Diagnosis of venous thrombosis and the post-thrombotic syndrome

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CHAPTER 7

Predictors of the post-thrombotic syndrome with non-invasive venous examinations in patients six weeks after a first episode of deep venous thrombosis

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Background Post-thrombotic syndrome is a chronic complication of deep venous thrombosis affecting a large number of patients. Because of its potential debilitating effects, identification of patients at high risk for the development of this syndrome is relevant and only a few predictors are known.

Objectives To assess the incidence and potential predictors of the post-thrombotic syndrome.

Methods We prospectively followed 111 consecutive patients for two years after a first episode of objectively documented deep venous thrombosis of the leg. With non-invasive tests, residual thrombosis, valvular reflux, calf muscle pump function, and venous outflow resistance were assessed at 6 weeks, 3 and 6 months, and at 1 and 2 years. The CEAP-classification served to record the occurrence and severity of the post-thrombotic syndrome. Regression analysis with area under the receiver operating characteristic (ROC) curve was performed to identify potential predictors.

Results The cumulative incidence of the post-thrombotic syndrome was 49% after one year, and the incidence and severity did not further increase afterwards. Men were at an increased risk compared to women (risk ratio (RR) 1.4, 95% confidence interval (CI) 0.9-2.2), as were patients over 50 years compared to younger patients (RR 1.4, 95%CI 0.9-2.1). Patients with thrombosis localized in the proximal veins at diagnosis had an increased risk of the post-thrombotic syndrome compared to patients with distal thrombosis (RR 2.3, 95%CI 1.0-5.6). The post-thrombotic syndrome developed in 32 out of 52 patients (62%) with residual thrombosis in the proximal veins six weeks after diagnosis, compared to 17 out of 45 patients (38%) without residual proximal thrombosis, leading to a 1.6-fold increased risk (95%CI 1.0-2.5). The presence of valvular reflux in the superficial veins was also a predictor at six weeks with a 1.6-fold increased risk compared to patients without superficial reflux (95%CI 1.1-2.3). A multivariate analysis of these predictors yielded a ROC area-under-the-curve of 0.72 (95%CI: 0.62-0.82).

Conclusion Post-thrombotic syndrome develops in half of all patients within one year, with no further increase up to two years of follow-up. Male sex, age over 50 years, proximal localization of the thrombus at entry, residual proximal thrombosis and superficial valvular reflux at six weeks are predictors of the post-thrombotic syndrome in patients with a first episode of deep venous thrombosis. Duplex scanning six weeks after diagnosis appears to be clinically useful to identify patients at risk of the post-thrombotic syndrome.

Introduction

Acute deep venous thrombosis may lead to chronic venous complications in 20 to 50% of patients (1). Factors that play a role in the pathophysiology of this so-called post-thrombotic syndrome are 1) damage to venous valves, which causes valvular reflux with diminished calf muscle pump function nd 2) persistent venous obstruction due to incomplete thrombus clearance. This leads to high walking venous pressure resulting in alterations of the skin microcirculation and morphological skin changes(2). These changes can be classified with the clinical score of the Clinical, Etiologic, Anatomic, and Pathophysiologic (CEAP) classification (3,4).

As the post-thrombotic syndrome reduces quality of life (5), and is costly to society (6), it would be desirable to identify patients at risk for post-thrombotic syndrome at an early stage. Strategies for the prevention and management of the post-thrombotic syndrome should be applied in these high-risk patients. Recurrent ipsilateral deep venous thrombosis is a risk factor and should be prevented with adequate anticoagulation therapy (7,8). Continuous use of elastic compression therapy after deep venous thrombosis reduces the risk of the post-thrombotic syndrome by approximately 50% (8,9). Non-invasive venous examinations, such as duplex scanning and strain gauge plethysmography may be useful to predict the development of post-thrombotic syndrome. With duplex scanning it is possible to measure the extent of the initial thrombus, residual thrombosis and valvular reflux, while strain gauge plethysmography quantifies venous outflow resistance and calf muscle pump function (10-13). These non-invasive examinations are however not routinely applied in clinical practice. Factors that have been associated with the development of the post-thrombotic syndrome are male sex, advanced age, increased body mass index, idiopathic deep venous thrombosis, proximal localization of deep venous thrombosis, extent of residual vein thrombosis, presence of valvular reflux, reduced calf muscle pump function, and increased venous outflow resistance (14-22). However, results of previous studies are conflicting with regard to the predictive value of these factors.

