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IN FOCUS

Post-thrombotic syndrome, recurrence, and death 10 years after the first episode of venous thromboembolism treated with warfarin for 6 weeks or 6 months

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Summary. *Background:* The influence of the duration of anticoagulant therapy after venous thromboembolism (VTE) on the long-term morbidity and mortality is unclear. *Aim:* To investigate the long-term sequelae of VTE in patients randomized to different duration of secondary prophylaxis. *Methods:* In a multicenter trial comparing secondary prophylaxis with vitamin K antagonists for 6 weeks or 6 months, we extended the originally planned 2 years follow-up to 10 years. The patients had annual visits and at the last visit clinical assessment of the post-thrombotic syndrome (PTS) was performed. Recurrent thromboembolism was adjudicated by a radiologist, blinded to treatment allocation. Causes of death were obtained from the Swedish Death Registry. *Results:* Of the 897 patients randomized, 545 could be evaluated at the 10 years follow-up. The probability of developing severe PTS was 6% and any sign of PTS was seen in 56.3% of the evaluated patients. In multivariate analysis, old age and signs of impaired circulation at discharge from the hospital were independent risk factors at baseline for development of PTS after 10 years. Recurrent thromboembolism occurred in 29.1% of the patients with a higher rate among males, older patients, those with permanent triggering risk factor – especially with venous insufficiency at baseline – signs of impaired venous circulation at discharge, proximal deep vein thrombosis, or pulmonary embolism. Death occurred in 28.5%, which was a higher mortality than expected with a standardized incidence ratio (SIR) of 1.43 (95% CI 1.28–1.58), mainly because of a higher mortality than expected from cancer (SIR 1.83; 95% CI 1.44–2.23) or from myocardial infarction or stroke (SIR 1.28; 95% CI 1.00–1.56). The duration of anticoagulation did not have a statistically significant effect on any of the long-term outcomes. *Conclusion:* The morbidity and mortality during 10 years after the first episode of VTE is high and not reduced by extension of secondary prophylaxis from 6 weeks to 6 months. A strategy to reduce recurrence of VTE as well as mortality from arterial disease is needed.

Keywords: death, deep vein thrombosis, myocardial infarction, post-thrombotic syndrome, pulmonary embolism, recurrence, stroke, warfarin.

Introduction

Venous thromboembolism (VTE) is associated with acute morbidity, including pain and swelling of the leg and, in case of symptomatic pulmonary embolism (PE), respiratory symptoms, heart failure, and sometimes death. Long-term sequels may also occur, such as the post-thrombotic syndrome (PTS) with pain, swelling, pigmentation, eczema, and ulceration of the skin after deep vein thrombosis (DVT), chronic pulmonary hypertension after PE, and recurrent thromboembolic events. The incidence of the PTS varies in reports published during the past decade from 7% to 82%, depending on the characteristics

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of the population and the duration of follow-up [1–8]. The severe PTS was observed in 0.7–29%, mainly depending on the definition of the syndrome and the duration of follow-up [1,3–5,8,9]. These studies were retrospective except for two trials, in which patients were randomized to use graded compression stockings for at least 2 years or no stockings [3,8]. The use of compression therapy was associated with a reduction of the incidence of PTS. Ipsilateral recurrence of DVT was shown in another study to be strongly associated with the risk for the PTS with a hazard ratio of 6.4 [1]. It is not known whether the duration of secondary prophylaxis with vitamin K antagonists has any effect on the risk of developing the PTS. It could be hypothesized that with a too short duration of anticoagulation there are, in addition to the symptomatic and objectively verified recurrent events, also more asymptomatic recurrences, which may have an impact on the venous circulation.

In the Duration of Anticoagulation (DURAC) I trial, patients with the first episode of VTE were randomized to secondary prophylaxis with vitamin K antagonists for 6 weeks or 6 months [10]. The longer duration was associated with a lower risk of recurrence after 2 years [10] and after 6 years of follow-up [11] without a statistically significant increase of the risk of major hemorrhage. In a *post hoc* analysis, the longer treatment also appeared to be associated with a lower risk of developing cancer after at least 6 years of follow-up [12]. The development of long-term sequels at 10 years of follow-up after the first episode of VTE, with emphasis on the PTS, is reported here.

Methods

The design of the study has been reported previously [10]. Briefly, patients with the first episode of DVT of the lower limb ($n = 790$) or PE ($n = 107$), objectively verified with venography or perfusion–ventilation lung scanning, respectively, were included after informed consent. Major exclusion criteria were diagnosis of cancer at any time before randomization, previous venous ulcer, and reasons to suspect poor compliance with the study procedures. After initial treatment with unfractionated or low-molecular-weight heparin and, if indicated, thrombolytic therapy (only 22 cases), the patients were assigned by central telephone randomization according to computer-generated lists at the time of discharge from the hospital to continue secondary prophylaxis with the vitamin K antagonists warfarin or dicoumarol for 6 weeks or 6 months. Patients and investigators were aware of the assignments. The treatment was targeted at an International Normalized Ratio (INR) of 2.0–2.85. The quality of anticoagulation was defined as 'good' if at least 75% of all INR results were at least 2.0. Patients with DVT were urged to use graduated and individually measured compression stockings for at least 1 year. The follow-up was clinical with visits after 1.5, 3, 6, 9, and 12 months, and then annually. Signs or symptoms of recurrent VTE had to be verified objectively with the same methods as used for the initial diagnosis, as previously described [10]. All such events were adjudicated by an independent radiologist, who was blinded to the duration of treatment.

