence after 1 year was 2% to 5%^{90,106,108}. Inclusion criteria and end points differed between studies. One study included patients with an idiopathic venous thrombosis of the arm and reported only venous thrombosis of the arm as a recurrent event⁹⁰. Two studies assessed risk factors for a recurrence among patients with primary or secondary venous thrombosis of the arm and included all types of venous thrombosis as recurrent events^{106,108}. Prothrombotic mutations appeared to be associated with a recurrent event in 1 study of 90 patients with a first primary venous thrombosis of the arm⁹⁰. However, another study did not confirm these results¹⁰⁶.

In the Multiple Environmental and Genetic Assessment of Risk Factors for Venous Thrombosis study (MEGA-study), 224 consecutive patients with a first venous thrombosis of the arm were included in the present follow-up study. The aim was to investigate survival and the incidence of recurrent venous thrombosis in any location in relation to risk factors such as the presence of a CVC, malignancy, prothrombotic mutations, and other putative risk factors.

Materials and Methods

Patient Selection

Two hundred twenty-four consecutive patients 18 to 70 years of age with a first venous thrombosis of the upper extremity were included between March 1999 and August 2004.

The MEGA study is a large population-based case-control study to assess risk factors for a first venous thrombosis. Details of this study have been given elsewhere^{7,86}. Patients were included from the files of six anticoagulation clinics, which monitor virtually all patients who receive treatment with vitamin K antagonists in the Netherlands, each in a well-defined geographical region. A venous thrombosis of the internal jugular vein, subclavian, axillary, brachial or the superficial basilic and cephalic veins was considered to be an upper extremity venous thrombosis. Fifteen patients were also diagnosed with a pulmonary embolism or a venous thrombosis of the lower extremity. Venous thrombosis of the upper extremity was confirmed with either ultrasound, contrast venography or computed tomography⁸⁶.

Data collection

In 2006, municipal registries were contacted to retrieve the most recent addresses of patients and to assess vital status. Causes of death were obtained from the Central Bureau of Statistics Netherlands (CBS), which stores all Dutch death certificates. An inquiry form was sent to patients who were still alive and who had initially agreed to participate in a follow-up study. The inquiry form asked about subsequent visits to anticoagulation clinics and the occurrence of a recurrent event in any location. Patients were sent a follow-up questionnaire about putative risk factors for a recurrent venous thrombosis, either by mail or via the Internet. Patients who did not reply were contacted by phone. Information about recurrences and duration of initial vitamin K antagonist treatment for all 224 patients also was obtained from anticoagulation clinics. Recurrences were included when confirmed by ultrasound, contrast venography or computed tomography according to the discharge letters. Information regarding putative risk factors at time of first venous thrombosis was obtained from the baseline questionnaire and from the discharge letters of the first thrombosis⁷. An event was defined as idiopathic in the absence of surgery, oral contraceptive use, injury and plaster cast in the previous 3 months, malignancy, absence of CVC in the previous month, and absence of puerperium, factor V Leiden mutation or prothrombin 20210A mutation. All participants gave informed consent. This study was approved by the Medical Ethics Committee of the Leiden University Medical Center, Leiden, the Netherlands.

Blood collection and laboratory analysis

Blood samples were taken at least 3 months after discontinuation of vitamin K antagonist treatment for the first thrombotic event. Blood draws were collected from 67 patients. Blood samples were drawn into vacuum tubes containing 0.1 volume 0.106 mol L⁻¹ trisodium citrate as anticoagulant. Blood samples were separated into plasma and cells through centrifugation. Prothrombin activity, Factor VII activity, Factor VIII activity, Factor X activity, and Factor XI activity were measured with a mechanical clot detection method on a STA-R coagulation analyzer. All measurements were performed following the manufacturer's instructions (Diagnostica Stago, Asnieres, France). Levels of factor IX antigen were determined by ELISA. Fibrinogen activity was measured on the STA-R analyzer according to methods of Clauss. In the presence of excess thrombin, the coagulation time

of a diluted plasma sample was measured. Von Willebrand factor antigen was measured with the immunoturbidimetric method, using the STA liatest kit (rabbit anti-human von Willebrand factor antibodies), following the instructions of the manufacturer (Diagnostica Stago). DNA was collected with buccal swabs from patients who were unable to give a blood sample and from all patients who were included beginning in June 2002. In total, DNA samples were collected from 178 patients. High molecular weight DNA was collected by using a salting-out method and stored at -20 °C until amplification. DNA-analysis of the factor V Leiden and prothrombin 20210A mutation was performed with a combined polymerase chain reaction method. Assessment of these mutations in DNA retrieved from buccal swabs was performed identically to the method for DNA obtained from whole blood. A detailed description of these methods was described previously⁷.