The objectives of the present study were to assess the incidence of post-thrombotic syndrome during two years of follow-up with standardized compression treatment after a first episode of deep venous thrombosis, and to determine the predictive value of non-invasive venous examination for the development of the post-thrombotic syndrome.

Methods

Study Design

Between May 2002 and September 2005, consecutive patients aged 18 to 70 with a first episode of deep venous thrombosis of the leg seen at the Meander Medical Center, Amersfoort, the Netherlands, were included in this follow-up study. All patients participated in the multicenter Multiple Environmental and Genetic Assessment (MEGA) of risk factors for venous thrombosis study (23). Patients with a life expectancy of less than one year and those with an inability to undergo ambulant compression therapy were excluded. Among the 134 eligible patients, 23 patients refused to participate, which led to 111 participating patients.

All patients were treated according to a standardized protocol with low molecular weight heparin and vitamin K antagonists for six months. Short-stretch elastic bandages were applied immediately after diagnosis. As soon as edema was reduced elastic therapeutic stockings were prescribed with compression class III (ankle pressure 35-45 mm Hg). The length of the bandages and the elastic therapeutic stockings were dependent on the localization of the thrombus. In case of proximal deep venous thrombosis thigh-length bandages and stockings were applied during three months, and followed by knee-length elastic compression stockings. In patients with distal deep venous thrombosis knee-length bandages and stockings were applied only. Elastic compression stockings were adapted for each patient by an experienced professional bandagist. Patients were instructed and motivated to wear the elastic compression stockings for at least two years. At each visit details on the frequency and duration of the use of elastic compression stockings were recorded.

Patients filled in a detailed questionnaire on demographic variables and acquired risk factors for venous thrombosis. The questionnaire covered the period of one year prior to the thrombotic event. Deep venous thrombosis was defined as idiopathic in the absence of malignancy, surgery, plaster cast, minor injury, bed rest at home or in the hospital, pregnancy and the use of female hormones. Body mass index was calculated from self-reported weight and height (kg/m^2).

All patients underwent physical examinations of the leg and non-invasive venous tests at regular intervals. The non-invasive venous tests consisted of duplex scanning and strain gauge plethysmography. These tests were performed at the time of diagnosis of deep venous thrombosis,

after six weeks, three and six months and after one and two years or when recurrent venous thrombosis occurred. Symptomatic recurrent deep venous thrombosis was objectively confirmed with duplex scanning.

A dermatologist who was unaware of the findings of non-invasive venous tests, performed the physical examinations of the leg and classified the skin changes in patients according to the clinical score of the Clinical, Etiologic, Anatomic, and Pathophysiologic (CEAP) classification (3,4). In this classification patients with class 0 represent no visible or palpable signs of the post-thrombotic syndrome; class 1 telangiectasies or reticular veins; class 2 varicose veins; class 3 oedema without skin changes; class 4 skin changes ascribed to venous disease (pigmentation, venous eczema, lipodermatosclerosis, white atrophy, corona phlebectatica); class 5 skin changes with healed venous ulcer and class 6 skin changes with active venous ulcer. The post-thrombotic syndrome was considered to be present if the score was 3 or more. The presence and severity of the post-thrombotic syndrome was assessed in the leg in which the deep venous thrombosis occurred.

