

# Postthrombotic syndrome and quality of life in patients with iliofemoral venous thrombosis treated with catheter-directed thrombolysis

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**Background:** Postthrombotic syndrome (PTS) is a common complication after iliofemoral venous thrombosis, often resulting in poor quality of life (QOL) among the affected patients. This study assessed development of PTS and its effect on QOL among patients treated for iliofemoral venous thrombosis by catheter-directed thrombolysis.

**Methods:** Patients admitted with an iliofemoral venous thrombosis and treated with catheter-directed thrombolysis at Gentofte University Hospital from 1999 to 2008 were invited to participate. Duplex ultrasound imaging was used to assess venous patency and valve function. Each patient completed the generic Short-Form 36-item (SF-36) health survey assessment, producing physical component (PCS) and mental component summary (MCS) scores, and the disease-specific Venous Insufficiency Epidemiological and Economic Study (VEINES)-Quality of Life (QOL)/Symptoms (Sym), questionnaires to assess QOL. PTS was assessed using the Villalta scale.

**Results:** The study included 109 patients. Median follow-up was 71 months. PTS developed in 18 patients (16.5%) and of those, initial thrombolysis was successful in 13. Patients with PTS had significantly worse mean  $\pm$  standard deviation scores than patients without PTS on VEINES-QOL ( $34.2 \pm 9.6$  vs  $53.1 \pm 6.6$ ;  $P < .0001$ ), VEINES-Sym ( $34.0 \pm 8.8$  vs  $53.2 \pm 6.6$ ;  $P < .0001$ ), SF-36 MCS ( $44.2 \pm 15.5$  vs  $52.3 \pm 11.0$ ;  $P = .005$ ), and SF-36 PCS ( $42.3 \pm 9.1$  vs  $53.5 \pm 7.8$ ;  $P < .0001$ ) subscales. Patients with reflux or chronic occlusions, or both, had significantly lower mean  $\pm$  SD scores than patients with patent veins without reflux on VEINES-QOL ( $43.5 \pm 14.3$  vs  $51.0 \pm 8.8$ ;  $P = .044$ ) and SF-36 PCS ( $47.2 \pm 10.9$  vs  $52.4 \pm 8.5$ ;  $P = .049$ ) scales.

**Conclusion:** PTS was associated with worse QOL, although only a few patients developed PTS after catheter-directed thrombolysis of iliofemoral venous thrombosis. Patients with patent veins and sufficient valves have higher QOL scores than patients with reflux and occluded veins. (J Vasc Surg 2011;54:18S-25S.)

Postthrombotic syndrome (PTS) is a common complication after deep venous thrombosis (DVT), especially after iliofemoral venous thrombosis. PTS is characterized by pain and heaviness in the affected limb, and some of the objective signs are edema, hyperpigmentation, venous ectasia, and venous ulcers. Several studies have shown frequencies of PTS of up to 30% to 40%, despite anticoagulation therapy.<sup>1,2</sup> In one study, the use of compression stockings reduced the rate of PTS approximately 50% compared with controls (hazard ratio for PTS in the stocking group was 0.49).<sup>3</sup>

Previous studies have mainly focused on immediate treatment results, complications, and recurrent thrombo-

sis. Lately, focus has turned toward the effect of PTS on quality of life (QOL), and recent research has shown that QOL among patients with PTS is poor.<sup>4,5</sup> Standardized instruments assessing QOL have been developed, among these the Venous Insufficiency Epidemiological and Economic Study (VEINES)-Quality of Life (QOL)/Symptoms (Sym) questionnaire that has been evaluated among patients with chronic venous disease and DVT.<sup>6,7</sup> Among patients with prior DVT, disease severity is worse and QOL is poorer compared with patients with other forms of chronic venous disease.<sup>8</sup> In 2005, Kahn et al<sup>4</sup> reported that QOL among patients with DVT remains poorer than population norms at 4 months and that worsening of the PTS score is associated with worsening of QOL. In another study, Kahn et al<sup>9</sup> reported that PTS has a significant impact on disease-specific QOL that may not be captured by generic QOL measures such as the Short Form 36-item (SF-36) health survey. Patient-reported QOL measures correlated well with physician-assessed PTS.<sup>9</sup>