Statistical Analysis

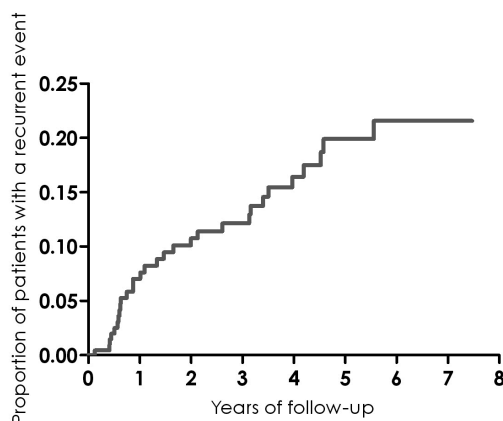
Cumulative incidence was estimated by the Kaplan-Meier technique. Incidence rates were the number of new events over the total number of person-years. Person-years were calculated from date of first event and from discontinuation of the initial vitamin K antagonist treatment until recurrent event, death or end of study, whichever came first. Participants who died during follow-up of a cause other than venous thrombosis were censored at date of death. Patients who were not able to complete the inquiry form were censored at their last contact within the MEGA study and considered study withdrawals. The end of study date was October 1, 2006. Hazard ratios (HRs) were estimated with a Cox proportional-hazards model. Adjustments were made for age and sex. We did not adjust for race because our follow-up study included >95% whites. Cox analysis was performed in the overall cohort of 224 patients and in 163 patients after they had discontinued vitamin K antagonist treatment. Median duration of vitamin K antagonist treatment was 6 months (5th percentile, 2 months; 95th percentile, 57months). High levels of prothrombin, factor VII activity, factor VIII activity, factor IX antigen, factor X activity, factor XI activity, von Willebrand factor, and fibrinogen were defined as a level above the 90th percentile in the group of patients without a recurrent event. Standardized mortality ratios (SMRs) were estimated for the overall patient group with the general Dutch population as a reference¹²⁵ and in men and women separately with the sex-specific population rates as reference. These SMRs estimate the rate of death relative to age- and sex-adjusted rates from the general population or, in other words, give the ratio of the observed and expected number of deaths when population rates are applied to the cohort. Data from 2003 were used to represent the average general population of the period from 1999 till 2006. Confidence intervals were based on a Poisson distribution. All analyses were performed with SPSS version 14 (SPSS Inc, Chicago, Ill). The authors had full access to and take responsibility for the integrity of the data. All authors have read and agreed to the manuscript as written.

Results

Patients

Of the 224 patients, 47% were men, and the median age at time of first thrombosis was 46 years (5th percentile, 21 years; 95th percentile, 67 years). The median follow-up period was 3 years (range 0 to 7.5 years). Of the 30 recurrences, 9 were during vitamin K antagonist treatment. Four of these 9 events were within the first 6 months of treatment. The overall 2-year cumulative incidence of a recurrent venous thrombosis was 8% (95% CI 4 to 12). The incidence rate was 43.2 per 1000 person-years (95% CI 27.8 to 58.7 per 1000 person-years), ie, >4% recurrence risk per year (The Table and Figure 1). The time between first and second events varied from 45 days to 5.5 years. Of the 30 recurrences, 18 were located only in the upper extremity, 1 in the arm in combination with a pulmonary embolism, 6 in the leg, 1 was a Budd-Chiari syndrome, and 4 were pulmonary emboli without a known origin. Of the 19 patients with a recurrent thrombosis in the arm, 14 thromboses were located in the same arm as the first occurrence, but 5 were on the opposite side. Of these 19 patients 8 had a malignancy, compared with 70 out of all 224 patients. Four of these 8 patients developed a recurrent thrombosis (50%) in the same arm as the first event. Of the 22 patients with a recurrent event without malignancy, 10 (45%) developed the event in the same arm as the first event.

