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Full Length Article

Post-thrombotic syndrome: Short and long-term incidence and risk factors

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ABSTRACT

Background: The reported incidences of post-thrombotic syndrome (PTS) after deep vein thrombosis (DVT) vary. Further, PTS symptom development over time and its long-term incidence are unknown.
Methods: Patients included in the MEGA study were interviewed at 1 year and completed a questionnaire at 8 years of follow-up regarding symptoms and signs of PTS based on the Villalta score after a first DVT diagnosis. The cumulative incidence of PTS at 0–1 and 1–8 year, changes in PTS classification and the effect of possible clinical and laboratory risk factors were determined.
Results: After 1 year, 361 out of 1657 patients diagnosed with DVT were classified as having PTS, for a 0–1 year cumulative incidence of 21.8% (95%CI 19.9–23.8), out of whom 92 (5.6%) had severe PTS. After 8 years 633 patients without previous PTS completed the second questionnaire, of whom 44 were classified as having PTS, for a 1–8 year cumulative incidence of 7% (95%CI 5.2–9.2); of these 13 (2.1%) were classified as severe PTS. During follow-up PTS complaints improved in 69% and worsened in 7% of patients. At 1 year, risk factors were female sex (RR 1.5; 95%CI 1.2–1.9) and obesity (RR 1.5; 95%CI 1.2–7.9), with the same effect sizes at 8 years. Provoked/unprovoked DVT, thrombus location, pregnancy, hormone use and several laboratory parameters did not affect risk of PTS, either at 1 or 8 years.
Conclusion: The incidence of PTS remained substantial up to 8 years after a first DVT. Symptoms improved in a large proportion of the cases. The short and long term risks were highest in women and obese patients.

1. Introduction

Approximately 20–50% of patients with a deep venous thrombosis (DVT) develop post-thrombotic syndrome (PTS) within 2 years despite treatment with anticoagulation [1–5]. The pathophysiology of PTS is complex and has not yet been fully characterised. Chronic venous hypertension caused by outflow obstruction and reflux by valvular incompetence appear to play a central role in PTS development [6,7]. PTS diagnosis is mostly based on the Villalta scale as recommended by the current guidelines and should be deferred until 3–6 months after the acute phase when initial pain and swelling associated with acute DVT have resolved [1,8].

Patients with PTS present a various spectrum of symptoms and signs of chronic venous insufficiency such as pain, feeling of heaviness, oedema, skin pigmentation and in more severe cases, venous ulcers. Patients usually develop these symptoms and signs within the first months to the first years after DVT diagnosis [9,10]. Little is known on the development of these symptoms and signs > 2 years after initial DVT diagnosis [4,11].

Recent studies identified older age, obesity (body mass index (BMI) > 30 kg m^{-2}), proximal DVT location and recurrent ipsilateral DVT as risk factors for PTS. According to the current literature there is no agreement regarding several other possible risk factors such as sex, provoked-, unprovoked DVT or inherited or acquired hypercoagulability [1,12]. This discrepancy in possible risk factors is mainly caused by different studied populations and the heterogeneous design of several studies.

In the current study we aimed to evaluate 0 to 1- and 1 to 8-year PTS cumulative incidence in patients diagnosed with a first DVT, and to determine how these symptoms and signs evolved over time (how many patients with PTS improved, worsened or stayed the same). Furthermore, we aimed to assess the effect of several risk- and treatment factors on PTS development after both 1-year and after 8-years of follow-up. This study is a continuation with additional information on a

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previously published study into the 1-year cumulative incidence and the assessment of several risk factors of PTS in patients included in the Multiple Environmental and Genetic Assessment (MEGA) study [5].

2. Methods

2.1. Study population

For this study we used data of patients diagnosed with a first DVT event available from the MEGA study. The MEGA study is a population-based case-control study into risk factors for venous thromboembolism (VTE). Between March 1999 and August 2004 consecutive patients aged between 18 and 70 years with an objectively diagnosed first VTE event and signed informed consent were included from six participating anticoagulation clinics. Patients with any psychological condition that would not permit completion of the study or who could not speak Dutch were excluded. Further details of the MEGA study have been described previously [13].

According to the protocol of the MEGA study all patients received a first questionnaire regarding known risk factors for VTE within a few weeks after VTE diagnosis. Most patients were treated with oral anticoagulation for a period of 3 to 6 months. Patients who discontinued to use oral anticoagulation were invited to the anticoagulation clinic three months after they discontinued oral anticoagulation. At the anticoagulation clinic the patients were seen by a research assistant who was not involved in the patient's treatment for an interview and blood sample collection. Patients who continued to use oral anticoagulation treatment were invited at 1 year of treatment for the interview and blood sample collection. Blood sample collection was requested until June 2002.

Between June 2008 and July 2009 all patients included in the MEGA study were evaluated for the development of a recurrent VTE in the previous period (the MEGA follow-up study). Additionally all patients received a second questionnaire that contained questions regarding risk factors for recurrent VTE and symptoms of PTS.

2.2. Study definitions

The 0–1 year cumulative incidence of PTS was defined as the incidence of PTS at the moment of the interview within 1 year after DVT diagnosis and the 1–8 year cumulative incidence of PTS was defined as the incidence of PTS during the MEGA follow-up study, starting from the first PTS assessment.