These studies, however, dealt exclusively with patients treated with anticoagulation therapy. This study investigated the long-term clinical outcome among patients with iliofemoral venous thrombosis treated with catheter-directed thrombolysis (CDT) to assess the development of

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PTS and to evaluate whether PTS and deep venous function are associated with QOL.

## METHODS

This study was approved by the National Ethics Committee (journal number H-D-2007-0120), and written informed consent was obtained from all patients before examination.

**Patients.** The study population was recruited among consecutive patients admitted with iliofemoral venous thrombosis at the Department of Vascular Surgery, Gentofte Hospital in Copenhagen, Denmark, and treated with CDT between June 1999 and July 2008. After CDT, all patients were treated with graduated compression stockings class II (23-32 mm Hg) and at least 1 year of anticoagulation therapy. Inclusion criteria were first episode of iliofemoral DVT with an open distal popliteal vein, age <60 years, and age of thrombus of maximum 14 days. Exclusion criteria were previous ipsilateral DVT, recent major surgery, malignancy, or other concomitant chronic disease, and have been described elsewhere.<sup>10</sup>

**Technique.** The popliteal vein was punctured under local anesthesia, and a multiple side-hole catheter with tip occlusion was placed in the thrombus. Infusion of tissue plasminogen activator (t-PA) and heparin was done with pulse-spray technique or continuously, and treatment continued until all thrombus had been resolved. Any residual stenosis in the iliac vein was treated with stent placement.<sup>10</sup>

**Follow-up.** For this study, all treated patients were invited in the period from September 2009 to March 2010 for clinical examination, including duplex ultrasound imaging where deep venous patency and function were assessed. We only included patients with at least 1 year of follow-up.<sup>11</sup> All patients were asked to complete the Danish version of the generic SF-36 questionnaire and a Danish version of the disease-specific VEINES-QOL/Sym questionnaire that was developed for this study.

**Ultrasound investigation.** At the clinical visit, every patient had a thorough ultrasound examination using a color duplex ultrasound scanner (Phillips iU22, Bothell, Wash). Patients were supine during the scan. Venous patency of the common iliac and external iliac veins was examined using a 5-2 MHz curved array transducer. The common femoral vein, the femoral vein, and the popliteal vein were scanned using a 9-3 MHz linear array transducer. Patency assessment of the veins included identification of chronic occlusions or chronic venous disease as indicated by the presence of old and echogenic thrombus, partial recanalization, thickened venous wall with irregularly flow lumen, intraluminal webs, decreased compressibility, decreased flow augmentation after distal compression, lack of phasicity with respiration, and possible collateral veins.<sup>12</sup>

For assessment of deep venous valve function, patients were scanned while standing and holding on to a support with their weight on the contralateral leg. Reflux was assessed in the common femoral and popliteal veins and defined as >1.0 second in the common femoral vein<sup>13</sup> and >0.5 second in the popliteal and superficial veins.<sup>14</sup> The

superficial veins (great saphenous and small saphenous vein) were scanned in the groin and in the popliteal fossa and were not examined any further if function was normal.

A standardized pneumatic cuff (Venopulse, STR, Teknik, Norway) with a cuff size of 17 cm was applied around the calf and then rapidly inflated, followed by deflation. This procedure was managed with a foot switch. The cuff was inflated to 150 mm Hg and inflation was automatically held for 3 seconds, followed by rapid deflation. A pressure of 150 mm Hg was applied because it is enough to neutralize the hydrostatic and gravitational pressures and to produce an upward blood flow. One experienced investigator (RB) performed all duplex ultrasound investigations.

