Diagnosis of venous thrombosis and the post-thrombotic syndrome

Tick, L.W.

CHAPTER 6

Risk factors for the post-thrombotic syndrome in patients with a first deep venous thrombosis

L.W.Tick, M.H.H.Kramer, F.R. Rosendaal, W.R. Faber, C.J.M. Doggen

Background The post-thrombotic syndrome (PTS) is a chronic complication of deep venous thrombosis and is characterised by signs and symptoms of venous hypertension. The objectives of this study were to determine the risk of PTS after deep venous thrombosis and to assess risk factors for PTS.

Methods Patients were recruited from the Multiple Environmental and Genetic Assessment (MEGA) study of risk factors for venous thrombosis. Consecutive patients who suffered a first deep venous thrombosis of the leg before the age of 70 were included in a follow-up study. All patients completed a questionnaire and DNA was obtained through blood samples or buccal swabs. PTS was ascertained in a structured interview using a clinical classification score.

Results The one-year cumulative incidence of PTS was 25%, and 7% for severe PTS. Elastic compression stockings were prescribed in 1412 (85%) patients. The majority used their stockings every day. Women were at increased risk compared to men (risk ratio (RR) 1.5, 95%CI 1.3-1.8). Similarly, obese patients had a 1.5 fold increased risk of PTS compared to patients with normal weight (RR 1.5, 95%CI 1.2-1.9), with a one-year cumulative incidence of 34% compared to 22%. Patients who already had varicose veins had an increased risk (RR 1.5, 95%CI 1.2-1.8) of PTS. Deep venous thrombosis in femoral and iliac vein was associated with a 1.3-fold increased risk of PTS compared to popliteal vein thrombosis (RR 1.3, 95%CI 1.1-1.6). Patients over 60 years were less likely to develop PTS than patients below the age of 30 (RR 0.6, 95%CI 0.4-0.9). Malignancy, surgery, minor injury, plaster cast, pregnancy or hormone use did not influence the risk of PTS, neither did the factor V Leiden or prothrombin 20210A mutation.

Conclusions PTS is a frequent complication of deep venous thrombosis, despite the widespread use of elastic compression stockings. Women, obese patients, patients with proximal deep venous thrombosis and those with varicose veins have an increased risk of PTS, whereas the elderly appeared to have a decreased risk.

Introduction

The post-thrombotic syndrome (PTS) is a chronic complication of deep venous thrombosis. Venous hypertension caused by venous valvular incompetence and persistent obstruction are likely to be the pathogenic mechanism underlying PTS.[1-4] PTS is characterized by symptoms such as a feeling of heaviness and pain and by signs such as oedema, hyperpigmentation and new venous ectasia. Severe PTS can lead to leg ulcers. Several studies assessed the incidence of PTS which varied from 15 to 50% between studies.[3-10] This wide range is due to differences in the definition of PTS, patient selection and study design. There is no gold standard test for the diagnosis of PTS and the diagnosis is primarily based on clinical features. Elastic compression stockings assist the calf muscle pump and reduce venous hypertension and reflux, thereby reducing edema and improving tissue microcirculation.[1] Randomized controlled trials have shown that daily use of elastic compression stockings after deep venous thrombosis reduces the risk of PTS by approximately 50%.[6,8,11]

In contrast to the many identified risk factors for deep venous thrombosis,[12] the only identified risk factors for PTS so far are recurrent, ipsilateral deep venous thrombosis and an increased body mass index (BMI).[7,8,13-18] Age, sex and duration of anticoagulant therapy did not appear to be associated with the risk of developing PTS, but results are conflicting, and most studies are characterized by small numbers of patients.[8,14-18]

Hypercoagulable states have been reported to be associated with venous leg ulcers.[19-21] However, factor V Leiden or prothrombin 20210A mutation were not associated with an increased risk of developing PTS.[8,14,18,21] One study even showed a reduced risk of PTS with the presence of factor V Leiden or prothrombin 20210 mutation.[17] Other venous thrombotic risk factors such as surgery and hormone use have not yet been investigated as potential risk factors for PTS.