PTS classification was assessed during the interview with the research assistant and based on a questionnaire in the follow-up study. The patients were asked for five symptoms and four signs based on the Villalta score (Supplement 1) [5,8]. For the presence of each sign or symptom the patient scored one point. A total score of 0 to 3 points indicated no PTS, a score of 4 to 6 points indicated moderate PTS and a score of 7 or more points or the presence of a venous ulcer indicated severe PTS. Previously it was shown that this post-thrombotic score and the Villalta score had an excellent relation (kappa 0.88; 95% confidence interval (CI) 0.79–0.96) [5].

Thrombus localisation was considered proximal when present in the femoral, iliac or inferior vena cava; popliteal when present in the popliteal vein and distal when the thrombus was limited to the calf veins [8]. A DVT was defined as provoked when it occurred in the presence of one or more of the following risk factors: surgery, minor injury, plaster cast, bedridden at home or in the hospital during the last 3 months before DVT diagnosis, active malignancy, female hormone use or pregnancy at the time of thrombosis or when a patient gave birth within 3 months prior to the thrombotic event as reported by the patient during the first questionnaire. Body mass index (BMI; weight/height^2) was classified as follows: $< 18.5\,kg\,m^{-2}$ as underweight, between 18.5 and $25\,kg\,m^{-2}$ as normal, between 25 and $30\,kg\,m^{-2}$ as overweight and $> 30\,kg\,m^{-2}$ as obesity.

2.3. Laboratory measurements

Blood samples were drawn from the antecubital vein into vacuum tubes containing $0.1\,06\,mol\,L^{-1}$ trisodium citrate. High molecular weight DNA was isolated form leukocytes using a standard salting-out procedure and stored at $-20\,°C$ until amplification. The following laboratory parameters were determined according to previously described methods: protein C, protein S and antithrombin (AT), FV Leiden (G1691A), prothrombin (G20210A) and FXIII Val34Leu mutation, level of FVIII, clot lysis time (CLT), high sensitive C reactive protein (HsCRP) and d-dimer [5,14,15].

2.4. Statistical analysis

The 0–1- and 1–8 year cumulative incidences and their corresponding 95%CIs were estimated by dividing the number of patients with a PTS score of > 3 points at 1 respectively 8 years of follow-up by the total number of patients who completed all questions regarding PTS at 1 respectively 8 years. For estimation of the 1–8 year cumulative incidence only the patients who did not have PTS at 1 year (based on a PTS score < 4 points) were selected. To evaluate how PTS classification evolved over time, all patients who were classified as PTS after 1 year and who completed all questions regarding PTS at 8 years of follow-up were selected.

The effect of several risk factors, treatment factors and laboratory parameters on PTS was assessed by calculating the risk ratios (RR) and their 95% CI. Adjusted RRs were calculated by fitting a generalized linear model with a log link function and a binomial distributed outcome. We adjusted for sex and age in all analyses and for height in all except for the risk factors sex, age and BMI. For assessment of the effect of risk factors at 1 year all patients who completed the first questionnaire regarding PTS were selected. For this analysis at 8 years of follow-up all patients who completed the second questionnaire regarding PTS and who did not have PTS at 1 year of follow-up were selected.

We could not determine the effect of a recurrent VTE on PTS incidence at 1 year. Since PTS is not a condition with a clear onset it was unknown whether the patients classified as PTS at this time point already had PTS before development of a recurrent VTE event. Nevertheless, we could evaluate the effect of a recurrent VTE event within 1 year on long-term incidence of PTS.

As blood sample collection took place at 6 months to 1-year of follow-up, the effect of the laboratory parameters on occurrence of subsequent PTS (CLT, HsCRP, d-dimer, protein C, protein S and AT) could only be assessed in patients who did not have PTS before this time point.

In approximately 50% of cases there were some missing data. Therefore, as a sensitivity analysis, we repeated all analyses regarding clinical and laboratory risk factors on PTS after conducting multiple imputation for all missing data. For evaluation at 1 year all patients diagnosed with a first episode of DVT in the lower extremity were selected for multiple imputation and at 8 years the patients who completed all questions regarding PTS during the interview and did not have PTS at 1 year. Ten datasets were imputed and the results were pooled according to Rubin's combination rules [16].

All analyses were performed using Stata 14.0 (Stata Corp., College Station, TX USA).

3. Results

3.1. Patients

Out of 3153 patients included in the MEGA study who were diagnosed with a DVT of the lower extremity, 1912 (60.6%) of these patients answered one or more questions regarding PTS In 1657 (52.6%) patients all questions regarding PTS after 1 year could be completed. At