For all patients included with DVT as the index event we collected information on chronic swelling or skin abnormalities to evaluate incidence of PTS prior to the inclusion. Ulcers were an exclusion criterion and would not be noted. Furthermore, at randomization, which occurred approximately 1 week after admission, the condition of the leg was graded according to a 5-point scale. One point each was awarded for an increase by more than 1 cm of the circumference (a) at the ankle, (b) at maximum calf level, (c) at 10 cm above patella, (d) teleangiectasia or varicose veins, and (e) hyperpigmentation, and three points or more were defined as evidence of 'impaired circulation'. At the follow-up visits from 6 weeks to 2 years, an expanded 8-point scale was used for the same purpose, with one additional point each for (f) a feeling of heaviness in the leg, (g) venous claudication, and (h) venous ulcer.

The trial was designed to end after 2 years, but the protocol was later amended to allow for an extended 10-year follow-up to study the occurrence of the PTS, late recurrent thromboembolism, and mortality. At the concluding 10-year visit, the clinical signs of the PTS were classified according to the updated standards of the International Consensus Committee on Chronic Venous Disease [13]. This places the patient into one of seven clinical classes, corresponding to: (C_0) no signs of venous disease, (C_1) teleangiectasia, reticular veins or malleolar flare, (C_2) varicose veins, (C_3) edema without skin changes, (C_4) pigmentation, venous eczema or lipodermatosclerosis, (C_5) skin changes as above with healed ulceration, and (C_6) skin changes as above with active ulceration. The patients were also asked about symptoms associated with venous disease, such as pain, heaviness, or skin irritation. The 10-year examination was performed by the investigators or by specially trained nurses, who had been provided with standardized color photographs representing the different classes.

Patients with objectively verified ipsilateral recurrence of DVT were excluded from this assessment, because of the strong association with the PTS. Patients with other types of recurrent VTE, and who thereby had reached an endpoint according to the original protocol, were contacted again for continued follow-up. Patients without telephone access and who did not respond to written invitations were checked against the Death Registry in Sweden. For suspected recurrences after 2 years of follow-up, ultrasonography of the leg veins in case of thrombosis in previously unaffected venous segments or with computed tomography of the pulmonary arteries was added as possible alternatives to venography or ventilation–perfusion lung scanning, respectively, for objective verification of the diagnosis. Cause of death was verified for all deceased patients by reviewing medical records, autopsy protocols, and the Death Registry.

For each year of follow-up after inclusion, the expected numbers of deaths from myocardial infarction (MI) or ischemic stroke were calculated by multiplication of the number of patients observed with the appropriate nationwide sex- and age-specific incidence rates in 5-year age groups,

provided by the National Board of Health and Welfare. Relative risk was expressed as standardized incidence ratio (SIR), which is the ratio of the observed numbers of incident deaths to those expected.

Laboratory analyses

Plasminogen activator inhibitor type 1 (PAI-1) and cardiolipin antibodies of IgG-type were determined at 6 months after the index event, as previously described [14,15]. Samples for analysis of the factor V G1691A mutation and the prothrombin G20210A polymorphism were obtained in all available patients of <70 years of age at 4–6 years after the index event, as previously reported [16]. On a subset of these patients, remaining plasma samples from 88 patients were subsequently used to measure the von Willebrand factor (VWF) antigen.

Statistical analyses

The sample size calculation for this study had only been performed for the initial objective to determine the risk of recurrence during 2 years with 6 weeks or 6 months of secondary prophylaxis. Ninety-five percent confidence intervals, using binomial distribution, were determined for all reported proportions. Univariate analysis of all proportions was performed with chi-squared analysis, using Yate's correction. In the multivariate analysis, all variables that yielded a *P*-value of <0.1 in the univariate analysis were entered. The PoLytomous Universal Model (PLUM) was used in the multivariate analysis, which was performed with SPSS software from Technologies4Targeting Ltd (Peterborough, UK).

The study was approved by the regional and local ethics committees and the amendment for extension of the trial was approved by the regional ethics committee of the Karolinska Institute.

Role of the funding sources

The sponsors did not have any influence on study design; on the collection, analysis, and interpretation of data; on the writing of the report; or on the decision to submit the paper for publication.