Duplex scanning was performed by one of three experienced vascular technologists with a Philips iU22 scanner with a 5 to 12 MHz linear array probe. Seventeen vein segments were examined with the patient in a 45° sitting position (10). The common femoral vein, superficial femoral vein, long and short saphenous vein, popliteal vein, posterior and anterior tibial veins, peroneal and gastrocnemial veins were examined. In the calf a distinction was made between the superficial and the deeper vein. Compressibility was assessed in the transverse plane. A vein was considered non-compressible when it was not completely compressed under gentle pressure of the duplex probe. A thrombosis score was based on the extent of occlusion by the thrombus (3). A vein segment scored one point when it was occluded completely or in part. A fully patent vein segment showed complete compressibility and flow, and scored zero points. Thrombosis score values for each patient were calculated by adding the thrombosis score values of each of the 17 vein segments. The thrombosis score was separately scored for the five proximal deep vein segments (common femoral, superficial femoral [proximal, middle, and distal], and popliteal veins), the eight distal deep vein segments (two posterior tibial, two anterior tibial, two peroneal, and two gastrocnemial), and the four superficial vein segments (long saphenous vein [proximal, middle, and distal] and short saphenous).

In the longitudinal plane, the presence of venous flow and valvular reflux was measured by duplex examination. Pathological valvular reflux was defined as a reversed flow duration of more than 1 sec in the proximal veins and more than 0.5 sec in the distal veins. Reflux score values were calculated by adding the number of vein segments with pathological valvular reflux (10).

Calf muscle pump function and venous outflow resistance were measured by a Filtrass angio strain gauge plethysmograph (compumedics ltd.) (11-13). Patients were examined in the supine position with the knees slightly bent at an angle of 90° and pneumatic cuffs around the thighs, and strain-gauges around the calves. The cuffs were inflated with a cuff pressure of 50 mmHg which resulted in an increase of venous volume and pressure. Maximum volume was achieved when the venous pressure equaled the effective congestion pressure. Then, with the cuffs still inflated, the patient was instructed to perform 10 dorsal extensions. The calf muscle pump action resulted in a volume decrease in the limb. In the period of rest after the exercise, with the cuffs still inflated, venous volume and pressure returned to their maximum value and the expelled volume was measured. By use of individual pressure-volume gradients, the expelled volume was converted to a pressure decrease. Pressure decrease (P1-P2) was expressed as a percentage of the initial pressure (P1) before the exercise and was a measure of the calf muscle pump function [PF = (P1-P2/P1) x 100%] (11).

Venous outflow resistance was assessed by measuring the maximum venous outflow at five different cuff pressures (60 to 20 mmHg). The maximum volume change ($\Delta V/V$) for each occlusion pressure was measured, and plotted against the effective cuff pressure. The slope of the line through the points gave an angle ß. In analogy with Ohm's law venous outflow resistance was calculated as 1/tangent ß and expressed in resistance units (RU): (mmHg x min)/%.

The study protocol was approved by the institutional review board and written informed consent was obtained from all participants.

Predictors

Based on previous studies, we a priori selected candidate predictors of post-thrombotic syndrome (14-22). These included sex, age, body mass index, varicose veins at diagnosis, idiopathic deep

venous thrombosis, localization of deep venous thrombosis, the extent of residual vein thrombosis quantified with the thrombosis score, and the presence of valvular reflux quantified with the reflux score, and calf muscle pump function and venous outflow resistance.

Statistical Analysis

The cumulative incidence of post-thrombotic syndrome was calculated as the number of patients with post-thrombotic syndrome divided by the overall number of patients. The relative risk of each predictor was calculated by risk ratios, with corresponding 95% confidence interval (95%CI). The risk ratios indicate the risk of post-thrombotic syndrome in the presence of a candidate predictor relative to the absence of that predictor. The chi-square test was used to assess differences between proportions. Subsequently, we included all candidate predictors with a P-value ≤0.10 in a multivariate logistic regression model. The ability of the model to discriminate between patients with and without post-thrombotic syndrome was estimated by the area-under-the-receiver operating characteristic (ROC) curve. All computations were performed with the use of SPSS software, version 14.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics of the 111 patients with a first episode of symptomatic deep venous thrombosis are summarized in Table 1. There were 52 women (47%), the mean age of all patients at time of diagnosis was 48 years (5^{th} -95^{th} percentile 27-68) and the overall mean age was 5 years higher in men than in women. Varicose veins, as assessed by the dermatologist, were present at entry in 15 patients (13%). Thrombosis was unilateral on the left side in 55 patients (50%), and none of the patients had bilateral deep venous thrombosis. Distal thrombosis was present in 18 patients (16%), and deep venous thrombosis was idiopathic in 34 patients (31%) (Table 1).