**Assessment of PTS.** Recommendations for standardization of PTS assessment have recently been published and were used in this study.<sup>11</sup> Patients were asked not to wear compression stockings on the day of assessment, and most patients were examined in the afternoon to facilitate manifestations of symptoms and signs of PTS.<sup>11</sup> Although most patients had been seen for follow-up annually, it was not possible to perform the Villalta scoring from previous visits because not all of the symptoms or objective findings needed for PTS scoring were recorded in the chart. Therefore, the PTS occurrence data could not be presented in a life table.

At the clinic visit, patients' legs were assessed using the Villalta scale.<sup>15</sup> The presence of five patient-rated leg symptoms (pain, cramps, heaviness, pruritus, and paresthesia) and six physician-rated clinical signs (edema, induration of the skin, hyperpigmentation, redness, venous ectasia, and pain during calf compression) were scored. A score of 0 (none) to 3 (severe) was assigned for each item, and the presence of a venous ulcer was recorded. A total Villalta score of  $\geq 15$  or the presence of a venous ulcer indicated severe PTS, a score of 10 to 14 represented moderate PTS, and a score of 5 to 9 showed development of mild PTS. A score <5 means that PTS is absent. In addition, the leg with previous DVT was classified according to the clinical component of the CEAP classification<sup>16</sup> in one of seven clinical classes ranging from C<sub>0</sub> (no evidence of venous disease) to C<sub>6</sub> (active ulceration).<sup>17,18</sup>

**QOL assessment.** Validated questionnaires in the form of the generic SF-36<sup>19,20</sup> and the disease-specific VEINES-QOL/Sym<sup>6,7</sup> were used for assessment of QOL. The SF-36 assesses eight health concepts and produces two summary scores: a Physical Component Summary (PCS) score describing physical health and a Mental Component Summary (MCS) score describing mental health.

The VEINES-QOL/Sym consists of 26 items and includes questions about specific symptoms (heavy legs, aching legs, swelling, night cramps, heat or burning sensation, restless legs, throbbing, itching, and tingling sensation), limitations in daily activities, and psychologic impact, as well as change in the patient's "leg problem" during the past year and the time of day when the leg problem is most intense. Two scores can be computed: the VEINES-QOL summary score, which assesses QOL, and the VEINES-

**Table I.** Baseline characteristics of patients (n = 109)

Characteristic	No. (%) or mean (range)
Sex	
Males	24
Females	85
Age, years	31 (15-58)
Limbs with DVT	
Left	86
Right	25
Iliofemoral	95
Iliac only	10
Femoral only	6
Stented limbs	62 (56)
Thrombophilia	52 (47)
Chronic occlusions not lysed	3 (2.8)
Chronic changes not lysed	2 (1.8)
Occlusion $\leq$ 1 week after CDT	3 (2.8)
Recurrent DVT since thrombolysis	3 (2.8)
Patients with caval atresia	8 (7)
Long-term anticoagulation	41 (38)

CDT, Catheter-directed thrombolysis; DVT, deep vein thrombosis.

Sym score, a validated subscale that measures symptoms. Higher scores represent higher QOL. Versions of the VEINES-QOL/Sym have been developed in English, French, Italian, French Canadian, and recently, Norwegian.<sup>21</sup> For our patients, we developed a Danish version by using accepted forward-backward translation methodology.<sup>22</sup>

**Statistical analysis.** Mean QOL scores in patients with and without PTS were compared. Furthermore, mean QOL scores in patients who had patent veins without reflux were compared with the patients who had reflux, chronically changed or occluded veins, or both. Analysis of variance was used to test the group differences while controlling for follow-up time and patients' age at thrombolysis. Because of non-normal distributions, the variables concerned were transformed into ordinal rank scores before entering the analysis.

Pearson correlation coefficient analysis was calculated to study the association between the Villalta score and VEINES-QOL/Sym scores. For all tests,  $P \leq .05$  was considered significant. Data were analyzed by means of SPSS 15.0 software (SPSS Inc, Chicago, Ill) and SAS 9.1 software (SAS Institute, Cary, NC).