Of the 224 patients, 31 patients were censored (because of recurrence, death resulting from causes other than venous thrombosis or withdrawal from the study) during the initial 6 months of treatment. Of the remaining 193 patients, 163 discontinued treatment during our study (115 within 6 months, 48 after >6 months), and 30 patients were still receiving anticoagulant treatment at the end of follow-up. Apart from the overall group of 224 patients,



Period in months	0-6	7-12	13-18	19-24	25-30	31-36	37-42	43-48	49-54	55-60	61-86
N at risk	224	184	155	144	138	128	110	102	85	69	59
N events	4	6	4	1	2	1	2	2	2	2	1

Figure 1. Kaplan Meier for risk of recurrent event in the overall group of 224 patients

Table 1. Risk factors at baseline and the risk of a recurrent event in the overall group of 224 patients with a first upper extremity venous thrombosis and the subgroup of 163 patients after discontinuation of vitamin K antagonist treatment

	Overall group of patients					Subgroup of patients after treatment				
	N	N Recurrences (%)	Incidence rate*	Hazard ratio	Adjusted Hazard Ratio\$	N	N Recurrences (%)	Incidence rate*	Hazard ratio	Adjusted Hazard ratios
Overall	224	30(13)	43.2			163	21 (13)	40.1		
Men	106	10(9)	29.9	1	1	81	6(7)	22.2	1	1
Women	118	20(17)	55.6	1.8 (0.9-3.9)	1.8 (0.9-3.9)	82	15(18)	59.2	2.6 (1.0-6.7)	2.6 (1.0-6.7)
Age < 50 years	123	20(16)	51.2	1	1	88	13(15)	44.5	1	1
Age > 50 years	101	10(10)	32.9	0.6 (0.3-1.3)	0.6 (0.3-1.3)	75	8(11)	34.6	0.8 (0.3-1.9)	0.8 (0.3-1.9)
No malignancy	154	22(14)	42.8	1	1	116	14(12)	34.6	1	1
Malignancy	70	8(11)	44.4	1.0 (0.5-2.3)	1.1 (0.5-2.4)	47	7(25)	58.7	1.6 (0.6-4.0)	1.9 (0.7-5.3)
No CVC	168	28(17)	53.3	1	1	123	19(15)	45.8	1	1
CVC	56	2(4)	11.9	0.2 (0.1-0.9)	0.2 (0.1-1.0)	40	2(5)	18.3	0.4 (0.1-1.7)	0.4 (0.1-1.6)
No Surgery	194	26(13)	48.1	1	1	135	17(13)	37.8	1	1
Surgery	30	4(13)	43.8	0.9 (0.3-2.7)	1.1 (0.4-3.2)	28	4(14)	53.7	1.4 (0.5-4.1)	1.5 (0.5-4.6)
Provoked	156	21(13)	43.8	1	1	110	16(15)	47	1	1
Idiopathic	68	9(13)	41.7	1.0 (0.4-2.1)	1.2 (0.5-2.7)	53	5(9)	27.3	0.6 (0.2-1.6)	0.8 (0.3-2.3)
Patients with location	162					124				
Subclavian vein	114	11(10)	28.1	1	1	88	9(10)	29.8	1	1
Non subclavian vein	48	10(21)	62.4	2.2 (0.9-5.2)	2.0 (0.8-2.7)	36	7(19)	60	2.0 (0.8-5.4)	1.9 (0.7-5.0)
Only subclavian vein	53	4(8)	21.7	1	1	40	3(8)	22	1	1
Other single vein	44	9(20)	62.0	2.8 (0.9-9.1)	2.7 (0.8-8.7)	32	6(19)	58.2	2.6 (0.6-10.3)	2.7(0.7-10.8)
Single veins	97	13(13)	39.5	1	1	72	9(13)	37.5	1	1
Multiple veins	65	8(12)	35.9	0.9 (0.4-2.1)	0.9 (0.4-2.2)	52	7(13)	39	1.0 (0.4-2.7)	1.0 (0.4-2.7)
Patients with known BMI	203					149				
BMI (kg/m2) <25	122	13(11)	34.1	1	1	90	9(10)	31	1	1