The objectives of the present large study were to assess the cumulative incidence of PTS after a first deep venous thrombosis and to assess the contribution of risk factors in the development of PTS.

Methods

Study Design

This study was performed in the Multiple Environmental and Genetic Assessment (MEGA) study of risk factors for venous thrombosis, a large population-based case-control study. Between March 1999 and June 2002, consecutive patients aged 18 to 70 years with a first episode of deep venous thrombosis of the leg were included from six participating anticoagulation clinics in the Netherlands. Discharge letters and radiology reports of the venous thrombotic event were obtained. Compression ultrasonography and Doppler ultrasound were by far the most commonly used diagnostic procedures (98%). Deep venous thrombosis was objectively confirmed in 97%.[22]

Patients who were unable to fill in a questionnaire (see below) because of language or severe psychiatric problems were excluded. Among the 2730 eligible patients, 132 died before they could participate, 31 patients were in the end stage of a disease and 651 patients could not be located or refused to participate. In April 2000 three questions regarding PTS were added to the interview (see below) and 157 patients, who were interviewed before this date, and 13 patients with missing items regarding PTS in the interview, were excluded. Of 78 patients no information on the left or right side of deep venous thrombosis was available which led to 1668 patients included in the present analysis.

All patients filled in a detailed questionnaire on acquired risk factors for venous thrombosis such as malignancy, surgery, minor injury, plaster cast, bedridden, pregnancy and use of female hormones. The questionnaire was sent within a few weeks after the event and covered the period of 1 year prior to the date of the thrombotic event. When the patient was unable to fill in the questionnaire, questions were asked by phone, using a standardized mini-questionnaire. Patients were divided in a group with idiopathic deep venous thrombosis and provoked venous thrombosis associated with one or more of the following risk factors; malignancy, surgery, plaster cast, minor injury, bedridden at home or in the hospital, pregnancy and the use of female hormones. Body mass index (BMI) was calculated from self-reported weight and height (weight/height^2). BMI was categorized according to the criteria of the World Health Organization (1998), defining BMI in adults under 18.5 kg/m^2 as underweight, a BMI between 18.5 and 25 kg/m^2 as normal, a BMI of 25 to 30 kg/m^2 as overweight and a BMI equal to or greater than 30 kg/m^2 as obesity.

Three months after the patients had discontinued their oral anticoagulant therapy, they were invited to the anticoagulation clinic. An independent research assistant, who was not involved in their treatment, interviewed the patients and took a blood sample. In those patients who continued to take oral anticoagulant therapy for more than 1 year after the event, blood samples were drawn during therapy. If patients were unable to come to the anticoagulation clinic, an interview was conducted by telephone and buccal swabs were sent by mail to replace the blood sample (229 out of 1668 patients (13.7%)).

During the in-person or telephone interview details on frequency and duration of the use of elastic compression stockings were asked. PTS was assessed by asking for five symptoms and four signs (table 1). These items were based on the Villalta scale and modified in order to be used in the interview.[7] Each item scored one point if present. The nine items were summed into a post-thrombotic score. PTS was considered absent with a post-thrombotic score between zero and 3 points. PTS was considered moderate in patients with a score between 4 and 6 points and severe with a score equal to or greater than seven or the presence of a venous ulcer. Only the symptoms and signs of the leg in which the deep venous thrombosis occurred, were used to assess the presence and severity of PTS. The study protocol was approved by the Ethics Committee of the Leiden University Medical Center, Leiden, The Netherlands. Written informed consent was obtained from all participants.[22]

Table 1. Post-thrombotic symptoms and signs in 1668 patients

Symptoms	N (%)	Signs	N (%)
Spontaneous pain in calf	433 (26)	Newly formed varicose veins	218 (13)
Spontaneous pain on walking	243 (15)	Swelling of foot or calf	576 (35)
Spontaneous pain on standing	293 (18)	Skin changes, pigmentation, discoloration	418 (25)
Pain worsening during the day	393 (24)	Skin changes with venous ulcer	48 (3)
Heaviness of leg	620 (37)		