## RESULTS

**Study patients.** We invited 117 patients previously treated with CDT for acute iliofemoral venous thrombosis to participate in the study. Three had experienced bilateral thrombosis, resulting in 120 limbs. However, during the time since the CDT occurred, one patient died of cancer, four patients (including one with bilateral thrombosis) moved out of Denmark and were lost to follow-up, and three patients refused to participate. This resulted in a study cohort of 109 patients with 111 lower limbs with previous iliofemoral DVT. Baseline characteristics of the 109 patients are presented in Table I.

Median follow-up was 71 months (range, 15-124 months), and at 6 years, the estimated percentage of patent veins without reflux was 87.5% (Fig 1). On the basis of the Villalta score for each patient, the 109 patients were classified as having or not having developed PTS during the 9-year period. PTS developed in 18 (16.5%); of these, 13 had initial successful thrombolysis, but the remaining five had chronic changes or chronic occlusions that could not be treated with thrombolysis. Mild PTS was diagnosed in 13 of the 18 patients and four had moderate PTS. Severe PTS developed in a patient who had been diagnosed with an insufficient popliteal vein 1 year before this investigation. At the time of follow-up, a venous ulcer had developed and duplex ultrasound imaging demonstrated a totally occluded femoral vein corresponding to a recurrent thrombosis several months before the examination. He was not receiving anticoagulation therapy at the time of the event. Of the five patients with chronic changes or occlusions, mild PTS developed in four and moderate PTS in one.

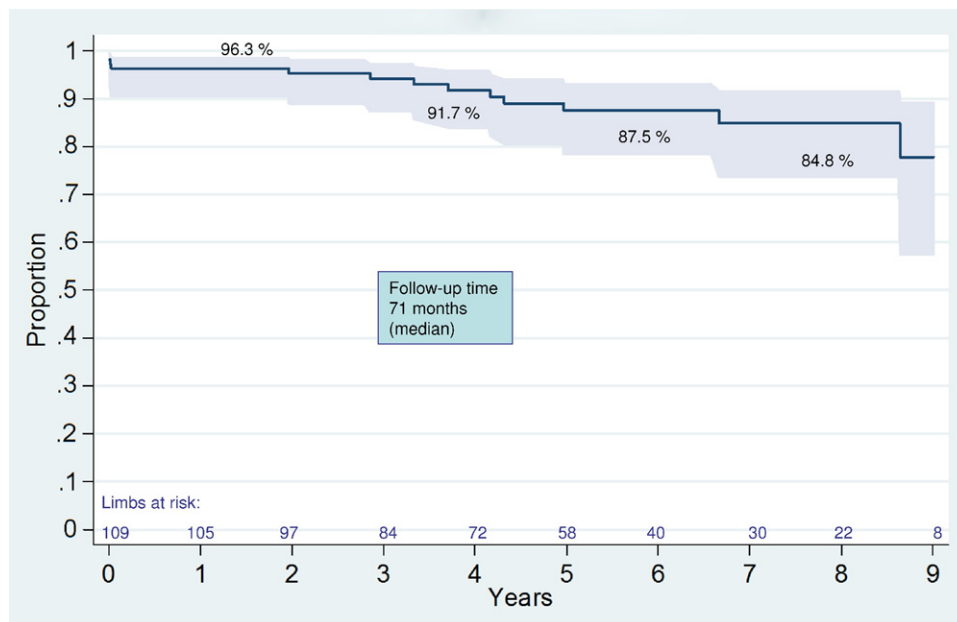
Of the 13 patients who developed mild PTS, seven were diagnosed with mild PTS because of a Villalta score of 5, exclusively based on symptoms. No objective signs were found in these patients. The duplex ultrasound investigation showed patent deep veins without reflux, and no superficial reflux was detected. Two further patients in the group with mild PTS had symptoms from their legs because of varicose veins and insufficiency of their great saphenous vein, and one of those also had caval atresia. Both patients had patent deep veins and no deep venous insufficiency.