A total of 94 patients (85%) completed the two years of follow-up, 11 patients did not complete the follow-up because they were unable to come to the hospital for all examinations, and six patients died of various causes. Recurrent symptomatic deep vein thrombosis was diagnosed in six patients. Two recurrences occurred in the ipsilateral leg and four in the contralateral leg. Median duration to recurrence was 7 months (5^{th}-95^{th} percentile 4-13). Three patients used vitamin K antagonists during their recurrence.

Table 1. Characteristics of 111 patients with a first episode of deep venous thrombosis of the leg

Characteristic	
Women, No (%)	52 (47%)
Age (years), mean (SD)	48 (12)
5th -95th percentile	27-68
BMI (kg/m2), mean (SD)	27 (4)
5th -95th percentile	21-36
Varicose veins at diagnosis	15 (13%)
Side of DVT	
left	55 (50%)
right	56 (50%)
Localization of DVT	
proximal	73 (66%)
proximal and superficial	13 (12%)
superficial	7 (6%)
distal	18 (16%)
Malignancy	6 (5%)
Surgery	25 (23%)
Plaster cast	9 (8%)
Minor injury	34 (31%)
Bed rest at home or in hospital	29 (26%)
Pregnancy	2 (2%)
Hormone use among women	24 (46%)
Idiopathic DVT	34 (31%)

BMI = body mass index, SD = standard deviation, DVT = deep venous thrombosis

Mean duration of initial bandages was 19 days (5th-95th percentile 8-36). Thigh-length compression therapy was used in 80 out of 111 patients (72%) for the first three months followed by knee-length stockings, the remaining 31 patients used knee-length compression therapy from diagnosis onwards. Elastic therapeutic stockings with compression class III were used in 107 out of 111 patients (96%), 4 patients (4%) used class II stockings. Despite the advise to use elastic compression stockings for two years, 22 patients used them for a shorter period. In seven of these patients this was due to intercurrent disease or death and 15 patients were non compliant because of other reasons. Good compliance (≥ 6 days per week) was reported by 74 patients (67%).

Anticoagulation was given during six months in 83 patients (75%), six patients (5%) were treated for a shorter period, with a mean duration of 95 days (5th-95th percentile 45-128). In 13 out of 22 patients

who were treated for more than six months, vitamin K antagonists treatment was continued for more than one year.

Incidence and Severity of the Post-thrombotic Syndrome

The cumulative incidence of PTS (CEAP ≥3) was 46% at 6 weeks after the deep venous thrombosis, 49% after one year and did not increase afterwards (Table 2). The incidence of CEAP classification 4 progressed from 26% at entry to 33% at 6 weeks and then also stabilized, at 39% after one and two years. The initial increase in CEAP classification 4 skin changes was mainly due to newly formed corona phlebectatica. None of the patients was diagnosed with CEAP classification 5 or 6. Post-thrombotic syndrome was established in the first year after deep venous thrombosis, without progression of the incidence or severity in the second year.

Table 2. CEAP score during follow-up in 111 patients with a first episode of deep venous thrombosis in the leg.

CEAP score	*Clinical signs*	*diagnosis*	*six weeks*	*three months*	*six months*	*one year*	*two* years*
0	No visible or palpable signs	25	44	42	42	39	42
1-2	Telangiectases, reticular veins, malleolar flare or varicose veins	6	10	12	10	12	14
3	Oedema, without skin changes	43	13	8	7	10	5
4	Skin changes ascribed to venous disease	26	33	38	41	39	39
5-6	Skin changes with (healed) ulceration	0	0	0	0	0	0
≥ 3	Post-thrombotic syndrome		46	46	48	49	44

All values are percentages of all patients, i.e. 25 means 25% of all patients had a CEAP score of zero at diagnosis
* in 13 patients CEAP was incomplete during two-years of follow-up