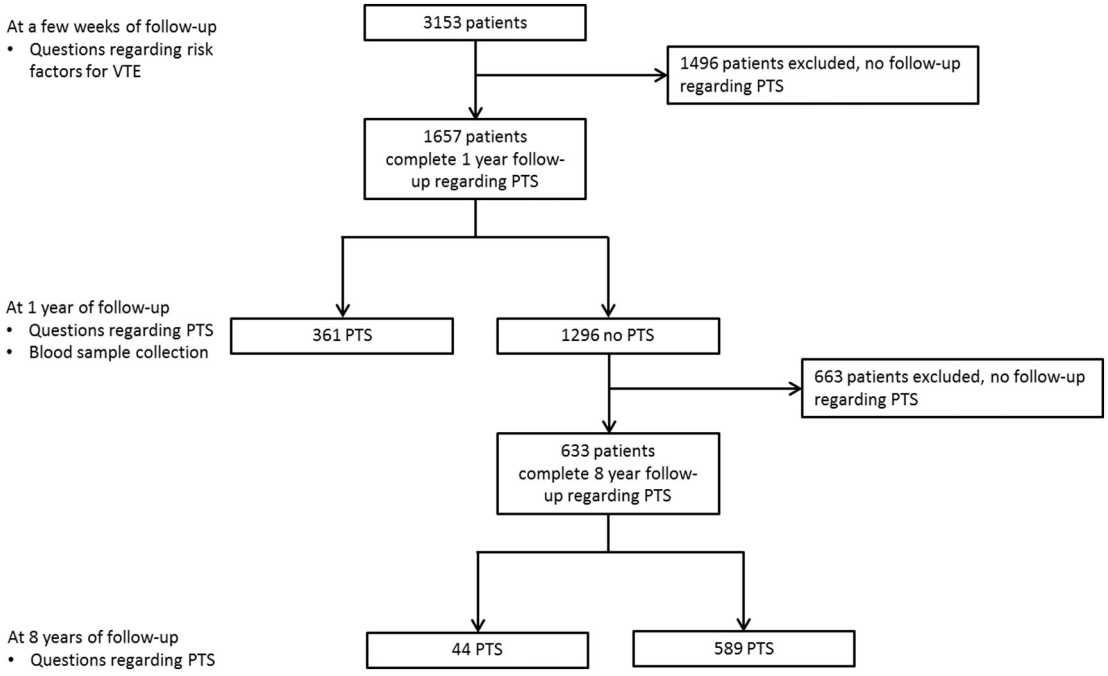

Fig. 1. Flow chart of patient inclusion.
Note: VTE: venous thromboembolism; PTS: post-thrombotic syndrome.

Table 1
Patient characteristics.

	Included for evaluation at 1 year of follow-up	Not included for evaluation at 1 year of follow-up	Included for evaluation at 8 years of follow-up	Not included for evaluation at 8 years of follow-up
Patients (n)	1657	1496	633	663
Age at DVT diagnosis (years, SD)	48 (13)	49 (13)	48 (12)	50 (14)
Male sex (n,%)	785 (47)	749 (50)	298 (47)	351 (53)
Height (m; mean, SD)	1.75 (0.09)	1.75 (0.09)	1.75 (0.09)	175 (0.1)
Weight (kg; mean, SD)	83 (17)	82 (16)	82 (16)	83 (16)
BMI (kg m^{-2}; mean, SD)	27 (4.8)	27 (4.7)	27 (4.6)	27 (4.5)
DVT location				
Proximal vein (n,%)	408 (25)	345 (23)	151 (24)	159 (24)
Popliteal vein (n,%)	528 (32)	377 (25)	204 (32)	212 (32)
Distal vein (n,%)	202 (12)	137 (9)	83 (13)	80 (12)
Unknown (n,%)	519 (31)	637 (43)	195 (31)	212 (32)
Provoked (n,%)	1201 (72)[a]	1094 (73)[b]	466 (74)[c]	199 (30)[d]
Unprovoked (n,%)	441 (27)[a]	380 (25)[b]	164 (26)[c]	457 (69)[d]
Duration of anticoagulation treatment (month; median, IQR)	5.6 (3.3–7.0)	5.6 (3.2–7.3)	5.8 (3.3–6.5)	5.9 (3.3–7.1)

DVT: deep vein thrombosis; SD: standard deviation; m: meter; kg: kilogram; BMI body mass index;
[a] Unknown in 15 patients.
[b] Unknown in 22 patients.
[c] Unknown in 3 patients.
[d] Missing in 7 patients.

8 years of follow up 846 (65.2%) out of 1296 patients without PTS after 1 year answered at least one question regarding PTS in the second questionnaire. Of these 1296 patients, 633 (48.8%) completed all questions regarding PTS at 8 years of follow-up (Fig. 1). There were no differences in baseline characteristics between patients who completed all questions regarding PTS, after 1 year of follow-up compared with those who also completed all questions after 8 years of follow-up. The baseline characteristics are shown in Table 1.

3.2. Short and long term PTS cumulative incidence

At 1 year, 361 out of 1657 patients were classified as having PTS for a cumulative incidence of 21.8% (95%CI 19.9–23.8). Ninety-two of these patients (5.6%) had severe PTS, of whom 47 (2.8%) patients reported to have a venous ulcer. After 8 years of follow-up, an additional 44 out of 633 patients, previously free of PTS, were classified as having PTS, for a cumulative incidence of 7.0% (95%CI 5.2–9.2). Of these, 13 of 633 (2.1%) were classified as severe PTS of whom 12 (1.9%) patients reported a venous ulcer (Table 2). The most frequently reported symptoms and signs at 1 year of follow-up were heaviness of the leg (37%), swelling of the foot or calf (35%) and spontaneous pain in the calf (26%). At 8 years of follow-up the most frequent symptoms and signs were newly formed varicose veins (30%), heaviness of the leg (22%) and swelling of the foot or calf (21%) (Table 3).

3.3. PTS symptoms development

A total of 195 patients classified as PTS at 1 year completed all

Table 2
1-year and 1–8 years PTS cumulative incidence.

