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Deep vein thrombosis : diagnostic and prognostic challenges

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Elastic compression stockings one year after DVT diagnosis: who might discontinue?

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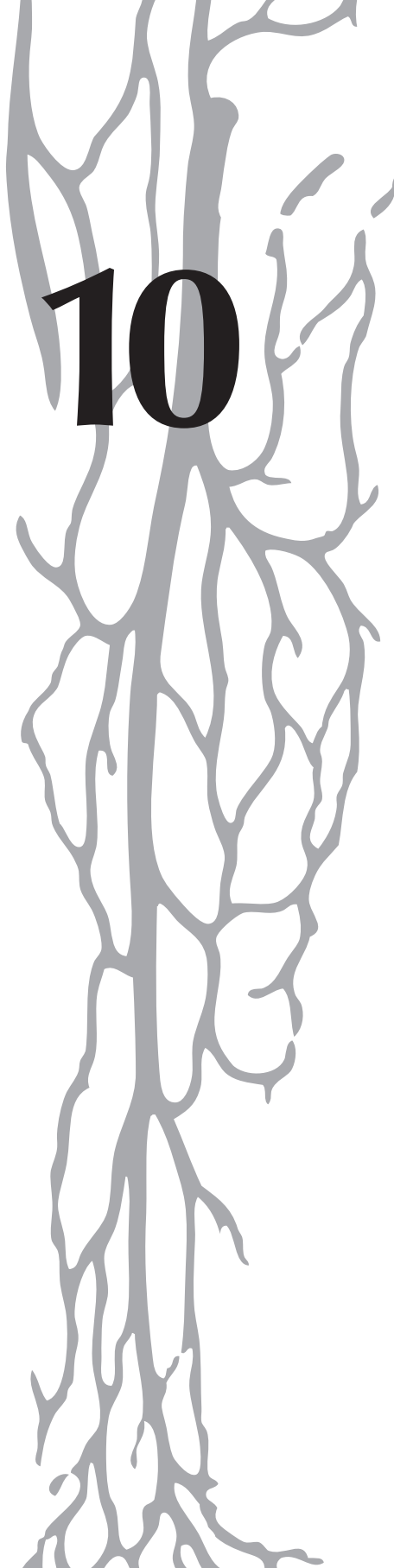

ABSTRACT

Background

Elastic compression stockings (ECS) are uncomfortable to wear but may prevent post-thrombotic syndrome (PTS). The ability to predict PTS may help clinical decision making regarding the optimal duration of ECS after deep vein thrombosis (DVT).

Aims

Predefined endpoint analysis of the Octavia study that randomized patients who compliantly used ECS up to one year after DVT to continue or discontinue ECS treatment. Primary aim was to identify predictors of PTS.

Methods

Patient characteristics were collected and ultrasonography was performed to assess reflux, residual thrombosis and persistent thrombus load 12 months after DVT. Multivariable analyses were performed to identify factors related to PTS.

Results

Thrombus score ≥3, BMI ≥26, duration of symptoms before DVT diagnosis ≥8 days and a Villalta score of 2-4 points were statistically significant predictors of PTS. The predictive value for PTS for the assessed variables was not different between the 2 treatment groups. In the stop ECS group, 3.2% (95%CI 0.08-18) of patients without any predictors for PTS were diagnosed with mild PTS during follow-up, and none with severe PTS, for a sensitivity of 98% (95% CI 89-100), a specificity of 14% (95% CI 10-20), a positive predictive value of 20% (95% CI 19-22), and a negative predictive value of 97% (95% CI 81-100).

Conclusion

We identified 4 predictors of PTS occurring in the 2nd year after DVT. Our findings may be used to decide on whether to continue ECS treatment for an additional year after one year of compliant ECS use, keeping in mind that patients with none of the predictors will have the lowest PTS incidence.