Table 1. Continued

	Overall group of patients					Subgroup of patients after treatment				
	N	N Recurrences (%)	Incidence rate*	Hazard ratio	Adjusted Hazard Ratio§	N	N Recurrences (%)	Incidence rate*	Hazard ratio	Adjusted Hazard ratio§
25-29	56	9(16)	46.9	1.3 (0.6-3.1)	1.6 (0.7-3.8)	44	7(16)	46.3	1.4 (0.5-3.8)	1.7 (0.6-4.8)
≥ 30	25	6(24)	90.2	2.5 (0.9-6.5)	2.7 (1.0-7.3)	15	3(20)	62.8	1.9 (0.5-7.0)	2.1 (0.5-8.1)
Women aged 18-50	64					43				
No oral contraceptives	28	7(25)	89.8	1	1	17	5(18)	103.9	1	1
Oral contraceptives	36	8(22)	68.5	0.8 (0.3-2.1)	0.8 (0.3-2.1)	26	5(14)	56.1	0.5 (0.2-1.9)	0.5 (0.2-1.9)
Patients with DNA sample	178					135				
Without FVL or G20210A	149	20(13)	41.3	1	1	112	13(12)	34.3	1	1
With FVL or G20210A	29	3(10)	27.3	0.7 (0.2-2.2)	0.7 (0.2-2.2)	23	3(13)	37.2	0.9 (0.3-3.5)	0.8 (0.3-3.0)

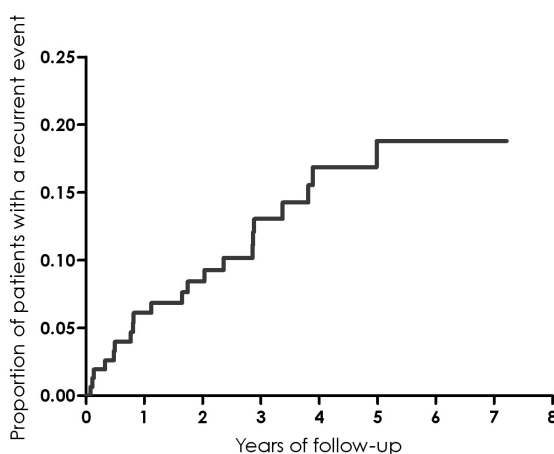
*per 1000 person-years; § All analyses were adjusted for age and sex, except when the analysis was restricted to one sex or age group

we also report the results of these 163 patients after their discontinuation of treatment. Of the 163 patients who discontinued vitamin K antagonist treatment, 21 subsequently had a recurrent event. The median follow-up after discontinuation of vitamin K antagonist treatment in these patients was 2 years (range 0 to 7.2 years) (Figure 2). The 2-year cumulative incidence was 7% (95% CI 2 to 12). The incidence rate after discontinuation was 40.1 per 1000 person-years (95% CI 23.0 to 57.3). The incidence of recurrence for the 61 patients who did not discontinue treatment at any time during follow-up (224-163=61, of whom 9 had a recurrence) was 122.5 per 1000 person-years 95% CI 42.4 to 202.4. Some of these (4 out of 9) were early recurrences, during the first 6 months of treatment; median duration of follow-up was 6 months (5th percentile, 1 month; 95th percentile, 75 months).

Risk factors at baseline

The table shows the effects of putative risk factors present at the time of first venous thrombosis on the incidence of a recurrent event for the overall group of 224 patients and for 163 patients after discontinuation of vitamin K antagonist treatment.

In the overall group female sex (adjusted HR [HRadj] 1.8; 95% CI 0.9 to 3.9), a first nonsubclavian vein thrombosis (HRadj, 2.0; 95% CI 0.8 to 2.7) and body mass index (BMI) ≥ 25 kg/m² (BMI 25-29 kg/m²: HRadj, 1.6; 95% CI 0.7 to 3.8; BMI ≥ 30 kg/m²: HRadj, 2.7; 95% CI 1.0 to 7.3) were associated with a higher risk of a recurrent event. A CVC at time of first venous thrombosis was associated with a decreased risk of recurrence (HRadj, 0.2; 95% CI 0.1 to 1.0). The other factors did not show an effect on recurrence risk (the Table).



Period in months	0-6	7-12	13-18	19-24	25-30	31-36	37-42	43-48	49-54	55-60	61-70
N patients at risk	163	138	128	120	107	98	86	69	54	50	41
N events	6	3	1	2	2	3	1	2	0	1	0

Figure 2. Kaplan Meier for risk of recurrent event in the subgroup of 163 patients after discontinuation of vitamin K antagonist treatment

The results in 163 patients after discontinuation of vitamin K antagonist treatment did not differ from the overall results for most putative risk factors. Only the effect of malignancy and oral contraceptive use seemed to be different. Malignancy at time of first thrombosis was associated with a weakly elevated risk of a recurrence (HRadj, 1.9; 95% CI 0.7 to 5.3), whereas women who used oral contraceptives at time of their first event had a decreased risk of a recurrent event (HRadj, 0.5; 95% CI 0.2 to 1.9). Most of these women (32 out of 36 for whom information about oral contraceptive use after the initial event was available) had discontinued oral contraceptives after the initial event.