	1 year 1657 (n)	Cumulative incidence	1–8 year 633 (n)	Cumulative incidence
PTS	361	22% (95%CI 20–24)	44	7.0% (95%CI 5.2–9.2)
Moderate PTS	269	16 (95%CI 15–18)	31	4.9 (95%CI 3.5–6.9)
Severe PTS	92	5.6 (95%CI 4.5–6.8)	13	2.1 (95%CI 1.2–3.5)
Venous ulcer	47	2.8 (95%CI 2.1–3.8)	12	1.9 (95%CI 1.1–3.3)

Note: PTS: post-thrombotic syndrome; CI: confidence interval.

Table 3
Post thrombotic symptoms and signs at 1 year and at 8 years of follow-up.

Symptoms/signs	1 year 1657 (n, %)	1–8 year 633 (n,%)
Spontaneous pain in the calf	429 (26)	60 (9.4)
Spontaneous pain on walking	239 (14)	29 (4.6)
Spontaneous pain on standing	291 (18)	22 (3.5)
Pain worsening during the day	388 (23)	43 (6.8)
Heaviness of leg	618 (37)	138 (22)
Newly formed varicose veins	217 (13)	193 (30)
Swelling of foot or calf	572 (35)	136 (21)
Skin changes, pigmentation, discoloration	415 (25)	81 (13)
Skin changes with venous ulcer	47 (2.8)	12 (1.9)

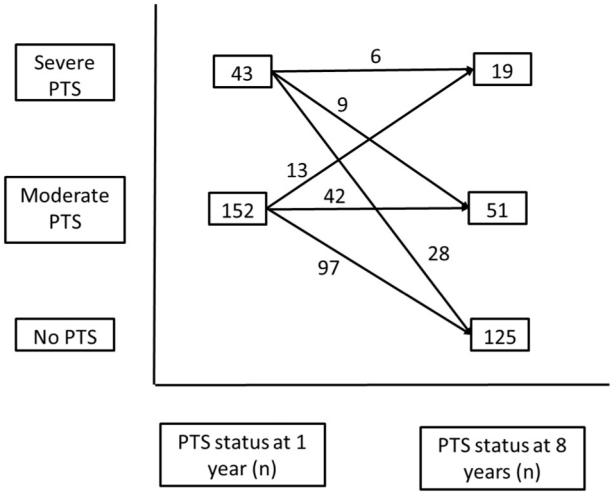

Fig. 2. Change of PTS classification over time.
Note: PTS: post-thrombotic syndrome.

questions regarding PTS at 8 years of follow-up. PTS classification improved after 8 years of follow-up in 134 (69%) patients. Of these patients, a total of 97 originally classified with moderate and 28 originally diagnosed with severe PTS were not classified as having PTS after 8 years. In 9 patients PTS classification changed from severe to moderate. In 42 (22%) patients classified as moderate and 6 (3.1%) patients classified as severe PTS, PTS classification did not change over time. PTS classification became worse in 13 (6.7%) patients (Fig. 2).

3.4. Risk factors for PTS development after 1 and 8 years of follow-up

At 1 year of follow-up the cumulative incidence of PTS was 27% in women and 16% in men. Women had a 1.7 times higher risk of PTS occurrence (RR 1.7; 95%CI 1.4–2.0) which remained elevated after adjustment for age (RR 1.5; 95%CI 1.2–1.9). The 1–8 year cumulative incidences of PTS in women and in men were 7.8% and 6.0% respectively, for an adjusted RR of 1.2 (95%CI 0.64–2.3) (Table 4). The absence of a long- term sex difference remained after multiple imputation (RR 1.1 (95%CI 0.75–1.6)) (Supplement 2).

The cumulative incidence of PTS was 13% in patients over 60 years of age while it was 25% in patients below 30 (RR 0.50; 95%CI 0.34–0.73). This difference persisted after adjustment for sex (RR 0.61; 95%CI 0.41–0.90). We did not find this age effect at 8 years of follow-up.

At 1 year patients shorter than 1.65 m compared with a height of 1.65–1.80 m had a higher risk of PTS development (adjusted RR 1.5; 95%CI 1.2–1.9). Patients who weighted 86–00 kg and > 100 kg had a higher risk of PTS development than those weighing 65–85 kg (adjusted RR 1.3; 95%CI 1.1–1.7 and adjusted RR 1.6; 95%CI 1.2–2.1 respectively). Obese patients had a 1.5 (95%CI 1.2–7.9) times higher risk of PTS compared to patients with a normal BMI. At long term follow-up compared with short term follow-up, the effect size was the same for obesity (adjusted RR of 1.5; 95%CI 0.70–3.5). After multiple imputation the adjusted RR for obesity at the long term follow-up was also 1.5 (95%CI 1.0–2.4) (Supplement 2).

Thrombus location or whether the inciting DVT was provoked or unprovoked or associated with pregnancy or female hormone use did not affect the risk of PTS, either at 1 or at 8 years. A recurrent VTE during the first year of follow-up possibly affected the risk of PTS on the long term (RR 1.7 (95%CI 0.63–4.4)). Multiple imputation did not reveal any differences in these RRs (Table 4, Supplement 2).