Laboratory Measurements

Blood was collected from the antecubital vein into vacuum tubes containing 0.106 mol/l trisodium citrate. High molecular weight DNA was isolated from leukocytes using a standard salting-out procedure and stored at -20ºC until amplification. When a blood sample was unavailable, three large cotton (buccal) swabs in a total of 6 ml SDS-proteinase K solution were obtained. DNA was extracted from these buccal swabs and frozen at −20 °C until further analysis.[22] The factor V Leiden mutation (G1691A) and the prothrombin (G20210A) mutation were simultaneously detected by duplex polymerase chain reaction.[24,25]

Statistical Analysis

The follow-up started at diagnosis of deep venous thrombosis in the leg and ended at the time of the interview. Cumulative incidence was estimated by Kaplan-Meier life table technique. The reported risk ratios are based on the method of Zhang.[23] In short, crude odds ratios were used to estimate the relative risk of PTS. Logistic regression was used to adjust for age and sex only, and for age and sex combined with BMI, duration of symptoms, varicose veins, localization of deep venous thrombosis, malignancy and elastic compression stockings. 95% Confidence intervals (CI) were calculated by using the standard error obtained from the logistic regression model. As PTS is common (over 10% incidence), these odds ratio overestimates the true relative risk. Therefore, the odds ratio and 95% CI were converted to the risk ratio by taking into account the prevalence of the risk factor in non-exposed individuals.[23]

As patients had various durations of follow-up and anticoagulation use, all analyses were stratified by follow-up and anticoagulation use period. Mantel-Haenszel common odds ratio was used to estimate the relative risk of PTS, taking these various durations into account. As these stratified odds ratios did not differ from the crude analyses, the risk ratios presented are adjusted for age and sex and other risk factors as indicated above.

All computations were performed with the use of SPSS software, version 14.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics of the 1668 patients are summarized in table 2. There were 880 (53%) women, mean age at diagnosis of deep venous thrombosis was 48 years and patients had a mean BMI of 27 kg/m^2. Median duration of symptoms before diagnosis of deep venous thrombosis was 4 days (5th - 95th percentile 0-69).

Table 2. Characteristics of 1668 patients with a first deep venous thrombosis of the leg

Characteristic	
Women No (%)	880 (53%)
Age (years), mean (SD*)	48 (13)
5th -95th percentile	26-67
BMI† (kg/m2), mean (SD)‡	27 (5)
5th -95th percentile	21-36
Duration of symptoms before diagnosis (days), median‡	
5th -95th percentile	4 0-69
Varicose veins at diagnosis§	470 (28%)
Side of DVT||	
left	972 (58%)
right	683 (41%)
bilateral	13 (1%)
Localization of DVT¶	
calf vein	203 (17%)
popliteal vein	498 (41%)
femoral and iliac vein	502 (42%)
Malignancy‡	137 (8%)
Recent surgery‡	357 (21%)
Minor Injury‡	405 (24%)
Plaster cast	105 (6%)
Pregnancy among women < 50 years‡	73 (13%)
Oral anticonceptive use among women < 50 years	417 (74%)
Hormonal replacement therapy among women ≥ 50 years‡	39 (13%)
Idiopathic DVT‡	389 (24%)
Factor V Leiden mutation‡	315 (19%)
Prothrombin 20210A mutation‡	92 (6%)

* SD = standard deviation
† BMI = body mass index
‡ unknown in ≤ 74 patients
§ unknown in 213 patients
|| DVT = deep venous thrombosis
¶ unknown in 465 patients

Thrombosis was unilateral on the left side in 972 (58%) patients, on the right side in 683 (41%), and bilateral in 13 (1%) patients. Deep venous thrombosis was idiopathic in 24% of all patients. Median duration of anticoagulation use was 6 months (5^{th} -95^{th} percentile 2-14). Median duration of follow-up was 10 months (5^{th} -95^{th} percentile 6-18).

Cumulative Incidence and Severity of the Post-thrombotic Syndrome

The one-year cumulative incidence of PTS was 25%, with a cumulative incidence of 7% for severe PTS. Table 1 shows the frequency of the nine post-thrombotic symptoms and signs. The most frequent symptom reported by 620 (37%) patients was a feeling of heaviness of the leg. Swelling of the foot or calf was present in 576 (35%) of the patients. An ulcer was present in 48 out of 1668 (3%) patients. Only 466 out of 1668 patients (28%) had a post-thrombotic score of zero points.