Residual Thrombosis and Valvular Reflux

In all veins thrombus resolution was a continuing process. The resolution of thrombus was more rapid and complete in patients with thrombosis in distal vein segments than in those with proximal thrombosis. At diagnosis 78% of the five proximal vein segments was occluded completely or in part, after six weeks this was reduced to 54%, and after two years 33% showed residual thrombosis (Table

3). The superficial and distal vein segments showed less residual thrombosis after two years, respectively 7% and 3%. Men had more proximal residual thrombosis at six weeks than women; 35 out of 55 men (64%), compared to 20 out of 47 women (43%). The thrombosis score declined from a mean of 3.8 non-compressible segments at diagnosis to 2.0 after six weeks and 0.8 after 2 years. Valvular reflux was present at an average of 0.6 segments at diagnosis and this increased slightly to 0.9 segments after 6 weeks and 1.1 after two years.

Table 3. Residual thrombosis and valvular reflux over time in patients with a first episode of deep venous thrombosis.

Vein segments	residual thrombosis			valvular reflux		
	diagnosis n=111	six weeks n=102	two years n=97	diagnosis n=72	six weeks n=102	two years n=97
Proximal, n (%)* (5 vein segments)	87 (78)	55 (54)	32 (33)	6 (8)	21 (21)	36 (37)
Superficial, n (%) (4 vein segments)	20 (18)	17 (17)	2 (7)	9 (13)	22 (22)	15 (16)
Distal, n (%) (8 vein segments)	69 (62)	29 (28)	3 (3)	5 (7)	0 (0)	7 (7)
Thrombosis score Reflux score, Mean** (range)	3.8 (0-11)	2.0 (0-9)	0.8 (0-5)	0.6 (0-5)	0.9 (0-7)	1.1 (0-7)

* n (%) is number and percentage of patients with residual thrombosis or valvular reflux at that specific point in time. For example 87 (87) means that 87 out of 111 patients (78%) had thrombosis in a proximal vein.
** Mean score of 17 vein segments

Functional Venous Hemodynamic Tests

At diagnosis, 22% of patients had a calf muscle pump function under 40%, six weeks later this was only 13%, and the number declined to 6% after one and two years (Table 4). Only 20% of patients had a calf muscle pump function greater than 60% at diagnosis, this number increased to 38% after six weeks and then stabilized at 40% after one and two years. Mean calf muscle pump function improved from 48% at diagnosis to 54% after 6 weeks and was stable at 56% at one and two years.

Mean venous outflow resistance declined during treatment from 3.0 RU at diagnosis to 2.5 RU after three months and remained stable during one year follow-up and showed an increase to 2.9 RU after two years of follow-up.

Table 4. Calf Muscle Pump and Venous Outflow Resistance measured by Strain Gauge Plethysmography during two-years of follow-up

	diagnosis	*six weeks*	*three months*	*six months*	*one year*	*two years**
CMP < 40%, n (%)**	22 (22)	13 (13)	13 (13)	11 (11)	6 (6)	6 (6)
CMP 40-60%, n (%)	59 (58)	50 (49)	41 (41)	43 (42)	51 (54)	51 (54)
CMP ≥ 60%, n (%)	20 (20)	38 (38)	47 (46)	48 (47)	37 (40)	37 (40)
CMP in %, mean (range)	48 (10-76)	54 (14-79)	55 (10-80)	56 (20-76)	56 (23-80)	56 (24-94)
VOR in RU, mean (range)	3.0 (0.6-17.2)	2.9 (0.3-25.0)	2.5 (0.7-19.3)	2.5 (0.6-9.2)	2.5 (0.4-13.2)	2.9 (0.7-16.1)

CMP=calf muscle pump function, VOR=venous outflow resistance, RU=resistance unit, SD=standard deviation
* in 17 patients strain gauge plethysmography was not complete during two-years of follow-up
**n (%) number and percentage of patients with calf muscle pump function below 40%

Predictors of the Post-thrombotic Syndrome

Men had a 1.4-fold higher risk of developing the post-thrombotic syndrome than women (risk ratio (RR) 1.4, 95% confidence interval (CI) 0.9-2.2) (Table 5).