3.5. Treatment factors associated with PTS development after 1 and 8 years of follow-up

Patients with PTS at 1 year had used oral anticoagulation for a longer time period. The adjusted RR for duration of use of 6–12 months was 1.3 (95%CI 1.1–1.6) and for > 12 months 1.4 (95%CI 1.1–1.9) compared with the reference of 3–6 months use. At 8 years the same effect sizes were found in the complete data as well as after multiple imputation for a duration of > 12 months (adjusted RR 1.7; 95%CI 0.7–4.0 and 1.5; 95%CI 1.0–2.3 respectively) (Supplement 2). At 1- and at 8 years follow-up, patients with PTS had worn elastic compression stockings more frequently, for an adjusted RR of never versus always use of 0.64; 95%CI 0.47–0.88 at 1 and 0.40; 95%CI 0.16–1.0 at 8 years follow-up. Furthermore, at 1 year of follow-up, patients with PTS had worn elastic compression stockings for a longer time period with an adjusted RR of 0.50 (95%CI 0.36–0.71) for none use and 0.65 (95%CI 0.47–0.88) for a duration of 3–6 months compared to the reference of > 12 months. After 8 years of follow-up the same association was found with an adjusted RR of 0.26 (95%CI 0.09–0.73) in patients who had worn elastic compression stockings for 0 months compared to the reference of > 12 months (Table 4).

3.6. Laboratory parameters associated with PTS development after 1 and 8 years of follow-up

At neither follow-up moment did the presence of Factor V Leiden, prothrombin 20210A, FXIII mutation of factor FVIII levels affect the risk of PTS. Levels of CLT, HsCRP, d-dimer, protein C, protein S and AT did not affect the risk of PTS at 8 years of follow-up (Table 4). After multiple imputation we did not find any changes to these RRs (Supplement 2).

Table 4
Risk factors associated with PTS 1 and 8 years after DVT diagnosis.