INTRODUCTION

Despite adequate anticoagulation therapy, 20-50% of patients develop post-thrombotic syndrome (PTS) after deep vein thrombosis (DVT).[1] The clinical presentation of PTS ranges from mild skin changes to severe venous ulcers.[2] The signs and symptoms of PTS are assessed and quantified in clinical scales such as the Villalta score, which are used to diagnose PTS.[3] To prevent PTS, elastic compression stockings (ECS) have been suggested to be helpful when patients wear them on a daily basis for 2 years.[4,5] Even so, stockings are constricting, can be itchy and difficult to apply, which can lead to a low adherence in many patients, leading to an absence of efficacy as shown in the SOX trial.[6] Therefore recently, two studies were performed to investigate if a shorter duration of ECS therapy is non-inferior to continuing ECS therapy for two years. The Octavia study showed that stopping ECS therapy in patients who did not develop PTS after a one-year period of compliant use of ECS was **not** non-inferior to continuing ECS therapy, indicating that ECS therapy should be generally continued for at least 2 years after DVT.[7] In contrast, the IDEAL DVT study showed that individualised therapy with compression therapy, i.e. stopping ECS therapy after a minimal duration of 6 months in case of a Villalta score ≤4 on two consecutive visits, was non-inferior to continuing ECS therapy for two years.[8]

The ability to predict PTS may help clinical decision making with regard to the optimal duration of ECS therapy after DVT. Extensive proximal DVT, ipsilateral recurrent DVT and insufficient anticoagulation treatment have been previously described as strong risk factors for PTS.[1] Obesity, primary venous insufficiency and residual venous obstruction have been widely shown as being associated with PTS as well.[9-11] Recently, three clinical prediction scores to predict PTS after DVT were derived, consisting of these easily accessible patients characteristics assessed at time of diagnosis of DVT.[12-14] With a substantial proportion of patients diagnosed with PTS after the first year of DVT diagnosis, the existing scores are not suitable for making long-term decisions on ECS therapy.[1,7]

The primary aim of this predefined secondary analysis of the Octavia study was to find independent predictors for long-term PTS development, i.e. beyond the first year of ECS therapy, to select patients who may stop ECS therapy after an initial treatment period of one year.

METHODS

Patients

Data from the multicentre single blind non-inferiority randomized controlled Octavia study were used to perform a pre-defined endpoint analysis. In the Octavia study, adequately anticoagulated (with VKA) patients from eight teaching hospitals in the

Netherlands who were compliant to compression therapy (knee length, ECS class III) for 12 months after a symptomatic, ultrasound proven proximal DVT (popliteal or more proximal vein) and were not diagnosed with PTS in these 12 months were randomized between continuation (continue-ECS group) and cessation (stop-ECS group) of ECS therapy. Patients were followed for 12 months. The primary endpoint was the incidence of PTS at the end of follow-up period. The diagnosis of PTS was assessed with a full colour visual guide and defined as a Villalta score of 5 points or more and/or the presence of a venous ulcer.[15]

Assessment of predictive values

At baseline, one year after DVT diagnosis patient characteristics at time of DVT diagnosis were collected including age, sex, BMI, smoking status, history of VTE, trauma or surgery <8 weeks or immobilisation >3 days before DVT, number of days of symptoms before DVT diagnosis, cancer, thrombophilia and oral anticonception use. Information about anticoagulant use and compliance to ECS therapy in the first year after DVT was collected. Physical examination was performed to assess the Villalta score one year after the index DVT diagnosis, at study entry. In the statistical analysis patients were divided in two groups: those with 0-1 points of the Villalta score and those with 2-4 points. In addition, in three of the study sites (Diakonessenhuis Utrecht, St Antonius Hospital Nieuwegein and University Medical Center Utrecht), 20 millilitres of blood was taken from each patient and stored in a -80 degrees fridge to assess for D-dimer, high sensitive CRP and fibrinogen levels in one batch at the end of the study.