Risk Factors for Post-thrombotic Syndrome

The one-year cumulative incidence of PTS in women was 31% compared to 17% in men. Women had a 1.5-fold higher risk of developing PTS than men (RR 1.5, 95%CI 1.3-1.8), also after adjustment for other risk factors ($RR_{adjusted}$ 1.5, 95%CI 1.1-1.9) (table 3).

The one-year cumulative incidence in patients over 60 years was 16%, which was much lower than the 26% cumulative incidence in patients below the age of 30 (RR 0.6, 95%CI 0.4-0.9). In obese patients the one-year cumulative incidence was 34%, compared to 22% in normal weight patients, leading to a 1.5-fold increased risk of PTS (RR 1.5, 95%CI 1.2-1.9). Height of patients did not affect the risk of PTS. Patients with more than two weeks of symptoms before the deep venous thrombosis had a 1.4 fold increased risk compared to patient with symptoms less than two weeks (RR 1.4, 95%CI 1.2-1.7). After adjustment for other risk factors for PTS this effect was no longer present ($RR_{adjusted}$ 1.2, 95%CI 0.9-1.6). Varicose veins were present in 470 out of 1455 (28%) patients prior to the deep venous thrombosis, in whom the one-year cumulative incidence of PTS was 30%. These patients had a 1.5-fold increased risk of PTS compared to patients without varicose veins (RR 1.5, 95%CI 1.2-1.8).

Table 3. Risk factors associated with post-thrombotic syndrome

Risk factor		N	N PTS	1 yr cum inc*	Risk Ratio†	Risk Ratio adjusted‡
Sex						
	women	880	235	31%	1.5 (1.3-1.8)	1.5 (1.1-1.9)
	men	788	129	17%	1	1
Age (years)						
	18-29	200	51	25%	1	1
	30-39	311	75	26%	1.0 (0.7-1.4)	0.8 (0.5-1.2)
	40-49	391	111	30%	1.2 (0.9-1.6)	1.1 (0.8-1.6)
	50-59	456	87	24%	0.9 (0.6-1.2)	0.7 (0.4-1.1)
	60-69	310	40	16%	0.6 (0.4-0.9)	0.4 (0.2-0.7)
BMI§						
	underweight	15	4	36%	1.3 (0.5-2.7)	1.4 (0.4-3.6)
	normal	549	109	22%	1	1
	overweight	702	132	22%	1.1 (0.8-1.3)	1.2 (0.9-1.6)
	obese	343	102	34%	1.5 (1.2-1.9)	1.9 (1.4-2.4)
Duration symptoms before diagnosis‖						
	≥2 weeks	368	105	29%	1.4 (1.2-1.7)	1.2 (0.9-1.6)
	<2 weeks	1240	245	24%	1	1
Varicose veins at diagnosis¶						
	yes					
	no	470	130	30%	1.5 (1.2-1.8)	1.5 (1.2-1.9)
		985	180	20%	1	1
Localization of DVT**††						
	calf vein	203	37	25%	0.9 (0.6-1.3)	0.9 (0.6-1.3)
	popliteal vein	498	100	23%	1	1
	femoral and iliac vein	502	128	26%	1.3 (1.1-1.6)	1.4 (1.1-1.8)
Malignancy‖						
	yes	137	19	15%	0.7 (0.4-1.0)	0.8 (0.4-1.4)
	no	1530	344	25%	1	1

* 1 yr cum inc = one-year cumulative incidence
† adjusted for age and sex if applicable
‡ adjusted for age, sex, and other risk factors for PTS if applicable (BMI, duration of symptoms, varicose veins, localization, malignancy, elastic compression stocking)
§ BMI = body mass index
‖ unknown in ≤ 74 patients
¶ unknown in 213 patients
** DVT = deep venous thrombosis
†† unknown in 465 patients

Newly formed varicose veins is one of the items of the post-thrombotic score. When this specific item was excluded from the post-thrombotic score the risk ratio for varicose veins was only slightly lower (RR 1.4, 95%CI 1.1-1.7). Proximal localization of thrombosis in the femoral and iliac vein was associated with a 1.3-fold increased risk of PTS compared to popliteal vein thrombosis (RR 1.3, 95%CI 1.1-1.6). Calf vein thrombosis conferred a similar risk for PTS as popliteal vein thrombosis. Patients with malignancy were less likely to develop PTS than patients without a malignancy (RR 0.7,

95%CI 0.4-1.0), which was less pronounced after adjustment for other risk factors ($RR_{adjusted}$ 0.8, 95%CI 0.4-1.4).