	1 year, n	PTS, n	RR (95%CI)	RR adjusted (95%CI)[a]		8 years, n	PTS, n	RR (95%CI)	RR adjusted (95%CI)[a]
Sex									
Men	785	127	1 (ref)	1 (ref)		298	18	1 (ref)	1 (ref)
Women	872	234	1.7 (1.4–2.0)	1.5 (1.2–1.9)		335	26	1.3 (0.72–2.3)	1.2 (0.64–2.3)
Age									
18–29	179	45	1 (ref)	1 (ref)		58	7	1 (ref)	1 (ref)
30–39	287	71	1.0 (0.71–1.4)	1.0 (0.75–1.45)		120	8	0.55 (0.21–1.4)	0.58 (0.22–1.5)
40–49	386	111	1.1 (0.85–1.5)	1.2 (0.92–1.66)		158	10	0.52 (0.21–1.3)	0.55 (0.22–1.4)
50–59	463	91	0.8 (0.57–1.1)	0.90 (0.66–1.2)		190	12	0.52 (0.22–1.3)	0.56 (0.22–1.4)
60–69	342	43	0.50 (0.34–0.73)	0.61 (0.41–0.90)		107	7	0.54 (0.20–1.5)	0.61 (0.20–1.9)
Height (m)	[b]					[m]			
< 1.65	203	68	1.6 (1.3–2.0)	1.5 (1.2–1.9)		65	2	0.42 (0.10–1.7)	0.38 (0.09–1.6)
1.65–1.80	993	207	1 (ref)	1 (ref)		406	30	1 (ref)	1 (ref)
> 1.80	413	73	0.85 (0.67–1.1)	1.1 (0.80–1.5)		150	9	0.8 (0.39–1.7)	1.0 (0.41–2.3)
Weight (kg)	[c]					[m]			
< 65	122	31	1.3 (0.92–1.8)	1.1 (0.73–1.5)		64	1	0.21 (0.03–1.5)	0.21 (0.03–1.5)
65–85	879	174	1 (ref)	1 (ref)		327	24	1 (ref)	1 (ref)
86–100	432	93	1.1 (0.87–1.4)	1.3 (1.1–1.7)		165	10	0.83 (0.40–1.7)	0.85 (0.40–1.8)
> 100	185	53	1.4 (1.1–1.8)	1.6 (1.2–2.1)		65	5	1.0 (0.42–2.6)	1.0 (0.40–2.7)
BMI (kg m^{-2})	[d]					[n]			
Underweight	15	4	1.3 (5.7–3.2)	1.3 (0.55–3.0)		4	0	n.a.	n.a.
Normal	544	108	1 (ref)	1 (ref)		225	12	1 (ref)	1 (ref)
Overweight	699	131	0.94 (0.75–1.2)	1.0 (0.83–1.3)		269	18	1.3 (0.62–2.5)	1.3 (0.64–2.7)
Obese	340	101	1.5 (1.2–1.9)	1.5 (1.2–7.9)		121	10	1.5 (0.69–3.5)	1.6 (0.70–3.5)
Unprovoked	[e]					[o]			
No	1201	282	1 (ref)	1 (ref)		466	36	1 (ref)	1 (ref)
Yes	441	15	0.72 (0.58–0.91)	0.96 (0.74–1.2)		164	7	0.55 (0.25–1.2)	0.60 (0.25–1.4)
DVT location	[f]					[p]			
Proximal vein	408	100	1.2 (0.92–1.5)	1.2 (0.93–1.5)		151	10	1.0 (0.44–2.1)	0.92 (0.43–2.0)
Popliteal vein	528	111	1 (ref)	1 (ref)		204	14	1 (ref)	1 (ref)
Distal vein	202	37	0.87 (0.62–1.2)	0.86 (0.61–1.2)		83	3	0.53 (0.16–1.8)	0.49 (0.14–1.7)
Female hormone use									
No	340	84	1 (ref)	1 (ref)		107	8	1 (ref)	1 (ref)
Yes	532	147	1.1 (0.86–1.4)	1.0 (0.77–1.3)		228	18	1.1 (0.47–2.4)	0.85 (0.37–2.0)
Pregnancy	[g]					[q]			
No	740	202	1 (ref)	1 (ref)		294	22	1 (ref)	1 (ref)
Yes	8	4	1.8 (0.91–3.7)	1.8 (0.91–3.7)		2	0	n.a.	n.a.
Duration of oral anticoagulation									
< 3 months	60	8	0.70 (0.36–1.3)	0.70 (0.36–1.4)		26	1	0.56 (0.08–3.9)	0.59 (0.08–4.2)
3–6 months	820	157	1 (ref)	1 (ref)		347	24	1 (ref)	1 (ref)
6–12 months	595	149	1.3 (1.1–1.6)	1.3 (1.1–1.6)		204	13	0.92 (0.48–1.8)	0.94 (0.47–1.9)
> 12 months	182	47	1.3 (1.0–1.8)	1.4 (1.1–1.9)		56	6	1.5 (0.66–3.6)	1.7 (0.71–4.0)
Frequency of elastic compression stockings	[h]					[r]			
Always	1079	243	1 (ref)	1 (ref)		394	32	1 (ref)	1 (ref)
Most of the time	188	46	1.1 (0.83–1.4)	1.0 (0.80–1.4)		29	3	1.3 (0.41–3.9)	1.4 (0.44–4.2)
Sometimes	100	31	1.4 (1.0–1.9)	1.4 (1.0–1.8)		19	2	1.3 (0.33–5.0)	0.69 (0.10–4.8)
Never	280	39	0.62 (0.45–0.84)	0.64 (0.47–0.88)		166	6	0.45 (0.19–1.0)	0.40 (0.16–1.0)
Duration of elastic compression stockings use	[i]					[s]			
0 months	304	43	0.50 (0.36–0.70)	0.50 (0.36–0.71)		150	4	0.26 (0.09–0.73)	0.26 (0.09–0. 73)
< 3 months	113	18	0.56 (0.35–0.90)	0.56 (0.35–0.89)		17	1	0.57 (0.08–4.0)	0.56 (0.08–3.9)
3–6 months	286	53	0.66 (0.48–0.90)	0.65 (0.47–0.88)		41	2	0.47 (0.12–1.9)	0.42 (0.10–1.7)
6–12 months	690	171	0.88 (0.69–1.1)	0.83 (0.65–1.0)		76	4	0.51 (0.18–1.4)	0.36 (0.11–1.2)
> 12 months	244	69	1 (ref)	1 (ref)		233	24	1 (ref)	1 (ref)
Recurrent VTE									
No	n.a.	n.a.	n.a.	n.a.		597	40	1 (ref)	1 (ref)
Yes	n.a.	n.a.	n.a.	n.a.		36	4	1.7 (0.63–4.4)	1.9 (0.71–5.1)
FV Leiden	[j]					[t]			
GG	1300	281	1 (ref)	1 (ref)		496	37	1 (ref)	1 (ref)
AG/AA	315	74	1.1 (0.87–1.4)	1.1 (0.89–1.4)		131	6	0.61 (0.26–1.4)	0.67 (0.29–1.6)
Prothrombin 20210A mutation	[k]					[t]			
GG	1525	330	1 (ref)	1 (ref)		594	38	1 (ref)	1 (ref)
AG/AA	91	25	1.3 (0.90–1.8)	1.3 (0.90–1.8)		33	5	2.4 (1.0–5.6)	2.6 (1.1–6.2)
FXIII mutation						[t]			
GG	923	196	1 (ref)	1 (ref)		349	19	1 (ref)	1 (ref)
GT	585	141	1.1 (0.94–1.4)	1.2 (1.0–1.4)		236	22	1.7 (0.95–3.1)	1.7 (0.90–3.1)
TT	106	18	0.8 (0.52–1.2)	0.8 (0.50–1.2)		42	2	0.87 (0.21–3.6)	0.94 (0.23–3.9)
Factor VIII activity	[l]					[u]			
< 25th percentile; < 111	362	87	1 (ref)	1 (ref)	< 109	146	7	1 (ref)	1 (ref)
25–50th percentile; 111–137	355	80	0.94 (0.72–1.2)	0.92 (0.71–1.2)	109–135	146	6	0.86 (0.30–2.5)	0.74 (0.24–2.3)
50–75th percentile; 137–167	351	83	1.0 (0.76–1.3)	1.0 (0.78–1.3)	135–163	145	16	2.3 (1.0–5.4)	2.4 (1.0–5.8)
> 75th percentile; 167–437	342	63	0.77 (0.57–1.0)	0.77 (0.57–1.0)	163–361	138	11	1.7 (0.66–4.2)	1.9 (0.75–4.9)
D-dimer (ng/mL)						[u]			

(*continued on next page*)

Table 4 (*continued*)