According to the CEAP classification, 83% were in the groups C<sub>0</sub> to C<sub>2</sub> (Table II). There were 13 patients (12%) in class C<sub>3</sub>, 6 with skin changes (C<sub>4</sub>-C<sub>6</sub>), of whom five were in group C<sub>4</sub>. The man with recurrent DVT, popliteal reflux, and a venous ulcer was in group C<sub>6</sub>.

**QOL scores.** Patients with PTS had significantly lower scores on the VEINES-QOL/Sym subscales than patients without PTS (Table III). Pearson correlation analysis showed a significant correlation between the Villalta score and VEINES-QOL ( $r = -0.75$ ;  $P < .0001$ ) and VEINES-Sym ( $r = -0.73$ ;  $P < .0001$ ; Fig 2).

The mean  $\pm$  standard deviation SF-36 PCS score was  $42.3 \pm 9.1$  in patients with PTS vs  $53.5 \pm 7.8$  in patients without PTS ( $P < .0001$ ). The mean SF-36 MCS score also differed significantly between patients with and without PTS ( $P = .005$ ; Table III).

Furthermore, VEINES-QOL/Sym scores were higher for patients with patent veins without reflux compared with patients with reflux chronic occlusion or changes, or both, in their deep veins; however, this only reached statistical significance for the VEINES-QOL score (Table IV). A significantly lower score of  $47.2 \pm 10.9$  was observed for the SF-36 PCS score in patients with reflux or chronic occlusion or changes, or both, of their veins vs  $52.4 \pm 8.5$  in patients with patent veins without reflux ( $P = .049$ ). However, no association was seen between the status of the deep veins and the MCS score ( $P = .674$ ).



**Fig 1.** Kaplan-Meier plot illustrates the estimated percentage of patients with patent veins without reflux. The shaded region indicates the confidence limit.

**Table II.** Frequency of the different CEAP C classes

CEAP class	Patients, No. (%)
C <sub>0</sub>	75 (68.8)
C <sub>1</sub>	5 (4.6)
C <sub>2</sub>	10 (9.2)
C <sub>3</sub>	13 (11.9)
C <sub>4</sub>	5 (4.6)
C <sub>5</sub>	0 (0)
C <sub>6</sub>	1 (0.9)
Total	109

When patients with and without reflux were compared, lower scores on the VEINES-QOL/Sym scales were observed; however, no significant difference was found (data not shown).

## DISCUSSION

In our study population of relatively young patients without major comorbidities, PTS developed in only 16.5% of the patients after a median follow-up of 71 months. Furthermore, 13 of 18 patients who developed PTS had mild PTS, and severe PTS developed in only one patient (<1% of all patients in the study). Controlling for age at thrombolysis and follow-up time, we found PTS was associated with worse disease-specific QOL as measured by the VEINES-QOL/Sym questionnaire and also was associated with worse generic QOL as measured by the SF-36 MCS and PCS. Furthermore, we found a significant negative correlation between PTS by means of the Villalta score and the VEINES-QOL/Sym scales.

**Table III.** Quality of life (QOL) according to patients' postthrombotic syndrome (PTS) status

Assessment <sup>a</sup>	Patient PTS status		P <sup>b</sup>
	With PTS (n = 18)	Without PTS (n = 91)	
VEINES			
Sym	34.0 ± 8.8	53.2 ± 6.6	<.0001
QOL	34.2 ± 9.6	53.1 ± 6.6	<.0001
SF-36			
MCS	44.2 ± 15.5	52.3 ± 11.0	.005
PCS	42.3 ± 9.1	53.5 ± 7.8	<.0001