Results

During the period April 1988 to April 1991, 897 patients were enrolled and randomized at 16 centers in Sweden; 443 were assigned to 6 weeks and 454 to 6 months of anticoagulation. At the 10 years visit, 545 patients were available for evaluation of PTS, 267 in the 6 weeks group and 278 in the 6 months group (Fig. 1). With additional treatment periods with vitamin K antagonists because of recurrent VTE, atrial fibrillation or other indications, their mean time on anticoagulation became 4.1 months and 9.9 months, respectively, over 10 years. The reasons for loss from follow-up regarding the PTS at 10 years are shown in Table 1. The majority of these patients, 88% in the 6 weeks group and 87% in the 6 months group, were not evaluated because of ipsilateral recurrent DVT or death before 10 years.

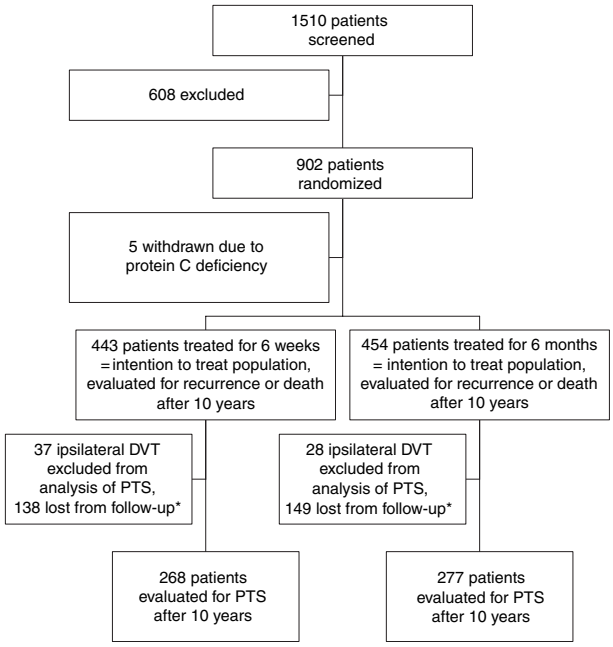

Fig. 1. Flow of patients in the study. *Loss from follow-up is detailed in Table 1.

Table 1 Reasons for no 10 years follow-up of the post-thrombotic syndrome (PTS), according to the length of treatment

Reason	6 weeks ($n = 443$)	6 months ($n = 454$)
Recurrent ipsilateral deep vein thrombosis (DVT)*	37	28
Death within 10 years†	118	125
Death after 10 years but before final assessment	8	11
No contact but alive‡	10	6
Emigration	2	2
Refusal to comply	0	2
Serious illness	1	1
Drug addiction	0	1
Total number lost (%)	176 (40)	176 (39)

*Ipsilateral recurrence was an exclusion criterion. Of those with ipsilateral DVT, nine in the 6 weeks group and four in the 6 months group died before 10 years from the index event.
†The patients with ipsilateral recurrence and later death are not counted here.
‡As checked with the Death Registry in Sweden.

Post-thrombotic syndrome

The distribution of patients according to the classification of the PTS and initial duration of treatment is shown in Fig. 2. Signs of PTS were seen in 307 patients (36.9% by intention to treat, 56.3% of those examined at 10 years). The difference between the two treatment groups was not statistically

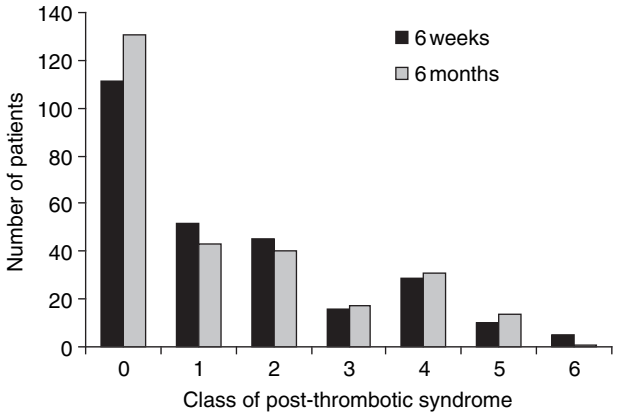

Fig. 2. Clinical class of post-thrombotic syndrome (PTS) by duration of secondary prophylaxis.

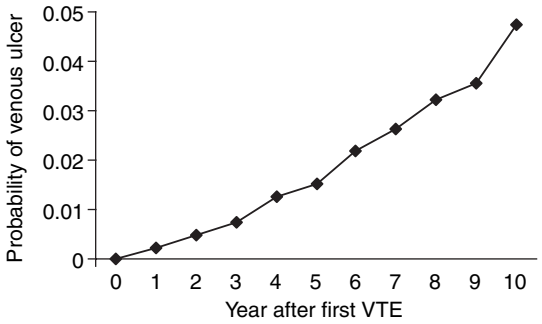

Fig. 3. Cumulative probability of developing a venous ulcer during the follow-up of 10 years.

significant ($P = 0.21$) (Table 2). Likewise, the difference in the number of patients with moderate-to-severe PTS (class 4–6) or severe PTS (Class 5–6) did not achieve statistical significance (Table 2). Neither did the proportion of patients reporting presence of symptoms at 10 years – 25.6% (95% CI 22.5–28.6) in the 6-week group vs. 20.4% (95% CI 18.0–22.7) in the 6-month group – differ significantly. Compression stockings had been used for a mean of 2.4 and 2.3 years among the patients with DVT and 6 weeks or 6 months of treatment, respectively. The probability of developing a venous ulcer over the 10 years, for which data were available from the entire study population ($n = 897$), appeared to increase proportionally with the duration of follow-up (Fig. 3).