Surgery, minor injury or plaster cast were not associated with the development of PTS, nor were pregnancy or the use of female hormones. Patients with an idiopathic deep venous thrombosis conferred a similar risk for PTS compared to patients with a provoked deep venous thrombosis (RR 0.9, 95%CI 0.7-1.2). The presence of factor V Leiden or the prothrombin 20210A mutation was not associated with the development of PTS (table 4).

Table 4. Risk factors not associated with post-thrombotic syndrome

Risk factor	N	N PTS	1 yr cum inc*	Risk Ratio†
Surgery‡				
yes	357	82	22%	1.1 (0.9-1.3)
no	1308	281	25%	1
Minor injury‡				
yes	405	87	25%	1.0 (0.8-1.2)
no	1251	274	25%	1
Plaster cast				
yes	105	24	28%	1.1 (0.7-1.5)
no	1563	340	24%	1
Pregnant among women <50 years‡				
yes				
no	73	23	35%	1.1 (0.8-1.6)
	489	141	32%	1
Oral anticonceptive use among women <50				
yes				
no	417	120	30%	1.0 (0.7-1.3)
	146	44	37%	1
HRT among women ≥ 50 years‡				
yes				
no	39	9	39%	1.0 (0.5-1.8)
	265	58	27%	1
Idiopathic DVT‡§				
yes	389	64	18%	0.9 (0.7-1.2)
no	1205	284	27%	1
Factor V Leiden mutation‡				
yes				
no	315	74	30%	1.1 (0.9-1.4)
	1311	284	24%	1
Prothrombin 20210A mutation‡				
yes				
no	92	25	24%	1.2 (0.9-1.7)
	1535	333	25%	1

* 1 yr cum inc = one-year cumulative incidence
‡ unknown in ≤ 74 patients
† adjusted for age and sex
§ DVT = deep venous thrombosis

Elastic Compression Stockings

Elastic compression stockings were prescribed in 1412 (85%) patients. The majority (77%) of these patients reported to wear their stockings every day, 300 (21%) patients did not wear them daily and only 30 (2%) never used their elastic compression stockings. In patients who used their elastic compression stockings daily the one-year cumulative incidence of PTS was 29% as compared to 33% in patients who did not use their elastic compression stockings daily.

Most patients (81%) started to wear elastic compression stockings within two months after the deep venous thrombosis. The one-year cumulative incidence of PTS in patients who started elastic compression stocking use within two months was 26% compared to 28% in patients who started use two months after the diagnosis.

Discussion

Twenty-five percent of all patients with a first deep venous thrombosis in the leg developed PTS within a year, even though a large majority of the patients reported to wear elastic stockings. Women, obese patients, patients with proximal deep venous thrombosis and those with varicose veins had an increased risk of PTS, whereas elderly patients appeared to have a decreased risk. Factor V Leiden and prothrombin 20210A mutation were not associated with the risk of PTS.

The 25% one-year cumulative incidence of PTS in our study is comparable with the 20 to 27% incidence of PTS after one to two years reported in patients who used elastic compression stockings.[3,6-10]

This is the first large follow-up study that assesses acquired and genetic risk factors for the development of PTS in 1668 patients with a first deep venous thrombosis. Women were at higher risk of PTS than men, with a cumulative incidence of 31% versus 17%. The influence of sex on the development of PTS showed contradictionary results in previous studies. Only one follow-up study in 244 patients showed an increased risk for women,[16] whereas another study showed an increased risk for men.[18] However, most studies did not find an association.[8,15,17] These contradictory results may be explained by small study populations[15,17] and the inclusion of patients with recurrent thrombosis.[8,16-18]

Recurrent deep venous thrombosis is a risk factor for PTS and might have concealed the impact of sex.