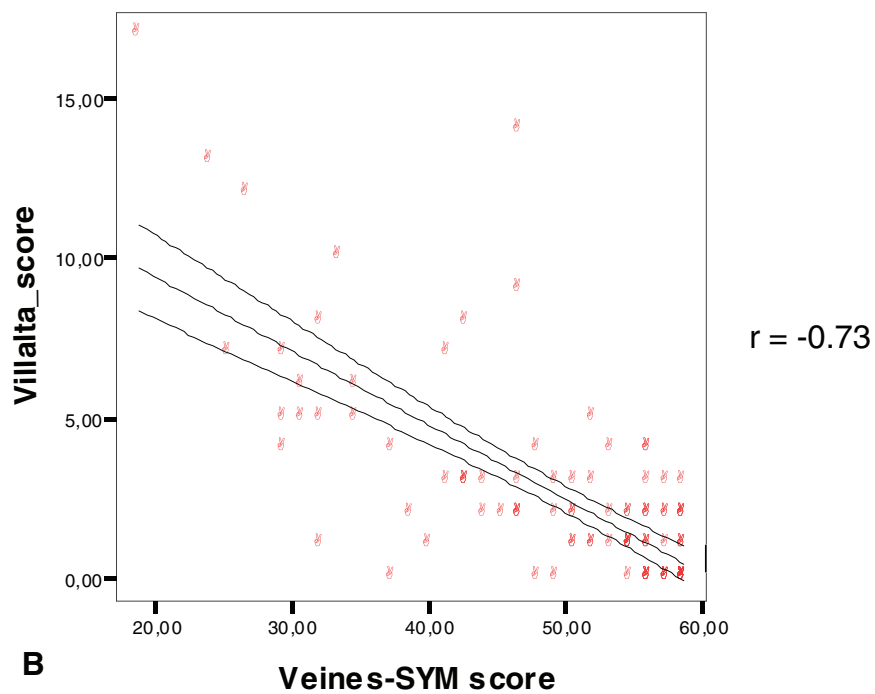
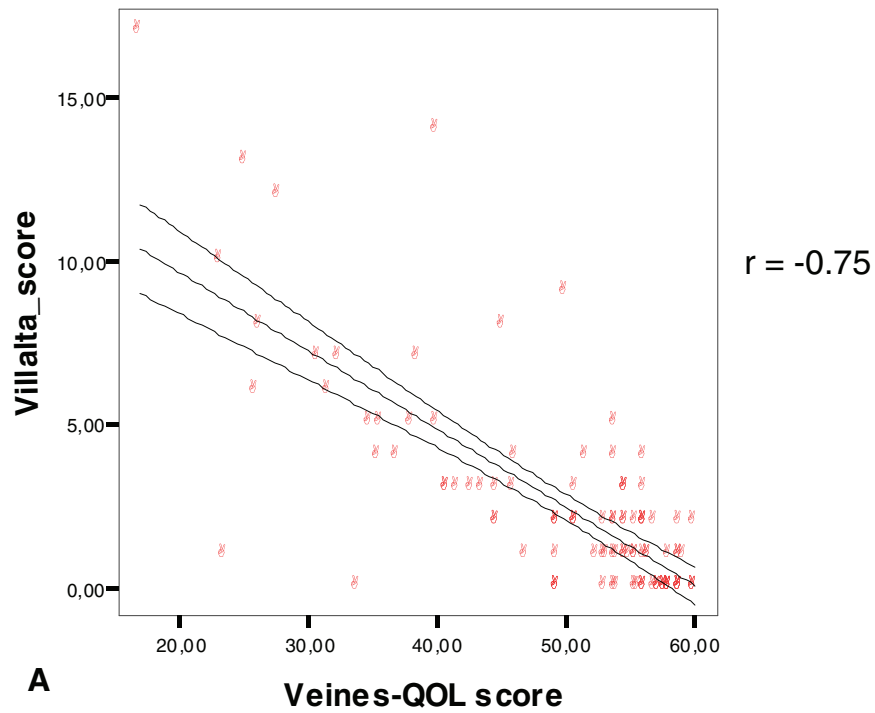
MCS, Mental Component Summary score; PCS, Physical Component Summary score; SF-36, Short-Form 36; Sym, symptom; VEINES, Venous Insufficiency Epidemiological and Economic Study.