The results of the univariate and multivariate analyses of baseline factors that could be associated with the development of the PTS are shown in Table 3. Old age and signs of impaired venous circulation at 1 week (discharge from the hospital) emerged as the only significant risk factors. The dependence on age is also evident when the mean class of PTS is plotted against the quintiles of age at the index event (Fig. 4). The older patients (≥60 years) had a higher proportion of proximal DVT and permanent or unknown triggering risk factor than the younger patients (58% vs. 42%; $P = 0.001$ and 64% vs. 46%; $P < 0.001$, respectively).

Although initial PE appeared to be less associated with PTS than initial DVT, it could be noted that 41% of the patients with PE had at least one manifestation of the syndrome after 10 years. Twenty-three patients had initial symptoms of both DVT and PE with objective verification of both diagnoses, and these were accounted for as cases with DVT.

Blood samples for analysis of cardiolipin antibodies and fibrinolytic parameters were only taken 6 months after the index event, but it is likely that such defects were present at the time of the initial event. Neither carriership of factor (F) V G1691A mutation or prothrombin G20210A polymorphism, nor presence of cardiolipin antibodies, elevated PAI-1 (30 U mL^{-1} or higher), or an increased level of VWF antigen (more than 1.5 IU mL^{-1}) was associated with an increased risk of developing PTS.

Among factors that only were established after baseline and that could influence the development of PTS were the use of compression stockings and recurrence of VTE. The mean class of PTS was paradoxically 1.05 among those who used the compression stocking for < 1 year and 1.61 among those who used it for at least 1 year ($P < 0.001$), or 1.21 and 1.60, respectively ($P < 0.01$), for patients with DVT as the initial diagnosis. The average number of years the patients used the compression stocking correlated with age, and the mean duration was 1.73 years (95% CI 1.34–2.12) for patients < 60 years of age and 2.44 years (95% CI 2.13–2.75) for patients of at least 60 years of age, $P = 0.005$.

The 8-point scale used for scoring symptoms and signs during the first 2 years of follow-up was predictive for development of PTS. The best discrimination was seen at 3 months and at 9 months when a score of 0 gave a mean class of PTS of 0.90 and 0.88, respectively, after 10 years compared with a mean class of PTS of 1.72 and 1.77, respectively, for those with scores 1–8 ($P < 0.001$). In other words, this scoring system used at 3 months predicted moderate (PTS class 4) to

Table 2 Major outcomes after 10 years, according to the length of secondary prophylaxis, calculated on intention to treat

Outcome	6 weeks ($n = 443$), *n* (%)	6 months ($n = 454$), *n* (%)	Odds ratio (95% CI)	*P*-value
*Post-thrombotic syndrome				
Any class	159 (39.2)	148 (34.7)	1.21 (0.91–1.60)	0.21
Classes 4–6 (moderate–severe)	46 (11.3)	47 (11.0)	1.03 (0.67–1.58)	0.98
Classes 5–6 (severe)	17 (4.2)	16 (3.8)	1.12 (0.57–2.22)	0.88
Recurrent thromboembolism	138 (31.2)	123 (27.1)	1.22 (0.91–1.62)	0.21
Death	127 (28.7)	129 (28.4)	1.01 (0.75–1.35)	0.99

*The numerator is patients without an ipsilateral recurrent deep vein thrombosis – 6-week group 406, 6 months group 426.

Table 3 Mean class of the PTS according to characteristics at baseline, with univariate and multivariate analysis of the distribution among the seven classes

		P-value	
Baseline characteristic	Mean class†	Univariate	Multivariate*
Duration of secondary prophylaxis			
6 weeks	1.44	0.098	0.58
6 months	1.35		
Quality of anticoagulation			
Poor	1.24	0.46	
Good	1.50		
Initial thrombolytic therapy			
Yes	1.69	0.51	
No	1.39		
Sex			
Male	1.60	0.006	0.097
Female	1.15		
Age			
<60	1.18	0.006	0.010
≥60	1.63		
Triggering risk factor for venous thromboembolism (VTE)			
Temporary	1.04	0.002	0.063
Permanent	1.61		
Signs of PTS present before VTE‡			
Yes	1.66	0.43	
No	1.43		
Signs at 1 week§			
0–2	1.35	0.002	0.036
3–6	1.94		
DVT or pulmonary embolism (PE)			
DVT	1.49	0.088	0.40
PE	0.85		
Extension of the DVT			
Proximal	1.72	0.002	0.28
Distal	1.26		
Side of the leg with DVT			
Right	1.46	0.75	
Left	1.53		