Ultrasound assessments

At baseline, 12 months after initial DVT diagnosis, a duplex and colour Doppler ultrasound was performed to assess for presence of reflux, 'the reflux score', residual thrombosis and 'the thrombus score'. The deep venous system, i.e. the common femoral vein, superficial femoral vein, profunda femoris, and popliteal veins, as well as the superficial venous system, i.e. proximal and distal saphenous veins, were evaluated for the presence of reflux and residual thrombosis. To assess reflux, patients were examined in supine position; a compression unit (100 mmHg) was placed distal from the examined venous segment. Flow and reflux of the valves were assessed in the longitudinal plane; pathologic reflux was defined as reversed flow duration of more than 1 second in the proximal veins and more than 0.5 seconds in the distal veins. This method has been shown to be highly reproducible.[16] The reflux score was defined as the total number of veins with pathologic reflux.[17] To assess residual thrombosis, vein segments were examined in the transverse plane. Residual thrombosis was defined as incomplete compressibility of a vein segment; 1 point was scored for partial incompressibility and 2 points for complete incompressibility. The thrombus score was assessed by counting the points for all vein

segments which is a validated method according to the International Consensus Committee on Chronic Venous Disease.[18]

Statistical analysis

Baseline characteristics of the continue-ECS group and stop-ECS group are expressed as numbers and percentages. We had a complete dataset for the outcome variables. Less than 1% of the data on the predictor variables was missing. Therefore we performed a complete case analysis. Continuous variables were changed to categorical by selecting the most predictive cut-off value for PTS, assessed by comparing the AUC of the ROC curves using the method proposed by Hanley & McNeil.[19] The first primary outcome of this study was to assess the predictive value of different clinical, biomarker and ultrasonography variables. The predictive values of all variables are presented as odds ratios (OR) with 95% confidence intervals (CI) calculated by univariate logistic regression analysis for the continue-ECS group and stop-ECS group separately. The second primary outcome was to find predictors to select patients who may benefit by continuing ECS therapy for 2 years to prevent PTS. To assess the effect modification of predictors for PTS by wearing ECS, ECS use was inserted as interaction term in the logistic regression analysis. Univariate tests of effect modification by ECS were performed first. The outcome measures of this analysis were odds ratios (OR) adjusted for wearing ECS, with statistical significance evaluated by the Wald test. For the multivariable analysis, it was predefined based on the sample size that only the four best predictors were run in multivariable backward conditional logistic regression analysis, again with ECS use as interaction term, OR as outcome and the Wald test for evaluation of statistical significance. Significant variables in multivariable analysis were considered to be independent predictors of PTS. Incidence of PTS was calculated in patients from the stop-ECS group and continue-ECS group separately without any versus with one or more of these independent predictors. Confidence intervals around these incidences were calculated based on the modified Wald method.[20] Based on these incidence numbers, positive predictive value, negative predictive value and relative risk for PTS based on presence of one or more versus none of these predictors were calculated. All statistics were performed using SPSS version 23 (IBM Corp, Armonk, NY). A p-value <0.05 was considered statistically significant.

RESULTS

A total of 518 patients were included in the Octavia study, of whom 256 were allocated to the stop-ECS group and 262 to the continue ECS group. From the stop-ECS group, 51 (19.9%, 95%CI 16-24) patients were diagnosed with PTS in the first year following randomisation, compared to 34 (13.0%, 95%CI 9.9-17) in the continue-ECS group [7].

Relevant baseline characteristics are shown in **Table 1**. After locking the database, 28% of patients turned out to be incorrectly treated with class II (23-32 mm Hg) graduated active stockings instead of the intended class III (34-46 mm Hg). Ultrasound and laboratory measurements are shown in **Table 2**. Laboratory measurements were performed in three study sites for a total of 135 (53%) of patients from the stop-ECS group and 140 (53%) of patients from the continue-ECS group.

Table 1. Baseline characteristics assessed at time of the index DVT diagnosis and 1 year after DVT