Among all 224 patients, 70 were diagnosed with malignancy at or shortly after the time of the initial event; 44 of these patients died during follow-up. The overall relative risk of recurrence in patients with malignancy was 1.1 (95% CI 0.5-2.4). Of the 47 patients with malignancy who discontinued vitamin K antagonist treatment 7 had a recurrent event after discontinuation (58.7 per 1000 person-years; 95% CI 15.2 to 102.3). Fourteen recurrences occurred in the 116 patients without malignancy (34.6 per 1000 person-years; 95% CI 16.5 to 52.8). Of the 61 patients who were treated with anticoagulants throughout follow-up, 23 had a malignancy. Of these 23 patients, 1 developed a recurrent venous thrombosis during vitamin K antagonist treatment (30.6 per 1000 person-years; 95% CI 0 to 122).

Coagulation Factors

A blood sample was drawn from 67 patients after they had stopped using vitamin K antagonists. Of these 67 patients, 10 experienced a recurrent event. HRs were calculated for elevated levels of factor IX and factor XI. Of 6 patients with elevated factor IX levels, 1 patient had a recurrent event, compared with 9 out of 61 patients with normal factor IX, which suggests a 2-fold increased risk (HRadj, 2.1; 95% CI 0.2 to 23.0). Of 6 patients with elevated factor XI levels, 1 patient had a recurrent event, compared with 9 out of 61 patients with normal FXI activity, again suggesting an elevated risk (HRadj, 3.3; 95% CI 0.4 to 30.5), although in both instances with a wide CI. None of the patients with high levels of factor II, factor VII, factor VIII, factor X, von Willebrand factor, and fibrinogen experienced a recurrent event.

Mortality

Fifty-five out of 224 patients (25%) died during follow-up, 34 of whom were women. Twenty five of these 55 patients died during the first year. Median age at death was 58 years (5th percentile 37 years, 95th percentile 69 years). Malignancy was the main cause of death. Forty-four out of 55 patients died of malignancy, of whom 26 were women, ie, of the 70 patients with a malignancy, 63% (44/70) had died at the end of follow-up. In comparison, among the 154 patients without malignancy, 11 patients (7%) had died. Other causes of death were the recurrent event itself (n=2), or death related to autoimmune diseases (n=2), pulmonary diseases (n=4) and heart failure (n=3).

The risk of death compared to the general population, expressed as an SMR was 5.4-fold (95% CI, 4.2 to 7.0) increased. The SMR was 7.7 (95% CI, 5.1 to 11.9) for men compared to the

male population and 15.5 (95% CI 11.1-21.6) for women compared to the female population. When patients with malignancy were excluded, the overall SMR was 1.1 (95% CI, 0.6 to 2.2); SMR was 0.5 (95% CI, 0.1 to 3.4) for men and 4.7 (95% CI, 2.3 to 9.9) for women.

Risk Factors Shortly Before a Recurrent Venous Thrombosis

Of the initial 224 patients, 72 were not able to fill in the questionnaire, 55 died, 2 emigrated, and 15 refused to participate in further follow-up. Of the remaining 152 patients, 126 patients returned the inquiry form, and 104 patients answered additional questions by mail, Internet or phone. Of these 104 patients, 13 were still using vitamin K antagonist treatment and were therefore excluded. Of 91 patients, 12 had a recurrent event. Four had a malignancy, 2 had surgery and 3 patients either carried the Factor V Leiden or the Prothrombin 20210A mutation, 1 event was related to pregnancy and 2 were idiopathic.

Discussion

We studied the risk of recurrent thrombosis and death in a large cohort of 224 patients with a first venous thrombosis of the upper extremity. The cumulative incidence of recurrence after 2 years was 8% (95% CI, 4 to 12%), and the incidence rate of recurrence was 43.2 per 1000 person-years (95% CI, 27.8 to 58.7). Women had a 2-fold higher recurrence risk than men and appeared to have, contrary to men, a decreased survival in the absence of malignancy. There appeared to be an increased risk of recurrence for patients with a first nonsubclavian vein thrombosis and for patients with a BMI $\geq 25\text{kg/m}^2$. Patients with a first thrombosis resulting from a CVC had a decreased risk of a recurrent event.