*Only characteristics with a *P*-value of <0.1 in the univariate analysis and pertaining to the population with initial DVT ($n = 466$) were entered. †According to the updated standards of the International Consensus Committee on Chronic Venous Disease with clinical classes 0–6. ‡Swelling of the leg, varicose veins or hyperpigmentation. §One point each for swelling of ankle, swelling of calf, swelling of thigh, teleangiectasia or varicose veins, and hyperpigmentation.

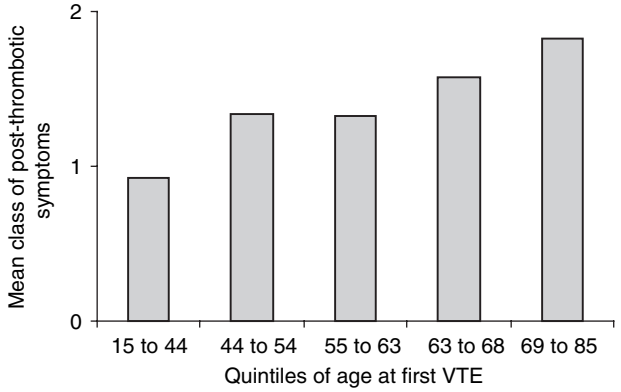

Fig. 4. Effect of increasing age on post-thrombotic syndrome.

severe (class 5 or 6) PTS after 10 years with a sensitivity of 83% and a specificity of 38%.

Patients without recurrent VTE during the follow-up had a mean class of PTS of 1.21 vs. 1.83 among those with any recurrence except for the ipsilateral leg (exclusion criterion), $P = 0.025$.

Recurrence of VTE

A total of 261 patients (29.1%) had a second episode of VTE during the 10 years follow-up, and the anatomical sites of these recurrences are shown in Table 4. A larger proportion of the recurrences were PE among the patients that previously had PE as opposed to DVT as the index event (73% vs. 20%; $P < 0.001$). The difference in proportion of patients with at least one recurrence during 10 years in the two treatment groups (Table 2), 31% in the 6-week group, and 27% in the 6-month group was not statistically significant ($P = 0.2$). The difference between the groups had been statistically significant from years 1–6, but not at any time point thereafter (Fig. 5). More males than females (34% vs. 22%) had a recurrence, Odds ratio 1.8 (95% CI 1.33–2.42), which appeared to be because of a significantly higher proportion of males with proximal DVT or PE vs. distal DVT ($P = 0.002$) and more permanent than temporary triggers ($P < 0.001$) among the males. Likewise, more patients of at least 60 years of age had a recurrence than the younger ones, 31% vs. 25%, Odds ratio 1.36 (95% CI 1.00–1.83). The condition of the leg at discharge from the hospital 1 week after the index event also appeared to predict for recurrence, diagnosed in 26% of patients having zero to two points on our scale experiencing a recurrence, vs. 34% of those with three to five points (Odds ratio 1.53; 95% CI 1.09–2.14). In the multivariate analysis of risk factors for recurrence permanent or unknown triggering factor, male gender, PAI-1 level >30 U mL^{-1} in plasma, and the FV Leiden mutation emerged as independent (Table 5).

The recurrence rate over 10 years differed according to the initial provoking risk factor, as shown in Fig. 6. Patients with an infection, immobilization, or traveling before the initial VTE had a similar rate of recurrences as those with unprovoked VTE, whereas those with venous insufficiency had the highest rate.

Death

During the 10 years after the index event, 256 patients (28.5%) died, 127 in the 6-week group and 129 in the 6-month group. There was no difference in mortality between the treatment groups at any time point – for patients with cancer as well as for those without. The causes of death are shown in Table 6. The SIR for death of any cause during this decade was 1.43 (95% CI 1.28–1.58), for death from MI or ischemic stroke 1.28 (95% CI 1.00–1.56), and for death from cancer 1.83 (95% CI 1.44–2.23). The distribution of these deaths over the follow-up period is shown in Fig. 7. Of the 13 patients with fatal PE, seven occurred in the 6-week group and 6 in the 6-month group. All these patients

Table 4 Site of first recurrent event of venous thromboembolism during 10 years, according to duration of secondary prophylaxis. Results are absolute numbers (% of all recurrences in that treatment group)

Anatomical site of recurrence	6 weeks ($n = 443$)	6 months ($n = 454$)	Total ($n = 897$)
Initial event was deep vein thrombosis (DVT) ($n = 790$)			
Ipsilateral leg	37 (27)	28 (23)	65 (25)
Contralateral leg	50 (36)	62 (50)	112 (43)
PE	27 (20)	17 (14)	44 (17)
Other*	1 (1)	2 (2)	3 (1)
Initial event was pulmonary embolism (PE) ($n = 107$)			
DVT	6 (4)	4 (3)	10 (4)
PE	17 (12)	10 (8)	27 (10)
All recurrences	138 (100)	123 (100)	261 (100)

*One patient in each group had recurrence as subclavian DVT and one in the 6 months group had mesenteric vein thrombosis.