Characteristics at time of the index DVT diagnosis	**Stop-ECS (n=256) N (%)**	**Continue-ECS (n=262) N (%)**
Age ≥65 years	88 (34)	86(33)
Male sex	152 (59)	155 (59)
BMI ≥26	163 (64)	162 (62)
Duration of symptoms before DVT diagnosis ≥8 days	84 (33)	90 (35)
History of VTE	37 (15)	38 (15)
Provoked index DVT	142 (55)	161 (62)
Cancer (active at diagnosis)	29 (11)	21 (8)
Thrombophilia*	17 (7)	24 (9)
History of varicose veins	36 (14)	29 (11)
Current or former smoking	67 (27)	68 (26)
Index DVT in left leg	158 (62)	144 (55)
Most proximal location of DVT:		
Iliac vein	23 (9)	25 (10)
Common femoral vein	44 (17)	31 (12)
Superficial femoral vein	58 (23)	54 (21)
Popliteal vein	131 (51)	152 (58)
Treatment of DVT, assessed 1year after DVT diagnosis		
LMWH use ≤6 days	36 (15)	41 (16)
VKA use ≤3 months	59 (24)	58 (23)
Anticoagulation treatment at baseline (1 year after DVT)	39 (15)	37 (14)
Frequent use of ECS at year 1 (≥6 days/week)	232 (91)	249 (95)
Villalta score 2-4 points at baseline	136 (53)	145 (56)

Note: BMI: Body Mass Index, VTE: Venous thromboembolism, DVT: Deep vein thrombosis, *Antithrombin, protein C or S deficiency, factor V Leiden or prothrombin mutation, presence of antiphospholipid antibodies, LMWH: low molecular weight heparin, ECS: elastic compression stockings, CRP: c-reactive protein

Predictors of PTS between one and two years after DVT diagnosis

With univariate logistic regression analysis, duration of symptoms ≥8 days before DVT diagnosis (OR 2.9, 95% CI 1.6-5.7), thrombophilia (OR 3.1, 95%CI 1.1-8.5), history of varicose veins at the moment of index DVT diagnosis (OR 2.7, 95%CI 1.3-5.8) and a Villalta score of 2-4 points 1 year after DVT diagnosis (OR 5.2, 95%CI 2.4-11) were statistical

Table 2. Ultrasound and laboratory measurements assessed 1 year after the index DVT diagnosis

Ultrasound measurements:	**Stop-ECS (n=256) N (%)**	**Continue-ECS (n=262) N (%)**
Reflux	180 (72)	174 (67)
Refluxscore ≥4*	57 (22)	53 (20)
Refluxscore, only deep veins ≥1*	145 (58)	136 (53)
Residual thrombosis	119 (46)	101 (39)
Thrombus score ≥3*	22 (9)	24 (9)
Laboratory measurements:	**Stop-ECS (n=135) N (%)**	**Continue-ECS (n=140) N (%)**
D-dimer >0.5 mg/L*	29 (21)	23 (16)
High sensitive CRP>3 mg/L*	43 (32)	52 (37)
Fibrinogen >4 g/L*	12 (9)	9 (6.4)

*Continuous variables were changed to categorical by selecting the most predictive cut-off value for PTS, assessed by comparing the AUC of the ROC curves using the method proposed by Hanley & McNeil

significant predictors for PTS in the stop-ECS group (**Table 3**). In the continue-ECS group, only a Villalta score of 2-4 points (OR 3.5, 95%CI 1.5-8.4) and Fibrinogen >4 g/L (OR 4.4, 95%CI 1.1-18) were significant predictors of PTS during follow-up. Univariate analysis in the complete study population with ECS use as interaction term showed no significant predictors, indicating that use of ECS did not change the predictive value of any of the variables to a relevant extent.

Multivariable analysis showed that a thrombus score ≥3 (OR 2., 95%CI 1.1-5.1), BMI ≥26 (OR 1.9 (95% CI 1.1-3.4), duration of symptoms before DVT diagnosis ≥8 days (OR 2.3, 95% 1.4-3.9), and a Villalta score of 2-4 points (OR 4.5, 95%CI 2.5-8.2) were independent predictors of PTS in both treatment arms of the study. Also, use of ECS therapy itself was an independent predictor for PTS with an OR 0.52 (0.34-0.93), indicating a ~50% lower risk (**Table 4**). Further analyses showed that although ECS use prevented PTS, patients with one of the risk factors had a higher risk of PTS in both treatment arms of the Octavia study. Sub analysis of patients that used class II and class III ECS graduated active stockings showed similar results for univariate and multivariable logistic regression analysis (data not shown).