After discontinuation of treatment (n=163) the 2 year cumulative incidence was similar at 7% (95% CI, 2 to 12%), which was also similar to incidences found in 2 previous smaller studies (4.2% and 7%) that included only patients after discontinuation of treatment^{90,108}. The incidence of recurrence in patients who did not discontinue treatment during our study was high (122.5 per 1000 person-years; 95% CI, 42.4 to 202.4). This result is difficult to interpret, for, firstly, this figure includes patients with early recurrences (during the first 6 months of treatment) and patients with end stage disease or a malignancy.

In one respect, our results are strikingly different from results of previous studies focusing on recurrence after a venous thrombosis of the leg. Men with a venous thrombosis of the leg clearly have a higher risk of recurrence than women^{24,30,36,126,127}. In contrast, in venous thrombosis of the arm we found an increased risk of recurrence for women. There is no clear explanation for the gender difference in patients with a venous thrombosis of the upper extremity. We found a reduced recurrence risk for women who used oral contraceptives at the time of their first thrombosis. However, most women discontinued oral contraceptive use after the initial event. Therefore, oral contraceptive use does not explain the difference in risk between men and women.

The incidence rate of recurrence appeared to increase with BMI, whereas BMI was not a clear risk factor for a first thrombotic event in the arm^{86,92,128}. First events in the subclavian vein tended to recur less often than thromboses in other veins of the arm. The reason may be the removal of the CVC in these patients because most CVCs are located in the subclavian vein. However, we do not have data about removal of CVCs and therefore we are not able to corroborate this explanation. Patients with malignancy appeared to have an increased risk of a recurrent event after treatment and prolonged treatment in these patients may be beneficial.

Only 14 of the 30 recurrences were in the same arm as the initial thrombosis. When we exclude the 4 pulmonary emboli with unidentified origin, we find that at least 12 recurrences, roughly half, occurred in another location. There were no differences in malignancy and prothrombotic defects between the patients with a recurrence in the same location and patients with a recurrent event in another location.

Nine of the 30 recurrence occurred during treatment. Four of these events were within 6 months after the first event; therefore, it is uncertain if they are true recurrence or extensions of the original clot. Only 1 of these 4 recurrences was in a different extremity. It should be noted that the results of the overall group did not differ from the results of the subgroup of 163 patients after discontinuation of treatment.

A thrombosis of the arm is associated with a poor prognosis: 25 % (55 of 224) patients died, and 25 of these deaths were in the first year after thrombosis. These were mainly patients with cancer.

The factor V Leiden and prothrombin 20210A mutation, present in 17% of patients, did not affect recurrence risk. This finding is in line with previous studies on recurrence risk after a first venous thrombosis of the leg^{22,23,36}. An analysis regarding levels of coagulation factors could be performed in 67 patients. Only a few patients had abnormal levels, and most of them did not have a recurrent event. Although our follow-up study on patients with a first venous thrombosis of the upper extremity is one of the largest studies performed so far, the number of patients with prothrombotic defects was small, and thus CIs were wide. Therefore, no firm conclusions can be drawn from these results and clinical strategies of testing for prothrombotic abnormalities cannot be recommended.

We were able to trace all 224 patients indirectly via anticoagulation clinics. One hundred and twenty six patients were contacted directly by the inquiry form. We did not have information about the exact location of the first venous thrombosis in all patients. Because the inability to contact patients and the absence of exact information in discharge letters are not likely to be related to location of the thrombus, we do not believe they biased our results. Information on risk factors preceding the second event was available for 91 patients who discontinued vitamin K antagonist treatment through a follow-up questionnaire. Only 2 of the 12 recurrent events in this group were idiopathic, indicating that patients with risk factors may need more attention. Four of these recurrences were in patients with malignancy.

Conclusions

Patients with a first venous thrombosis of the arm have an increased risk of death compared to the general population that is mainly due to malignancy. Eight percent of the patients experienced a recurrence within 2 years. Being female, having a BMI $>25 \text{ kg/m}^2$, and having a first nonsubclavian vein thrombosis seem to be the most important risk factors for a recurrent venous event in patients with a venous thrombosis of the upper extremity.