Patients over 50 years had a 1.4-fold increased risk of the post-thrombotic syndrome compared to patients below this age (RR 1.4, 95%CI 0.9-2.1). The risk of the post-thrombotic syndrome was 2.3-fold higher in patients with thrombosis localized in the proximal veins compared to distal thrombosis (RR 2.3, 95%CI 1.0-5.6). Post-thrombotic syndrome developed in 39 out of 64 patients (61%) with residual thrombosis, i.e. thrombosis score ≥1, six weeks after diagnosis, compared to 10 out of 33 patients (30%) without residual thrombosis, leading to a two-fold increased risk (RR 2.0, 95%CI 1.6-3.5). Patients with residual thrombosis in the proximal veins, i.e. proximal thrombosis score ≥1, also had an increased risk compared to patients without proximal residual thrombosis (RR 1.6, 95%CI 1.0-2.5).

Table 5. Risk of post-thrombotic syndrome one year after deep venous thrombosis in 99 patients.

	With PTS N=49 N (%)	Without PTS N=50 N (%)	Rate ratio (95%CI)	P-value*
Sex				
men	30 (58)	22 (42)	1.4 (0.9-2.2)	<0.1
women	19 (40)	28 (60)		
Age				
≥50 years	24 (59)	17 (41)	1.4 (0.9-2.1)	0.1
<50 years	25 (43)	33 (57)		
BMI				
≥25 kg/m^2	33 (51)	32 (49)	1.1 (0.7-1.7)	0.7
<25 kg/m^2	16 (47)	18 (53)		
Varicose veins at diagnosis				
yes	8 (62)	5 (38)	1.3 (0.8-2.1)	0.4
no	41 (48)	45 (52)		
Idiopathic DVT				
yes	14 (45)	17 (55)	0.9 (0.5-1.4)	0.6
no	35 (51)	33 (49)		
DVT localization				
proximal	45 (55)	37 (45)	2.3 (1.0-5.6)	<0.05
distal	4 (23)	13 (77)		
TS at 6 weeks**				
≥1	39 (61)	25 (39)	2.0 (1.6-3.5)	<0.01
<1	10 (30)	23 (70)		
$TS_{proximal}$ at 6 weeks**				
≥1	32 (62)	20 (38)	1.6 (1.1-2.5)	<0.05
<1	17 (38)	28 (62)		
Reflux score at 6 weeks**				
≥1	19 (66)	10 (34)	1.5 (1.0-2.2)	<0.05
<1	30 (44)	38 (56)		
Superficial reflux at 6 weeks**				
yes	13 (72)	5 (28)	1.6 (1.1-2.3)	<0.05
no	36 (46)	43 (54)		
Popliteal reflux at 6 weeks**				
yes	8 (67)	4 (33)	1.4 (0.9-2.2)	0.2
no	41 (48)	44 (52)		
CMP at 6 weeks**				
<60 %	33 (57)	25 (43)	1.3 (0.8-2.0)	0.2
≥60 %	16 (44)	20 (56)		
VOR at 6 weeks**				
≥1.5 RU	38 (53)	34 (47)	1.1 (0.7-1.7)	0.8
<1.5 RU	11 (50)	11 (50)		

PTS=post-thrombotic syndrome, BMI=body mass index, DVT=deep venous thrombosis, TS=thrombosis score, CMP=calf muscle pump function, VOR=venous outflow resistance, RU=resistance unit
* P-value of chi-square test
** Unknown in ≤5 patients

The presence of valvular reflux in one or more vein segments six weeks after diagnosis, i.e. reflux score ≥1, compared to no reflux showed a 1.5-fold increased risk of the post-thrombotic syndrome (RR 1.5, 95%CI 1.0-2.2). Post-thrombotic syndrome developed in 13 out of 18 patients (72%) with

superficial valvular reflux six weeks after diagnosis, compared to 36 out of 79 patients (46%) without superficial reflux. The presence of superficial valvular reflux was a predictor of the post-thrombotic syndrome with a 1.6-fold increased risk compared to patients without superficial reflux (RR 1.6, 95%CI 1.1-2.3). The combination of residual thrombosis in the proximal veins and the presence of superficial valvular reflux was seen in eight patients of whom seven developed the post-thrombotic syndrome (88%) at one year.