Our finding that obesity was associated with PTS has been reported before.[14-18] Excess body weight might increase venous pressure and promote reflux in already compromised veins. Moreover, a high BMI might be related to a lack of physical exercise and therefore a poor function of the muscle pump. Obesity is highly prevalent in the general population, with a prevalence of 21% in our study population, and showed an increased risk of PTS, with a cumulative incidence of 34% after one year. It is of interest that a high BMI is a risk factor for PTS, as obesity is a potentially modifiable risk factor and thus weight reduction may play a role in the prevention of PTS.

This study identified the presence of varicose veins before the development of deep venous thrombosis as a risk factor for PTS. Patients with varicose veins might have a diminished calf muscle pump function due to preexisting reflux, leading to higher walking venous pressure and the development of chronic venous insufficiency.[1] Our study found that proximal deep venous thrombosis is a risk factor for PTS.[18,26] This association between localization of the initial thrombus and PTS was not observed in all previous studies.[7,18] It is an important finding that calf vein thrombosis conferred a similar risk for PTS as popliteal vein thrombosis. This finding stresses the importance of treatment for symptomatic calf vein thrombosis.

The reduced PTS risk in older patients is an interesting finding and in contradiction to the increased risk in elderly patients reported in some,[8,16,18] but not all other studies.[15,17] We included patients below 70 years, where older patients were included in other studies, which makes it difficult to compare the results.[8,15-17] The reduced PTS risk may reflect differences in thrombus propagation in elderly patients. Recanalization of the thrombus is a relatively fast process, and most vein segments are recanalized within three months. In older patients thrombus evolution is an unstable process with continuing propagation for two years[27] and therefore older people might develop PTS later than younger people.

In our study neither factor V Leiden nor prothrombin 20210A mutation were associated with the onset of PTS, which is in contrast to what has been suggested by other investigators.[19-21] This is an

important observation as the role of inherited thrombophilia with regard to the risk of PTS is not well established.[8,14,17-21] It was recently shown that factor V Leiden and prothrombin 20210A mutation do not, increase the risk of a recurrent thrombotic event.[28] These results suggest that inherited thrombophilic work-up is not likely to confer clinical benefit to the patient regarding the prediction of the development of PTS.

This study describes the widespread use of elastic compression stockings. Wearing elastic compression stockings is a hassle in daily life for patients. It can be difficult to put them on and take them off, and they can be discomforting. The appearance of elastic compression stockings is also considered a reason for non-regular use. Despite these disadvantages the majority of these patients reported to be compliant and use their stockings every day. This is in accordance with a survey that shows that patients with deep venous thrombosis are willing to comply with elastic compression stocking therapy.[29] There may have been an overreported use of elastic compression stockings because of socially desirable response behaviour. This may explain the minimal difference in risk of PTS between patients who used elastic compression stockings daily and patients who did not.

The 25% one-year cumulative incidence of PTS is based on symptoms and signs reported by patients. There is no gold standard test for the diagnosis of PTS. This diagnosis can be based on clinical signs and symptoms or on objective assessment of venous valvular insufficiency and venous hypertension. We used a standardized clinical scale, with signs and symptoms to define presence and severity PTS, which was derived from the Villalta scale. Sustained venous hypertension, the underlying pathogenic mechanism of PTS, can be reliably measured by invasive ambulatory venous pressure tests. This technique requires special equipment, is invasive, time-consuming and cumbersome. It has been shown that PTS diagnosed with the Villalta scale is associated with an increased mean invasive venous ambulatory pressure of over 40 mmHg,[30] suggesting that the use of this scale seems justified. However, until uniform diagnostic criteria for PTS diagnosis are defined, this will remain a limitation of all clinical studies.

We assessed the presence and severity of PTS at a median of ten months after diagnosis of deep venous thrombosis. It usually takes 3 to 6 months after an acute deep venous thrombosis for the initial pain and swelling to resolve and the diagnosis of PTS should be deferred until later.[9,10,27] In

most cases PTS will become apparent within 1 year after the acute deep venous thrombosis, with little increase in incidence thereafter.[9] Thus, the 25% one-year cumulative incidence we found may have been an underestimation.