Incidence of PTS in patients with one or more and without predictors

In the stop-ECS group, 31 (12%, 95%CI 9.1-16) out of 256 patients had none of the 4 predictors identified with multivariable analysis. One out of these 31 patients (3.2%, 95%CI 0.08-18) was diagnosed with mild PTS (Villalta score 5) during follow-up (**Table 5a)**. The percentage of patients with PTS increased in the group of patients with one or more predictors for PTS: 6.6% (95%CI 2.5-15) of patients with 1 predictor developed PTS, 25.5% (95%CI 18-35) with 2 predictors, 28% (95% CI 17-42) with 3 predictors and 60%

Table 3. Univariate logistic regression analysis

Baseline features	**Stop ECS group** OR (95% CI), p value	**Continue ECS group** OR (95% CI), p value
Age≥65	1.3 (0.69-2.4), 0.42	1.3 (0.62-2.8), 0.47
Male sex	1.1 (0.58-2.0), 0.82	0.98 (0.47-2.0), 0.96
BMI≥26	1.9 (0.94-3.7), 0.08	2.2 (0.94-5.0), 0.07
Duration of symptoms before DVT diagnosis ≥8 days	2.9 (1.6-5.7), 0.001#	1.9 (0.92-4.0), 0.08
History of VTE	1.6 (0.71-3.6), 0.25	1.3 (0.50-3.4), 0.59
Provoked index DVT	0.97 (0.52-1.8), 0.93	2.2 (0.97-5.2), 0.06
Trauma (<8 weeks before DVT)	0.97 (0.46-2.0), 0.97	2.0 (0.91-4.3), 0.09
Surgery (<8 weeks before DVT)	1.4 (0.59-3.3), 0.45	1.2 (0.44-3.4), 0.70
Immobilisation>6 days	1.6 (0.62-4.0), 0.35	1.5 (0.49-4.9), 0.46
Pregnant, post-partum or use of hormonal replacement therapy	0.73 (0.33-1.6), 0.44	0.94 (0.40-2.2), 0.89
Cancer (active at diagnosis)	0.61 (0.20-1.8), 0.38	1.6 (0.52-5.2), 0.40
Thrombophilia*	3.1 (1.1-8.5), 0.03#	1.4 (0.44-4.3), 0.59
History of varicose veins	2.7 (1.3-5.8), 0.01#	1.9 (0.71-5.1), 0.20
Current or former smoking	1.3 (0.64-2.5), 0.50	1.4 (0.65-3.1), 0.39
Index DVT in left leg	1.2 (0.62-2.2), 0.62	1.2 (0.58-2.5), 0.63
Most proximal location of DVT:		
Iliac vein	0.48 (0.14-1.7), 0.27	0.85 (0.23-3.1), 0.81
Common femoral vein	0.61 (0.25-1.5), 0.28	1.2 (0.42-3.5), 0.74
Superficial femoral vein	0.67 (0.31-1.5), 0.33	0.64 (0.23-1.8), 0.39
Popliteal vein (reference)		
Treatment of DVT		
LMWH use ≤6 days	1.3 (0.58-3.0), 0.50	0.94 (0.34-2.6), 0.94
VKA use ≤3 months	0.79 (0.37-1.7), 0.55	1.8 (0.81-3.9), 0.15
Anticoagulation treatment at baseline (1 year after DVT)	1.8 (0.81-3.9), 0.15	1.1 (0.38-2.9), 0.92
Frequent use of ECS at year 1 (≥6 days/week)	1.1 (0.36-3.4), 0.85	0.71 (0.15-3.4), 0.67
Villalta T=0 2-4 points	5.2 (2.4-11), 0.00#	3.5 (1.5-8.4), 0.005#
Ultrasound measurements		
Reflux	1.1 (0.60-2.1), 0.88	1.1 (0.51-2.5), 0.77
Refluxscore total ≥4	1.1 (0.53-2.3), 0.81	1.8 (0.80-4.0), 0.16
Refluxscore, only deep veins ≥1	1.0 (0.53-1.9), 0.91	1.2 (0.54-2.6), 0.69
Residual thrombosis	1.1 (0.62-2.1), 0.68	1.0 (0.49-2.2), 0.95
Thrombus score ≥3	2.0 (0.77-5.2), 0.15	2.5 (0.92-6.8), 0.07
Laboratory measurements		
D-dimer>0.5 mg/L	1.0 (0.40-2.53), 0.98	1.0 (0.31-3.3), 0.97
High sensitive CRP>3 mg/L	1.7 (0.77-3.8), 0.19	1.55 (0.64-3.76), 0.34
Fibrinogen>4 g/L	0.87 (0.22-3.4), 0.85	4.4 (1.1-18), 0.04#