	1 year, n	PTS, n	RR (95%CI)	RR adjusted (95%CI)[a]		8 years, n	PTS, n	RR (95%CI)	RR adjusted (95%CI)[a]
	n.a.	n.a.	n.a.	n.a.	< 213	144	10	1 (ref)	1 (ref)
	n.a.	n.a.	n.a.	n.a.	213–319	143	10	1.0 (0.43–2.3)	1.1 (0.46–2.7)
	n.a.	n.a.	n.a.	n.a.	319–534	144	9	0.90 (0.38–2.1)	1.0 (0.40–2.5)
	n.a.	n.a.	n.a.	n.a.	534–3142	144	11	1.1 (0.48–2.5)	1.2 (0.50–3.0)
CLT						[u]			
< 25th percentile	n.a.	n.a.	n.a.	n.a.	< 60	143	12	1 (ref)	1 (ref)
25–50th percentile	n.a.	n.a.	n.a.	n.a.	60–68	143	7	0.58 (0.24–1.4)	0.67 (0.27–1.7)
50–75th percentile	n.a.	n.a.	n.a.	n.a.	68–78	145	9	0.74 (0.32–1.7)	0.87 (0.37–2.1)
> 75th percentile	n.a.	n.a.	n.a.	n.a.	> 78	143	12	1 (0.46–2.2)	1.1 (0.49–2.6)
HsCRP (mg/L)						[u]			
< 25th percentile	n.a.	n.a.	n.a.	n.a.	< 0.8	144	9	1 (ref)	1 (ref)
25–50th percentile	n.a.	n.a.	n.a.	n.a.	0.8–1.8	147	9	1.0 (0.40–2.4)	1.2 (0.46–2.9)
50–75th percentile	n.a.	n.a.	n.a.	n.a.	1.8–4.0	140	13	1.5 (0.66–3.4)	1.7 (0.72–4.0)
> 75th percentile	n.a.	n.a.	n.a.	n.a.	> 4.0	143	9	1.0 (0.41–2.5)	1.0 (0.38–2.6)
Protein C activity (%, 100% = 1 IU/mL)						[v]			
Normal	n.a.	n.a.	n.a.	n.a.		556	38	1 (ref)	1 (ref)
Decreased (< mean-2SD)	n.a.	n.a.	n.a.	n.a.		17	2	1.7 (0.45–6.6)	0.87 (0.13–6.0)
Protein S antigen (U/dL)						[w]			
Normal	n.a.	n.a.	n.a.	n.a.		518	38	1 (ref)	1 (ref)
Decreased (< mean-2SD)	n.a.	n.a.	n.a.	n.a.		10	0	n.a.	n.a.
Antithrombine activity						[u]			
Normal	n.a.	n.a.	n.a.	n.a.		556	38	1 (ref)	1 (ref)
Decreased (< mean-2SD)	n.a.	n.a.	n.a.	n.a.		19	2	1.5 (0.40–5.9)	1.6 (0.40–6.1)

Note: PTS: post-thrombotic syndrome; RR: risk ratio; CI: confidence interval; m: meter; kg: kilogram; BMI: body mass index; DVT: deep vein thrombosis; VTE: venous thromboembolism; CLT: clot lysis time; HsCRP high sensitive C reactive protein.

[a] Adjusted for sex, age and height when possible.
[b] Missing in 48 patients.
[c] Missing in 39 patients.
[d] Missing in 59 patients.
[e] Missing in 15 patients.
[f] Missing in 519 patients.
[g] Missing in 124 woman.
[h] Missing in 10 patients.
[i] Missing in 20 patients.
[j] Missing in 42 patients.
[k] Missing in 41 patients.
[l] Missing in 247 patients.
[m] Missing in 12 patients.
[n] Missing in 14 patients.
[o] Missing in 3 patients.
[p] Missing in 195 patients.
[q] Missing in 39 women.
[r] Missing in 25 patients.
[s] Missing in 116 patients.
[t] Missing in 6 patients.
[u] Missing in 58 patients.
[v] Missing in 60 patients.
[w] Missing in 105 patients.

4. Discussion

We showed that in patients with a first DVT, the 1-year PTS cumulative incidence was 22% while an additional 7% developed PTS between 1-to-8 years after DVT diagnosis. Between 1 and 8 years, PTS classification improved in 69%, stayed the same in 25% and became worse in 7% of patients during follow-up. Risk factors for PTS development at 1 year were female sex, shorter height and obesity, while elderly patients appeared to have a lower risk of PTS. Only obesity showed to be a relevant risk factor for the long term follow-up. We further demonstrated that patients with PTS had more often been treated with oral anticoagulants for a period of > 6 months and had worn elastic compression stockings more frequently and for a longer duration. Whether or not the patient's DVT was provoked or unprovoked DVT, thrombus location and several laboratory parameters were not associated with PTS development either at 1 and 8 years.