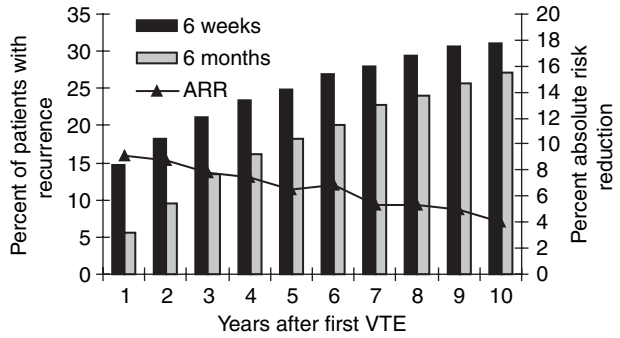

Fig. 5. Cumulative percentage of patients with a recurrent episode of venous thromboembolism (VTE), according to initial duration of anticoagulation and absolute risk reduction (ARR) over 10 years of follow-up. Footnote: The best curve fit assumes the equation of $y = 7.42 \times \ln(x) + 13.6$ and $y = 9.63 \times \ln(x) = 3.69$ for the patients treated for 6 weeks and 6 months, respectively, where y is the cumulative risk of recurrence in % and x is the time after the index event in years.

died from PE after the cessation of anticoagulant therapy, and the diagnosis was verified by autopsy in 12 cases and by lung scanning in one case. In three additional patients, the cause of death was considered as probable PE (cancer, chest pain, and sudden death; total hip arthroplasty without thromboprophylaxis and sudden death; echocardiography demonstrating dilated right ventricle immediately before death).

Seven fatal hemorrhages occurred between 2 and 8 years after the index event, corresponding to an incidence of 0.09 per 100 patient-years. Only one was during anticoagulant therapy, which had been restarted because of atrial fibrillation. Five patients died of intracerebral hemorrhage, one of subarachnoid hemorrhage and one of hypovolemic shock after pelvic fracture.

Discussion

This randomized-controlled trial on the secondary prophylaxis after VTE is unique with its long follow-up in combination with a large number of patients included. The possibility of following and retrieving patients in any part of Sweden as well the access to information on individuals from the Death Registry has allowed for analysis of data with minimal loss from follow-up regarding the recurrence or death. In the 10-year evaluation of PTS, only 4.9% of patients were lost because of other reasons than death before that date. The participating centers ranged from local hospitals in small- and medium-sized towns to university hospitals in the capital. The results should therefore be representative for the general population of patients with VTE, with an exclusion for pediatric VTE.

We and others [9] used the clinical classification recommended by the International Consensus Committee on Chronic Venous Disease for evaluation of PTS [13]. Several authors have instead used the Villalta scale [17,18] or a variety of other scoring systems [1,3,4,8,19]. A comparison between studies is therefore difficult, but severe PTS is in most systems equal with healed or active venous ulcers, corresponding to classes 5 and 6 in our study. We found a probability of developing the severe syndrome of 4.8% after 10 years (Fig. 2). Mohr *et al.* [4] observed a cumulative incidence of venous ulcers of 1.5% after 10 years in a retrospective cohort, whereas Brandjes *et al.* [3] reported an incidence of 2% over 5–6 years in a trial with or without compression stockings. It has been claimed that the majority of patients with the severe syndrome present within 2 years from the thrombotic event [3], but a steady increase over 10–20 years was observed by us and Mohr *et al.* [4], and the length of our follow-up should thus be valuable.

Age was the most important risk factor for the development of PTS in spite of the fact that the compliance with the use of compression stockings was better among the elderly. Our observation that increased use of compression stockings appeared to be associated with more severe PTS is probably because of confounding by the association between age and PTS. Although patients with initial PE alone had a lower risk of PTS, as also reported by others [4], the risk was considerably higher than in a recently published retrospective cohort study [20]. It could therefore be argued that this subset of patients, or perhaps only the older patients with PE, should routinely be provided with compression stockings. Our results also indicate that it could be of some value to examine the patients 3 months after the initial event and to try and persuade those with symptoms or signs of impaired venous circulation and still not

Table 5 Risk factors for recurrence of venous thromboembolism (VTE) over 10 years