Note:#p<0.05 BMI: Body Mass Index, VTE: Venous thromboembolism, DVT: Deep vein thrombosis, *Antithrombin, protein C or S deficiency, factor V Leiden or prothrombin mutation, presence of antiphospholipid antibodies, LMWH: low molecular weight heparin, ECS: elastic compression stockings, CRP: c-reactive protein

Table 4. Multivariable backward conditional logistic regression analysis, adjusted for ECS use

Variables*	β	Odds ratio (95%CI)
Use of ECS	-0.577	0.52 (0.34-0.93)
Thrombus score ≥3	0.877	2.4 (1.1-5.1)
BMI≥26	0.645	1.9 (1.1-3.4)
Duration of symptoms before DVT diagnosis ≥8 days	0.843	2.3 (1.4-3.9)
Villalta T=0 2-4	1.504	4.5 (2.5-8.2)

Variables entered on step 1: Use of ECS, Thrombus score ≥3, BMI>25, Duration of symptoms before DVT diagnosis ≥8 days, Villalta T=0 ≥2, Use of ECS Thrombus score ≥3, Use of ECS*BMI>25, Use of ECS* Duration of symptoms before DVT diagnosis ≥8 days, Use of ECS* Villalta T=0 ≥2

Table 5. Number(percentage) of patients diagnosed with PTS with no, one or more predictors

5a: Stop- ECS group:

	No PTS (Villalta <5)	Mild PTS (Villalta 5-9)	Moderate PTS (Villalta 10-14)	Severe PTS (Villalta ≥15)	PTS overall (Villalta 5-≥15)
0 predictors*	30 (97)	1(3.2)	0	0	1 (3.2)
1 predictor	71 (93)	5 (6.6)	0	0	5 (6.6)
2 predictors	70 (74)	22 (23)	2 (2.1)	0	24 (26)
3 predictors	36 (72)	12 (24)	2 (4.0)	0	14 (28)
4 predictors	2 (40)	2 (40)	1 (20)	0	30 (60)

* predictors: thrombus score ≥3, duration of symptoms before DVT diagnosis ≥8 days, Villalta score ≥2, BMI≥26

5b. Continue-ECS group:

	No PTS (Villalta <5)	Mild PTS (Villalta 5-9)	Moderate PTS (Villalta 10-14)	Severe PTS (Villalta ≥15)	PTS overall (Villalta 5-≥15)
0 predictors*	18 (86)	3 (14)	0	0	3 (14)
1 predictor	96 (95)	4 (4.0)	1 (1.0)	0	5 (5.0)
2 predictors	77 (89)	9 (10)	0	1 (1.2)	10 (12)
3 predictors	31 (67)	14 (30)	1 (2.2)	0	15 (33)
4 predictors	4 (57)	3 (43)	0	0	3 (42)

* predictors: thrombus score ≥3, duration of symptoms before DVT diagnosis ≥8 days, Villalta score ≥2, BMI≥26

5c. All patients

	No PTS (Villalta <5)	Mild PTS (Villalta 5-9)	Moderate PTS (Villalta 10-14)	Severe PTS (Villalta ≥15)	PTS overall (Villalta 5-≥15)
0 predictors*	48 (92)	4 (8)	0	0	4 (8)
1 predictor	167 (94)	9 (5)	1 (0.6)	0	10 (6)
2 predictors	147 (81)	31 (17)	2 (1)	1 (0.6)	34 (19)
3 predictors	67 (70)	26 (27)	3 (3)	0	29 (30)
4 predictors	6 (50)	5 (42)	1 (8)	0	6 (50)