We conclude that PTS remains a frequent complication in patients with deep venous thrombosis despite the frequent use of elastic compression stockings. Female sex, older age, obesity and varicose veins were all associated with the development of PTS, whereas genetic risk factors were not.

Acknowledgment

The authors wish to thank the (former) directors of the Anticoagulation Clinics of Amersfoort (Dr M.H.H. Kramer), Amsterdam (Dr M. Remkes), Leiden (Dr F.J.M. van der Meer), The Hague (Dr E. van Meegen), Rotterdam (Dr A.A.H. Kasbergen) and Utrecht (Dr J. de Vries-Goldschmeding) who made the recruitment of patients possible. The interviewers Ms. J.C.M. van den Berg, Ms. B. Berbee, J.E. Kroon, Ms S. van der Leden, Ms M. Roosen and Ms E.C. Willems of Brilman performed the blood draws. Ms I. de Jonge, Ms R. Roelofsen, Ms M. Streevelaar, Ms L.M.J. Timmers and Ms J.J. Schreijer are thanked for their secretarial and administrative support and data management. The fellows Ms I.D. Bezemer, Ms J.W. Blom, MD, Ms A. van Hylckama Vlieg, PhD, Ms E.R. Pomp and Ms K.J. van Stralen took part in every step of the data collection. Ms C.J.M. van Dijk, R. van Eck, J. van der Meijden, Ms P.J. Noordijk and Ms Th. Visser performed the laboratory measurements. H.L. Vos supervised the technical aspects of DNA analysis. We express our gratitude to all individuals who participated in the MEGA study. This research was supported by the Netherlands Heart Foundation (NHS 98.113), the Dutch Cancer Foundation (RUL 99/1992) and the Netherlands Organisation for Scientific Research (912-03-033| 2003). The funding organizations did not play a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript.