Baseline characteristic	Incidence of recurrences (%)	*P*-value	
		Univariate	Multivariate*
Age (years)			
≥60	31	0.049	0.18
<60	25		
Sex			
Male	34	< 0.001	0.002
Female	23		
Triggering risk factor			
Non-temp.	34	< 0.001	0.003
Temporary	21		
Signs of PTS present before VTE†			
Absent	30	0.044	
Present	23		
Type of VTE			
PE	35	0.15	
DVT	28		
Extension of DVT			
Proximal	33	0.003	
Distal	23		
Extension of VTE			
Proximal/PE	33	0.001	0.20
Distal	23		
Side of leg with DVT			
Left	30	0.4	
Right	27		
Signs at 1 week‡			
3–6	35	0.013	0.16
0–2	26		
Duration of secondary prophylaxis			
6 weeks	31	0.2	
6 months	27		
Quality of anticoagulation			
Good	31	0.089	0.056
Poor	25		
Factor V G1691A			
Heterozygous	35	0.05	0.028
Wild type	25		
Factor V G1691AA			
Homozygous	55	0.07	0.030
Wild type	25		
Prothrombin G20210A			
Heterozygous	32	0.8	
Wild type	28		
Cardiolipin antibodies (IgG)			
Positive	33	0.3	
Negative	28		
Plasminogen activator inhibitor-1			
>30 U mL^{-1}	39	0.015	**0.005**
<30 U mL^{-1}	27		

*In the multivariate analysis risk factors with a *P*-value of < 0.1 in the univariate analysis and that are not clearly dependent on each other, such as 'signs of PTS present before VTE' and 'signs at 1 week' as well as 'extension of DVT' and 'extension of VTE' were entered. †Swelling of the leg, varicose veins or hyperpigmentation. ‡One point each for swelling of ankle, swelling of calf, swelling of thigh, teleangiectasia or varicose veins, and hyperpigmentation.

PTS, post-thrombotic syndrome; PE, pulmonary embolism; DVT, deep vein thrombosis.

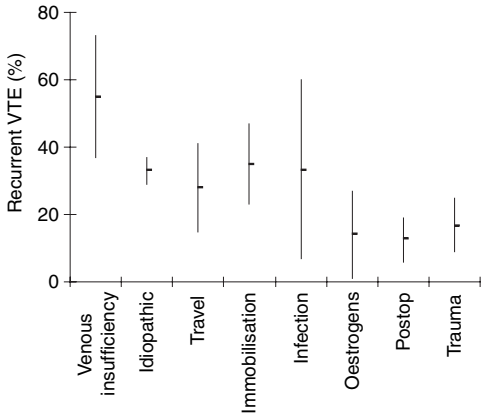

Fig. 6. Rate of recurrence according to the initial provoking risk factor with 95% confidence intervals.

Table 6 Causes of death during 10 years after first event of VTE

Cause of death	*n*	% of all deaths
Cancer*	72	28
Myocardial infarction	50	20
Other cardiac death	40	16
Ischemic stroke	24	9
Infection	21	8
Pulmonary embolism	13	5
Major hemorrhage	7	3
Respiratory failure	7	3
Aortic aneurysm	4	2
Renal failure	4	2
Sudden death of unknown cause	2	1
Dementia	2	1
Other†	10	

*Three additional patients had end-stage cancer disease, but the cause of death was labeled as pulmonary embolism. †One each of drowning, suicide, chronic alcohol abuse, burns injury, grand mal epilepsy, ileus, rheumatoid arthritis, vasculitis, visceral vein thrombosis, and old age.

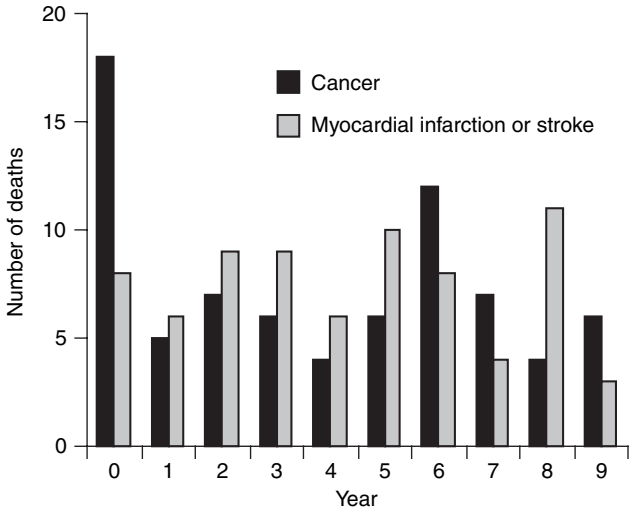

Fig. 7. Distribution of deaths, caused by cancer or by the composite of myocardial infarction and ischemic stroke, during 10 years of follow-up.

using the stockings to do so. We were unable to confirm a recent report that the quality of anticoagulant treatment is of importance for prevention of PTS [21].