* predictors: thrombus score ≥3, duration of symptoms before DVT diagnosis ≥8 days, Villalta score ≥2, BMI≥26

(95%CI 23-88) with 4 predictors. From the 225 patients with one or more predictors for PTS 41 (18%, 95%CI 14-24) were diagnosed with mild PTS (Villalta score 5-9), 5 (2.2%, 95%CI 0.81-5.2) with moderate PTS (Villalta score 10-14) and none with severe PTS, for a positive predictive value of 20% (95% CI 19-22), and a negative predictive value of 97% (95% CI 81-100). Relative risk of PTS in patients with 1-4 predictors was 6.34 (95%CI 0.91-44).

In the continue-ECS group 21 out of 262 patients had none of the 4 predictors (8.4%; **Table 5b**). Three out of these 21 patients were diagnosed with mild PTS during follow-up (14%, 95%CI 4.1-35). The incidence of PTS increased also with the number of predictors in the continue-ECS group: incidences were 5.0% (95%CI 1.9-11) (1 predictor), 12% (95%CI 6.2-20) (2 predictors), 33% (95%CI 21-47) (3 predictors) and 43% (95%CI 16-75) (4 predictors) respectively. From the 241 patients with one or more predictors for PTS, a total of 33 (14% 95%CI 10-19) were diagnosed with PTS during follow-up.

DISCUSSION

In this pre-defined endpoint analysis from the Octavia study, we identified 4 predictors of PTS occurring in the 2nd year after DVT, being, duration of symptoms before DVT diagnosis ≥8 days, BMI≥26, a thrombus score ≥3 and a Villalta score of 2-4 points, assessed 1 year after DVT diagnosis. Patients without any of these identified risk factors who discontinued ECS treatment had a low 3.2% incidence of mild PTS, and none developed severe PTS. However, since the upper level of the confidence interval was 18%, we cannot ultimately prove that the risk of developing PTS in this cohort is negligible. Even so, with an increasing risk associated with more predictors present, our data may be used to counsel the optimal duration of treatment in the individual patient in clinical practice. ECS treatment may be considered to be discontinued with few or none of the predictors present, especially in those patients who experience ECS treatment as very uncomfortable. Of note, only 8-12% patients had none of the predictors present, indicating that the impact of this strategy would be low.

The recently published IDEAL-DVT study confirmed that it may be possible to individualize ECS treatment. Patients were randomized to standard duration ECS therapy (24 months) or an individualised duration of ECS based on the Villalta score during follow-up.[8] All patients were treated with ECS class III. In the individualised ECS duration group, patients with a Villalta score ≤4 on two consecutive visits stopped ECS, after a minimal duration of ECS therapy of 6 months. Because the incidence of PTS was comparable between the two groups, it was concluded that individualised therapy is non-inferior to continuing ECS for 24 months. Our study provides some external validation of the

IDEAL-DVT, since we demonstrated that a higher Villalta score at one year following an index DVT diagnosis was associated with a higher risk of PTS.

Three other recent studies assessed clinical predictors for PTS. In the first study, two clinical risk scores for post-thrombotic syndrome were derived, including the variables age, BMI, varicose veins, smoking, residual vein obstruction, female sex, ileofemoral thrombosis and history of deep vein thrombosis. One assessed the 2-year risk of post-thrombotic syndrome at the moment of the index DVT diagnosis and the other assessed the risk of post-thrombotic syndrome in the sub-acute phase, 6 months after diagnosis of deep vein thrombosis.[12] The Sox-PTS score included 3 variables assessed at time of index DVT diagnosis which were predictive for PTS: DVT in iliac vein, BMI ≥35 and a moderate-severe Villalta score at moment of index DVT diagnosis.[14] The third score was derived for patients aged ≥65 years only.[13] Our study is different from previous ones and therefore not directly comparable, since we studied predictors for PTS occurring in the second year after DVT.