Body mass index, varicose veins at diagnosis or idiopathic deep venous thrombosis were not associated with the development of the post-thrombotic syndrome, nor were calf muscle pump function or venous outflow resistance.

Thus, sex, age, localization of deep venous thrombosis, (proximal) thrombosis score at 6 weeks, reflux score, and the presence of superficial valvular reflux at 6 weeks, were associated (all P-value ≤ 0.1) with the development of the post-thrombotic syndrome (Table 5). Proximal thrombosis score and superficial valvular reflux were included in a multivariate model together with sex, age and localization. This model yielded a ROC area-under-the-curve of 0.72 (95%CI: 0.62-0.82). Subsequent addition of venous outflow resistance and calf muscle pump function to this model resulted in a minor improvement with a ROC area-under-the-curve of 0.75 (95%CI: 0.66-0.85). Replacement of proximal thrombosis score with overall thrombosis score and superficial valvular reflux with overall reflux score led to a ROC area-under-the-curve of 0.77 (95%CI: 0.68-0.87). Subsequent addition of idiopathic thrombosis showed the highest ROC area-under-the-curve of 0.79 (95%CI: 0.70-0.88). Addition of body mass index or varicose veins at diagnosis did not show further improvement of the ROC area-under-the-curve.

Discussion

This study revealed that the post-thrombotic syndrome occurs in half of all patients within one year after a first episode of symptomatic deep venous thrombosis of the leg when elastic compression stockings are applied. Non-invasive venous examination six weeks after diagnosis showed that residual thrombosis of the proximal veins and valvular reflux in the superficial veins were predictors of the post-thrombotic syndrome. Other predictors included proximal localization of thrombosis at diagnosis, age over 50 years and male sex.

Residual thrombosis and valvular reflux were measured with duplex examination in 17 vein segments of the leg, which is an elaborate examination even in the hands of experienced vascular technicians. Both proximal thrombosis score, which quantifies the occlusion of five proximal vein segments, and the superficial reflux score, which quantifies valvular reflux in the four superficial vein segments, were predictors of post-thrombotic syndrome. Previous studies showed that (proximal) thrombosis score and (superficial) reflux score, measured three to six months after diagnosis, are predictors of post-thrombotic syndrome (15,16,18,20). Here we show the predictive value of a simplified duplex examination as early as six weeks after deep vein thrombosis.

Proximal localization of thrombosis at diagnosis showed an increased risk of the post-thrombotic syndrome. Results of previous studies have been inconsistent with regard to the relationship between localization of the initial thrombus and the subsequent development of the post-thrombotic syndrome (7,21,24). An explanation for the increased risk of the post-thrombotic syndrome may be that patients with proximal thrombosis have more residual thrombosis, and residual thrombosis increases the risk for the post-thrombotic syndrome. Another possible explanation is that the collateral circulation in the proximal veins is less extensive compared to the distal veins of the calf, as each artery in the calf is accompanied by two veins.

We found that older age and male sex conferred an increased risk of developing the post-thrombotic syndrome. The increased risk in elderly patients has been reported in some (8,21), but not all studies (19,22). Male sex was a risk factor in one other study (21). The higher risk of the post-thrombotic syndrome in men might be related to the older age of men in this study and the higher rate of proximal residual thrombosis. The reason why men might have a delayed thrombus regression is currently unknown but can explain the higher risk of recurrent thrombosis in men (17, 25-27). Overall, the predictive value of age and sex were not consistent in previous studies.

In contrast to other studies body mass index was not associated with the development of the post-thrombotic syndrome in our study (19,21,22). Furthermore, we did not show a predictive value of the non-invasive examination of calf muscle pump function and venous outflow resistance in the univariate analysis. Adding these tests to the multivariate model showed only a minor improvement of

the ROC area-under-the-curve. This is in contrast to previous studies that identified venous outflow resistance as a predictor of the post-thrombotic syndrome (15,20).