The statistically significant difference in the incidence of recurrent VTE between the two treatment groups in our study, as previously reported [10,11], was only sustained for 6 years, which may seem disappointing. The 'catch-up' phenomenon occurred later in this study than previously described by others [22], but the difference may be because of different time points of discontinuation of anticoagulation or to the sample size. The absence of a plateau in the cumulative recurrence curve reinforces the notion that VTE is a chronic disease and even after a decade the risk of recurrence is present, as also shown by Prandoni *et al*. [1]. It is desirable to have an estimate of the risk of recurrence already at the time of starting the secondary prophylaxis for better planning of the treatment. The triggering event gives some information in this respect and VTE provoked by a permanent or unknown risk factor carries a higher risk of recurrence than VTE provoked by a temporary risk factor [10,23]. In a recent cohort study, it was shown that in addition to (a) recent surgery with a low incidence of recurrence, and (b) non-identified risk factor with a high incidence of recurrence, there is (c) an intermediate group of risk factors, including fractures with plaster cast, estrogens, immobilization, or a history of travel [24]. The results presented here indicate that patients with signs of venous insufficiency already before the first episode of VTE have a risk of recurrence that is even higher than those with unprovoked VTE, perhaps because of the fact that they may have had previous, undiagnosed episodes. Furthermore, in cases where the provoking factor was attributed to temporary immobilization, infection or travel, the risk of recurrence appeared higher than in those with trauma, surgery or estrogen therapy, and of the same magnitude as with unprovoked VTE. This raises the hypothesis that perhaps the travel or infection (in many of the cases a respiratory infection) was only coincidental and not a true or at least not the sole triggering factor.

Somewhat surprisingly, the influence of some of the thrombophilic risk factors differed from what we have previously observed and published after 2–4 years. The presence of cardiolipin antibodies appeared as a predictor of both recurrence and of death during the first 4 years of follow-up [15], but was not associated with the long-term incidence of recurrence. This may be because of the higher mortality in these patients. Conversely, elevated PAI-1 or the presence of FV Leiden in heterozygous form, which did not present as important risk factors after a few years of follow-up [14,16], emerged as stronger risk factors during the extended follow-up. The differential importance of the various risk factors during the course of follow-up has not been well described in the literature, but it seems very plausible that some risk factors, such as the properties of the initial thrombosis, are more important early on whereas genetic defects gain momentum in the long run. This should be taken into account for the design of future studies.

The mortality of patients with the first episode of VTE over the following decade is 43% higher than expected from population data. This is only partly because of the well-known association between thrombosis and cancer [12,25,26], but is also generated by cardiovascular deaths. Prandoni *et al*. [27] demonstrated an association between atherosclerotic disease, as expressed by the presence of carotid plaques, and venous thrombosis, and there was also an increased risk of cardiovascular events among patients with idiopathic PE [28]. The common denominator for venous and arterial disease is unknown, but the antiphospholipid syndrome may contribute [15].

A limitation of this study is that patients with ipsilateral recurrence of DVT were excluded from the evaluation of PTS. However, our objective was to assess the long-term consequences of the first episode of VTE. Prandoni *et al*. [1] showed that ipsilateral recurrence was a strong risk factor for PTS with a hazard ratio of 6.4, and none of the other clinical features had a significant association with the risk of developing PTS when this was included in the analysis. Moreover, if the recurrent ipsilateral DVT is more extensive than the index event, it may obscure the effect of the latter on the development of PTS.

Another limitation is the open design. It did not appear to influence the willingness to perform diagnostic imaging studies, which was equal in the two treatment groups during the first 2 years [10] as well as subsequently, and therefore bias regarding recurrences is unlikely. We cannot exclude that the classification of PTS may have been influenced by knowledge of treatment duration, but in the absence of significantly worse results in the 6-week group this is not very plausible.

We conclude that the diagnosis of a first event of VTE is followed by a decade with increased morbidity and mortality. Secondary prophylaxis with vitamin K antagonists for 6 months compared with 6 weeks offers an advantage regarding fewer recurrent events during the following 6 years. Beyond that time point, the choice between these treatment alternatives does not seem to make a significant difference, neither on the risk of recurrence, nor on the development of PTS or mortality after 10 years of follow-up. It is plausible that an extension of the treatment by 4.5 months at the beginning is completely insufficient to achieve any effects on PTS or recurrence after 10 years, and reduction of mortality has not been achieved in any study with different duration of anticoagulant therapy for VTE. Further prolongation of the secondary prophylaxis may reduce the risk of some of these endpoints, albeit with an appreciable cumulative risk of major bleeding [29] and with costs for constant monitoring with laboratory tests.

Conflict of interest disclosure

S. Schulman has received honoraria for consultancies to AstraZeneca, Organon, Sanofi-Synthélabo and Boehringer-Ingelheim. P. Lindmarker has received honoraria for consultancies to AstraZeneca and Sanofi-Aventis.

Addendum

S. Schulman coordinated the trial, interpreted the data and prepared the manuscript. P. Lindmarker and S. Schulman performed the statistical analysis. M. Beckman did the blinded adjudication of thromboembolic events. The remaining investigators contributed to the study design and to the clinical follow-up as well as commented on the manuscript.

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