Most of the predictors identified in the current analysis have been associated with a higher risk of PTS in prior studies. Residual thrombosis for example was found to be associated with a 3-fold higher risk of PTS in a large study including 869 consecutive patients with proximal DVT who were assessed for residual thrombosis by ultrasound after three months of treatment.[11] The pathophysiologic mechanism of residual thrombosis causing PTS has also been widely described. Residual thrombosis causes damage to the venous valves, which leads to valve incompetence, reflux and venous hypertension, finally resulting in an absence of pressure decrease in the venous system during walking, the latter being one of the main pathophysiological mechanisms of PTS.[2] The second predictor, obesity, has been more often described as well.[9,21,22]

The third predictor, duration of symptoms before DVT diagnosis >8 days has not been previously described. However, this delay in diagnosing DVT is associated with a longer delay in initiation of adequate anticoagulant treatment. It has been shown earlier that absence of anticoagulant treatment strongly increases the risk of PTS,[23] as does sub-therapeutic use of vitamin K antagonists.[24,25]

The fourth identified predictor was a Villalta score of 2-4 points with PTS defined as a Villalta score ≥5. The likely associations explain this finding. First, it is plausible that patients with pre-clinical PTS one year after a DVT diagnosis are more likely to have progressive symptoms and meet the diagnostic criteria of PTS than patients with no signs of PTS at all. Second, a Villalta score of 2-4 points may not only be caused by preclinical PTS, but may also be due to venous insufficiency or other causes. The latter has been shown to be associated with higher risk of PTS.[10,26]

Interestingly, in univariate analysis, with popliteal vein thrombosis as reference, iliac vein thrombosis showed an OR of 0.48 (95% CI 0.14-1.7) and 0.85 (95% CI 0.23-3.1) in the stop-ECS group and continue-ECS group for PTS respectively. This is in contrast with

previous studies where iliac vein thrombosis was an important risk factor for PTS.[22] Since in this study only patients who did not develop PTS during the first year after DVT were included, we hypothesise that iliac vein thrombosis could mainly be a risk factor for early PTS within the first year after a DVT diagnosis.

The biomarkers that were measured in 275 patients from this study, e.g. CRP, D-dimer and fibrinogen, showed no predictive value for PTS. Only a fibrinogen level of >4g/dl was associated with PTS in the continue-ECS group. Previous studies have evaluated the association with D-dimer, CRP, fibrinogen and PTS.[9,27,28] One study assessed D-dimer levels one year after DVT in 228 patients. The authors of that study reported a significantly higher D-dimer level in patients with PTS as opposed to those without PTS, although after multivariate adjustment, D-dimer was not found to be independently predictive of PTS.[27] In contrast, CRP levels >5 mg/L did show a strong and independent association with PTS for an OR of 8.0 (95%CI 2.4-26). An association between fibrinogen and PTS has not been found in previous studies and should be further investigated in future studies.[29]

The main strength of this study is that this represents a pre-defined endpoint analysis from a randomised controlled trial. A limitation of this study is that laboratory tests were not performed in all patients. Further, only patients who already used ECS compliantly during the first year after PTS diagnosis were included, and patients who already developed PTS during the first year after DVT were excluded. Therefore, the results of this study cannot be generalised to unselected patients with DVT. Moreover, our findings require external validation before they may be incorporated in clinical practice. This is mainly necessary because of the multiple analysis steps were taken to identify the predictors. Nonetheless, results of the IDEAL study and the Octavia study both strongly suggest that it should be possible to better individualise ECS therapy in the future. It remains to be determined which clinical, radiological and biochemical variables are to be included in the optimal risk stratification tool for this purpose.

In conclusion, this study shows that a thrombus score ≥3, BMI ≥26, duration of symptoms before DVT diagnosis ≥8 days, and a Villalta score 2-4 were independent predictors of PTS in patients with proximal DVT who completed 1 year of compliant ECS use and were not diagnosed with PTS in the first year after DVT. The incidence of PTS in patients without any of these predictors was lower than in patients with one or more of these predictors present. Our findings may be used to individualise ECS treatment after one year of compliant ECS use.

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