<sup>a</sup>Higher scores indicate better outcome. Scores are shown as mean ± standard deviation.

<sup>b</sup>Analysis of variance controlling for follow-up time and age at thrombolysis.

As demonstrated by Kahn et al,<sup>9</sup> we also found an association between PTS and disease-specific QOL as measured by the VEINES QOL/Sym questionnaire. However, we also found an association between PTS and generic QOL, but this was not found by generic QOL measures in the study by Kahn et al.<sup>9</sup> A possible explanation may be that the study populations had differences in thrombus location and differences in follow-up time.

In a recent study by Grewal et al,<sup>23</sup> patients treated with CDT or pharmacomechanical procedures were divided in two groups according to their degree of clot lysis (above and below 50% lysis). The SF-36 mean PCS was significantly higher in patients with >50% lysis compared with the



**Fig 2.** Correlation is shown between the Villalta score and scores on the (A) Venous Insufficiency Epidemiological and Economic Study (VEINES)-Quality of Life (QOL) and (B) Symptoms (Sym), questionnaires. The *outer curves* represent 95% confidence limits. A high Villalta score represents worse postthrombotic syndrome; lower VEINES-QOL and VEINES-Sym scores represent worse quality of life.

**Table IV.** Quality of life (QOL) according to reflux or occlusion/chronic changes, or both, vs patent veins without reflux

Assessment <sup>a</sup>	Vein status reflux and/or occlusion/changes (n = 15)	Patent veins without reflux (n = 94)	p <sup>b</sup>
VEINES			
Sym	44.0 ± 13.9	51.0 ± 9.0	.088
QOL	43.5 ± 14.3	51.0 ± 8.8	.044
SF-36			
MCS	53.2 ± 9.7	50.6 ± 12.5	.674
PCS	47.2 ± 10.9	52.4 ± 8.5	.049

MCS, Mental Component Summary score; PCS, Physical Component Summary score; SF-36, Short-Form 36-item health survey; Sym, symptom; VEINES, Venous Insufficiency Epidemiological and Economic Study.

<sup>a</sup>Higher scores indicate better outcome. Scores are shown as mean ± standard deviation.

<sup>b</sup>Analysis of variance controlling for follow-up time and age at thrombolysis.

other group.<sup>23</sup> When compared with the general population in the United States of America, both groups of patients treated with CDT had lower SF-36 scores, though. Nevertheless, improved QOL was linearly correlated with the amount of thrombus resolution.<sup>23</sup>

Because the purpose of CDT is to eliminate thrombus, restore venous patency, and preserve venous valve function, we compared the patients with patent veins and sufficient valves with the group of patients with reflux or chronically occluded or changed veins, or both. This showed higher VEINES-QOL/Sym scores in patients with patent deep veins without reflux; however, this only reached statistical significance for the VEINES-QOL score. The SF-36 PCS scores were also significantly different in these two groups; however, no association was seen between the status of the deep veins and the SF-36 MCS score. These results show that the VEINES-QOL/Sym questionnaire has a better sensitivity in capturing these vein-specific differences than the SF-36 questionnaire.

To our knowledge, no other studies have related QOL to vein function (patent veins without reflux). We found positive association between vein status and the disease-specific VEINES questionnaire.

Several studies during the last decades have shown that PTS develops in up to almost half of the patients with DVT treated exclusively with anticoagulation therapy.<sup>1</sup> This represents results from patients with DVT in general and not only those with iliofemoral thrombosis, the latter being a group of patients having the highest risk of PTS. Furthermore, PTS develops within the first 2 years after the thrombotic event, and about 3% of patients develop severe PTS during that period.<sup>1</sup> However, recent studies using CDT or pharmacomechanical thrombolysis have shown that a more aggressive approach in thrombus removal may reduce post-thrombotic morbidity compared with anticoagulation alone.<sup>10,23-26</sup> Our results with a long-term frequency of only 16.5% suggest that CDT is effective in reducing the incidence of PTS.