The overall risk of 49% post-thrombotic syndrome that we observed after one year, is comparable with the incidence of the post-thrombotic syndrome after one to two years reported in other studies that used the CEAP classification (15,16,20). Studies that used the Villalta scale to classify the post-thrombotic syndrome, observed a lower incidence of 20 to 40% (7,9,18,22). The Villalta scale uses symptoms and signs whereas the CEAP classification uses clinical signs that represent a progressive gradation of disease severity. A higher incidence of the post-thrombotic syndrome using the CEAP score in comparison to the Villalta scale was also shown in a study that compared the different classifications for the post-thrombotic syndrome (28). Until uniform diagnostic criteria for the post-thrombotic syndrome are defined, the ability to compare results from different studies will remain limited.

None of the patients in our study had a CEAP classification 5 or 6. The use of immediate short-stretch elastic bandages followed by class III elastic therapeutic stockings probably reduced the development of the post-thrombotic syndrome and may be the explanation for the absence of venous ulceration (8,9,20,29).

The true time of onset of the post-thrombotic syndrome after an objectively diagnosed first deep venous thrombosis is uncertain. Earlier studies, one with a follow-up of twenty years, suggested a gradual increase in incidence of the post-thrombotic syndrome over the years (7,29,30). More recent studies with a follow-up period of five years showed that the post-thrombotic syndrome develops within two years (8,9,20,31). Our results show that the post-thrombotic syndrome is established within one year after deep venous thrombosis, without an increase in the incidence or severity of the post-thrombotic syndrome after one up to two years, in patients treated with immediate adequate compression therapy.

A strength of this study is the high percentage of complete follow-up. Our study shows that one year follow-up allows sufficient time for the post-thrombotic syndrome to become apparent. Hence, future

studies focusing on the development of post-thrombotic syndrome, can be limited to a one-year follow-up duration.

A possible clinical implication of our findings is that a simplified duplex scanning should be performed in all patients six weeks after deep vein thrombosis to identify patients at high risk for the post-thrombotic syndrome. This syndrome developed within one year in 88% of patients who were treated with compression therapy with a duplex scanning at six weeks that showed combined residual proximal thrombosis and superficial valvular reflux.

Another important reason to implement non-invasive examination with duplex scanning six weeks after diagnosis is to differentiate between symptomatic recurrent thrombosis and residual thrombosis with post-thrombotic complaints during follow-up. In patients with recurrent thrombosis treatment should be focused on anticoagulation therapy, whereas compression therapy is the treatment strategy in patients with residual thrombosis and post-thrombotic complications. Recurrence rate after a symptomatic first deep venous thrombosis is high with 5% after 2 years up to 25% after 5 years (7,25-27,32). Patients with residual thrombus have an increased risk of recurrence and the post-thrombotic syndrome (15,17,18,20,32). Duplex scanning six weeks after diagnosis elucidates the changes of the thrombus in the individual patient and enables the physician to compare residual thrombus with recurrent thrombus when a patient returns with symptoms after a deep venous thrombosis.

The results of this study may have implications for the advised duration of elastic compression stockings. We identified that men over 50 years with proximal deep venous thrombosis and residual proximal thrombosis or superficial valvular reflux six weeks after diagnosis were at increased risk of developing the post-thrombotic syndrome. These high-risk patients are candidates for long term compression therapy. A question that remains to be answered is how long patients with an indication for long term compression therapy should continue this therapy: two years, or even longer. In patients without these predictors or signs of the post-thrombotic syndrome, compression therapy could be stopped after adequate treatment and recovery of deep venous thrombosis in the first three to six months. Prospective studies should confirm whether it is safe to withhold compression therapy in these patients.

We conclude that the post-thrombotic syndrome develops in one half of all patients within one year, with no increase in incidence or severity up to two years of follow-up. Male sex, age over 50 years, proximal localisation of thrombus at diagnosis, residual thrombosis in the proximal veins and valvular reflux in the superficial veins six weeks after diagnosis are predictors of the development of the post-thrombotic syndrome in patients with a first episode of deep venous thrombosis. A simplified duplex scanning six weeks after diagnosis of deep venous thrombosis enables the identification of patients at high risk of the post-thrombotic syndrome.

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