The 0–1-year PTS cumulative incidence of 22% we found is in accordance with previously reported 1-year incidences of between 17%–27% in patients after a first DVT [17–20]. Several studies reported on PTS incidence during long term follow-up. A prospective cohort study of 528 patients after a first DVT diagnosis showed a PTS cumulative incidence of 24.5% after 2 years, of 29.6% after 5 years and of 29.8% after 8 years [4]. A second study reported PTS incidences of 14.9% at 1 year and 19.5% after 5 years in 167 patients [21]. Another study reported on PTS incidence after 1, 2 and 6 years of follow-up based on the CEAP classification in 93, 65 and 48 patients. This study showed much higher cumulative incidences of 49% after 1 year, 55% after 2 years and 56% after 6 years of follow-up, although PTS diagnosis was based on a different score and a limited number of patients was followed [22]. In these long term studies, changes in PTS symptoms during follow-up were not reported while these numbers are relevant in evaluating the development of PTS over time. In our study we have shown that between 1 and 8 years of follow-up PTS classification improved in 69% and worsened in 7% of patients. This is in line with a prospective multicentre follow-up study in 387 patients diagnosed with DVT who were scored according to the Villalta score at 1, 2, 8, 12 and

24 months [9]. Approximately half of the 49 patients with moderate or severe PTS patients after 1 year improved to none or mild at the end of the follow-up period. In a subsequent study, it might be worthwhile evaluating these changes every 1 or 2 years in order to obtain more detailed insight into long term PTS development.

According to our findings at 1 year, women had a 1.5 times higher risk of PTS than men. The literature, however, shows no consistent relationship with sex [1]. We were further able to confirm obesity, as previously described, as a risk factor for PTS development [1]. Interestingly, at 1 year of follow-up, patients with PTS reported to use oral anticoagulation for a longer time period than patients without PTS. A possible explanation for this might be that patients with symptoms and signs of PTS were treated for a longer period of time because of their complaints. Another likely explanation is that these patients were interviewed at a later moment and therefore had a longer period of time to develop PTS. A previous randomized trial on duration of anticoagulation treatment and PTS development, however, showed that anticoagulation treatment for 6 weeks compared with 6 months did not affect the risk of PTS after 10 year of follow-up [11]. A second study also observed no influence of duration of anticoagulation treatment on the risk of PTS after at least 18 months of follow-up [23]. The same explanation is probably true for our finding that patients with PTS wore elastic compression stockings more frequently and for a longer period of time than patients without PTS. Studies regarding the use of elastic compression stockings on PTS development are not consistent due to differences in study design and PTS definition [10,19,24–27].

None of the analysed laboratory parameters were associated with PTS development. A recent meta-analysis also did not find an effect of factor V Leiden, deficiencies of protein S, C and AT, or levels of factor VIII on PTS development [28]. As reported in a recent systematic review, the literature is conflicting regarding an association between D-dimer at presentation and PTS development as well as for D-dimer measured in the early-subacute phase (1–4 months after DVT diagnosis) and the late-subacute phase (5–12 months after DVT diagnosis) on PTS. However, these results were based on very heterogeneous data [29]. In the current study we showed that D-dimer determined at 1 year of follow-up did not affect the risk of PTS on the long term.

The strength of this study lies in the large unselected cohort of patients followed for a long time period which gave us the opportunity to evaluate the cumulative incidence of PTS at 1 and at 1–8 year of follow-up and to assess the clinical course of PTS over time as well as the effect of several risk factors.

This study also had some limitations. First, PTS diagnosis was based on symptoms and signs as reported by the patient based on the Villalta score and not objectively evaluated by a clinician as recommended in the guidelines. Based on a previously reported excellent relation of this post-thrombotic score and the Villalta score [5] we assume this might have influenced our data only minimally. Second, PTS evaluation did not take place at the same time point for every patient: for the 0–1 year cumulative incidence this was between 6 months and 1 year and for the 1–8 year cumulative incidence this was at some point during follow-up. Further it was unknown at what point in time patients began to develop symptoms and signs of PTS, for which reason we could not evaluate incidences within finer time frames. Further, it is unknown whether the symptoms and signs reported by the patient were due to PTS or already present before DVT diagnosis. This is nevertheless a limitation of all studies in this field because it is difficult to classify PTS before DVT diagnosis. Fourth, we could only determine the effect of several laboratory parameters (CLT, HsCRP, d-dimer, protein C, protein S and AT) on long-term PTS development because they were not measured before PTS development at one year of follow-up. Fifth, the missing data at 1- and 8–years of follow-up may not have been completely random and could have introduced selection bias. Lastly, only a limited number of patients completed the long term follow-up questionnaire which led to smaller subgroups and wider 95% CIs. Nevertheless, the effect sizes were largely the same as for the risk factors during 0–1 year of follow-up.

We conclude that in our study population, the incidence of PTS remained substantial up to eight years after a first DVT and that PTS symptoms improved in almost 70% of PTS patients and worsened in 7%. The risk of PTS development is highest in women and obese individuals.

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Conflicts of interest

None of the authors has a conflict of interest with regard to the content of this study.

Author contributions

Yvonne M. Ende-Verhaar was responsible for design of the study, data analysis and interpretation as well as drafting of the manuscript.

Lidwine W. Tick was responsible for design of the study and critically revised the manuscript for important intellectual content.

Frederikus A. Klok was responsible for design of the study and critically revised the manuscript for important intellectual content.

Menno V. Huisman was responsible for design of the study and critically revised the manuscript for important intellectual content.

Frits R. Rosendaal was responsible for design of the study and critically revised the manuscript for important intellectual content.

Saskia le Cessie was responsible for data analysis critically revised the manuscript for important intellectual content.

Suzanne C. Cannegieter was responsible for design of the study, data analysis and interpretation as well as drafting of the manuscript.

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Appendix A. Supplementary data

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