A previous study showed that the most important factor with regard to prognosis after DVT was the status of the distal deep veins; when patent and competent, the long-term prognosis was good, both with regard to symptoms and the development of skin changes.<sup>27</sup> Furthermore, limbs with PTS have been found to have three times the risk of having combined reflux and obstruction than limbs without PTS.<sup>28</sup> Labropoulos et al<sup>29</sup> recently determined the incidence and signs and symptoms of chronic venous disease and recurrent thrombosis in relation to the location and extent of the initial thrombus. Recurrent thrombosis and skin damage was more likely to develop in patients with multiple sites of thrombosis than in patients with thrombosis in a single vein segment. Patients with reflux and obstruction presented more skin damage than those with reflux or obstruction alone.

We only found six patients in the CEAP groups C<sub>4</sub> to C<sub>6</sub> after a median follow-up of almost 6 years, even though all patients had had an iliofemoral venous thrombosis. A recent study evaluating the clinical progression of CEAP classes in patients with DVT treated exclusively with anticoagulation<sup>30</sup> found that skin damage was documented in 4% after 1 year and had increased to 25% of the patients at 5 years. A change in clinical class was seen in 30% of postthrombotic limbs from years 1 to 5, and the most important predictor of progression was ipsilateral recurrent thrombosis.<sup>30</sup>

As mentioned, seven study patients were characterized as having mild PTS, a diagnosis exclusively based on symptoms. All of these patients had patent deep veins without reflux. However, it is important to recognize that PTS produces a range of symptoms and signs and that the diagnosis of PTS should be determined from both symptoms and clinical signs.<sup>18</sup>

Our study has some limitations. Although data were prospectively collected, there was no control group of patients with iliofemoral venous thrombosis treated with anticoagulation alone. Because our patients were relatively young and healthy, no comorbid conditions were recorded, nor was body mass index, which has been described to negatively influence outcome. Because patients were seen as part of a yearly routine investigation and invited to participate in this study, the ultrasound investigations were not blinded.

Some patients in the study may have been misclassified because the diagnosis of PTS was derived from symptoms and clinical signs and no single objective test exists to diagnose the condition. However, all patients were assessed using four different validated instruments (SF-36, VEINES, CEAP, and Villalta) and our median follow-up was 71 months (range, 15-124 months).

The small number of patients with PTS is a limitation, and even though we controlled the analysis for potential confounding from age and follow-up time, other nonmeasured confounding might have played a role.

Another limitation of our study might be that our Danish version of the VEINES questionnaire has not been psychometrically validated. However, we performed the

accepted forward-backward translation methodology and found a strong and significant correlation between PTS and VEINES-QOL/Sym, respectively.

One experienced ultrasound investigator performed all ultrasound examinations, which might be a limitation. However, in case of any doubt about the findings, patients were scanned again by another experienced investigator.

Because we included all consecutive patients in this study, we also included eight patients with atresia of the inferior vena cava treated with CDT. The results concerning reflux and patency in these patients did not differ from the main group.<sup>31</sup>

## CONCLUSIONS

This study emphasizes that CDT of iliofemoral venous thrombosis is effective in preserving venous patency and venous valve function and that patients with patent deep veins and sufficient valves have higher QOL scores than patients with reflux and occluded veins. Furthermore, although the incidence was low, PTS was associated with worse QOL in patients with iliofemoral venous thrombosis treated with CDT.

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## AUTHOR CONTRIBUTIONS

Conception and design: RB, HS, MD, NB

Analysis and interpretation: RB, MD, LJ

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Final approval of the article: RB, HS, MD, MJ, SJ, LJ, NB

Statistical analysis: RB, MD, LJ

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