References

1. Neumann HA, Veraart JC. Morphological and functional skin changes in postthrombotic syndrome. Wien Med Wochenschr. 1994;144:204-6.
2. Roumen-Klappe EM, den Heijer M, Janssen MC, Vleuten van der, C, Thien T, Wollersheim H. The post-thrombotic syndrome: incidence and prognostic value of non-invasive venous examinations in a six-year follow-up study. Thromb Haemost. 2005;94:825-30.
3. Ginsberg JS, Hirsh J, Julian J, LaandeVries vander M, Magier D, Mackinnon B, et al. Prevention and treatment of postphlebitic syndrome: results of a 3-part study. Arch Intern Med. 2001;161:2105-9.
4. Franzeck UK, Schalch I, Jager KA, Schneider E, Grimm J, Bollinger A. Prospective 12-year follow-up study of clinical and hemodynamic sequelae after deep vein thrombosis in low-risk patients (Zürich study). Circulation. 1996;93:74-9.
5. Ziegler S, Schillinger M, Maca TH, Minar E. Post-thrombotic syndrome after primary event of deep venous thrombosis 10 to 20 years ago. Thromb Res. 2001;101:23-33.
6. Brandjes DP, Büller HR, Heijboer H, Huisman MV, de Rijk M, Jagt H, et al. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. Lancet. 1997;349:759-62.
7. Prandoni P, Lensing AW, Cogo A, Cuppini S, Villalta S, Carta M, et al. The long-term clinical course of acute deep venous thrombosis. Ann Intern Med. 1996;125:1-7.
8. Prandoni P, Lensing AW, Prins MH, Frulla M, Marchiori A, Bernardi E, et al. Below-knee elastic compression stockings to prevent the post-thrombotic syndrome: a randomized, controlled trial. Ann Intern Med. 2004;141:249-56.
9. Kahn SR, Ginsberg JS. Relationship between deep venous thrombosis and the postthrombotic syndrome. Arch Intern Med. 2004;164:17-26.
10. Kahn SR. The post-thrombotic syndrome: progress and pitfalls. Br J Haematol. 2006;134:357-65.
11. Partsch H, Kaulich M, Mayer W. Immediate mobilisation in acute vein thrombosis reduces post-thrombotic syndrome. Int Angiol. 2004;23:206-12.
12. Rosendaal FR. Venous thrombosis: a multicausal disease. Lancet. 1999;353:1167-73.
13. McColl MD, Ellison J, Greer IA, Tait RC, Walker ID. Prevalence of the post-thrombotic syndrome in young women with previous venous thromboembolism. Br J Haematol. 2000;108:272-4.
14. Biguzzi E, Mozzi E, Alatri A, Taioli E, Moia M, Mannucci PM. The post-thrombotic syndrome in young women: retrospective evaluation of prognostic factors. Thromb Haemost. 1998;80:575-7.
15. Ageno W, Piantanida E, Dentali F, Steidl L, Mera V, Squizzato A, et al. Body mass index is associated with the development of the post-thrombotic syndrome. Thromb Haemost. 2003;89:305-9.
16. van Dongen CJ, Prandoni P, Frulla M, Marchiori A, Prins MH, Hutten BA. Relation between quality of anticoagulant treatment and the development of the postthrombotic syndrome. J Thromb Haemost. 2005;3:939-42.
17. Kahn SR, Kearon C, Julian JA, Mackinnon B, Kovacs MJ, Wells P, et all. Predictors of the post-thrombotic syndrome during long-term treatment of proximal deep vein thrombosis. J Thromb Haemost. 2005;3:718-23.
18. Stain M, Schonauer V, Minar E, Bialonczyk C, Hirschl M, Weltermann A, et al. The post-thrombotic syndrome: risk factors and impact on the course of thrombotic disease. J Thromb Haemost. 2005;3:2671-6.
19. Maessen-Visch MB, Hamulyak K, Tazelaar DJ, Crombag NH, Neumann HA. The prevalence of factor V Leiden mutation in patients with leg ulcers and venous insufficiency. Arch Dermatol. 1999;135:41-4.
20. Hafner J, Kuhne A, Schar B, Bombeli T, Hauser M, Luthi R, et al. Factor V Leiden mutation in postthrombotic and non-postthrombotic venous ulcers. Arch Dermatol. 2001;137:599-603.
21. MacKenzie RK, Ludlam CA, Ruckley CV, Allan PL, Burns P, Bradbury AW. The prevalence of thrombophilia in patients with chronic venous leg ulceration. J Vasc Surg. 2002;35:718-22.
22. Blom JW, Doggen CJM, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA. 2005;293:715-22.
23. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. JAMA. 1998;280:1690-1.
24. Bertina RM, Koeleman BP, Koster T, Rosendaal FR, Dirven RJ, de Ronde H, et al. Mutation in blood coagulation factor V associated with resistance to activated protein C. Nature. 1994;369:64-7.
25. Poort SR, Rosendaal FR, Reitsma PH, Bertina RM. A common genetic variation in the 3'-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. Blood. 1996;88:3698-703.
26. Mohr DN, Silverstein MD, Heit JA, Petterson TM, O'Fallon WM, Melton LJ. The venous stasis syndrome after deep venous thrombosis or pulmonary embolism: a population-based study. Mayo Clin Proc. 2000;75:1249-56.
27. Haenen JH, Wollersheim H, Janssen MC, 't Hof MA, Steijlen PM, van Langen H, et al. Evolution of deep venous thrombosis: a 2-year follow-up using duplex ultrasound scan and strain-gauge plethysmography. J Vasc Surg. 2001;34:649-55.

28. Christiansen SC, Cannegieter SC, Koster T, Vandenbroucke JP, Rosendaal FR. Thrombophilia, clinical factors, and recurrent venous thrombotic events. JAMA. 2005;293:2352-61.
29. Kahn SR, Elman E, Rodger MA, Wells PS. Use of elastic compression stockings after deep venous thrombosis: a comparison of practices and perceptions of thrombosis physicians and patients. J Thromb Haemost. 2003;1:500-6.
30. Kolbach DN, Neumann HA, Prins MH. Definition of the post-thrombotic syndrome, differences between existing classifications. Eur J Vasc Endovasc Surg. 2005;30:404-14.