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# THE CLINICAL COURSE OF DEEP-VEIN THROMBOSIS. PROSPECTIVE LONG-TERM FOLLOW-UP OF 528 SYMPTOMATIC PATIENTS

PAOLO PRANDONI, SABINA VILLALTA, PAOLA BAGATELLA, LAURA ROSSI, ANTONIO MARCHIORI, ANDREA PICCIOLI, ENRICO BERNARDI, BRUNO GIROLAMI, PAOLO SIMIONI, ANTONIO GIROLAMI
*Institute of Medical Semeiotics, University Hospital of Padua, Italy*

**ABSTRACT**

**Background and Objective.** In contrast to the extensive documentation on the short-term outcome of patients with acute deep vein thrombosis (DVT) of the lower extremities, little is known about the long-term clinical course of this disease. To determine the clinical course of patients with a first episode of symptomatic DVTn over an 8-year follow-up period. The primary aims were to assess the long-term incidence of recurrent venous thromboembolism and that of the post-thrombotic syndrome. In addition, we determined mortality and evaluated potential risk factors for all these outcomes.

**Methods.** This was designed as a prospective cohort follow-up study. Consecutive symptomatic outpatients with a first episode of venography proven DVT were treated with an initial course of full-dose (low molecular weight) heparin, followed by at least three months of oral anticoagulants. After discharge, they were instructed to wear compression elastic stockings for at least two years. Follow-up assessments were scheduled at three and six months, and then every six months up to eight years. Diagnosis of recurrent venous thromboembolism was made according to standard criteria. The presence of post-thrombotic syndrome was evaluated using a standardized scale.

**Results.** A total of 528 consecutive patients with a first episode of venography confirmed DVT were included in the study. The cumulative incidence of recurrent venous thromboembolism after two, five and eight years was 17.2, 24.3 and 29.7%, respectively. Malignancy and impaired coagulation inhibition increased the risk of recurrent venous thromboembolism (RR=1.48 and 2.0, respectively). In contrast, surgery and recent trauma or fracture were associated with a diminished risk of recurrent venous thromboembolism (RR=0.65 and 0.39, respectively). The cumulative incidence of post-thrombotic syndrome after two, five and eight years was 24.5, 29.6 and 29.8%, respectively. The development of ipsilateral recurrent DVT was strongly associated with the risk for post-thrombotic syndrome (risk ratio, 2.4). Survival after eight years was 69%. The presence of malignancy increased the risk of death remarkably (risk ratio, 7.1).

**Interpretation and Conclusions.** Symptomatic DVT carries a high risk for recurrent venous thromboembolism that persists for many years, especially in patients without transient risk factors for DVT. The post-thrombotic syndrome occurs in almost one-third of patients and is strongly related to recurrent ipsilateral DVT. Our findings challenge the widely adopted short course of anticoagulation in patients with symptomatic DVT.


*Key words: deep vein thrombosis, treatment*

Deep vein thrombosis (DVT) of the lower extremity is a serious disorder, with an estimated incidence of 1 per 1000 per year.[1-3] The disease can occur after surgical procedures and trauma, in the presence of malignancy or inherited coagulation disorders, but also without any apparent etiologic moment.[3] Patients with DVT are usually treated with an initial course (5 to 10 days) of (low molecular weight) heparin followed by 3 to 6 months of oral anticoagulant therapy. This treatment regimen reduces the risk of short-term thromboembolic complications to approximately 5%.[4-8] The long-term clinical course of DVT may be complicated by pulmonary embolism, recurrent episodes of DVT and the development of serious post-thrombotic sequelae.[9] The purpose of the current investigation was to assess the long-term clinical course of a first episode of symptomatic DVT in a large series of consecutive patients who were followed up for a long time. The investigation incorporates and extends the findings of a smaller cohort recently published.[9]

*Correspondence: Dr. Paolo Prandoni, Istituto di Semeiotica Medica, via Ospedale Civile 105, 35128 Padova, Italy. Tel. international + 39.49.8212656. Fax. international +39.49.657391.*

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## Methods

### Study design

This was a prospective cohort follow-up study to determine the clinical course of patients with a first episode of documented symptomatic DVT of the lower extremities. The primary aims were to assess the long-term incidence of recurrent venous thromboembolism and that of the post-thrombotic syndrome. In addition, we determined mortality and evaluated potential risk factors for all these outcomes.

### Identification of inception cohort

The Department of Internal Medicine of the University of Padua (Italy) serves as a primary care referral center for patients with clinically suspected venous thromboembolism for a community of approximately 500,000 people. All consecutive outpatients with a first episode of clinically suspected DVT who were referred to us by their general practitioners underwent noninvasive testing.[10-13] Patients were potentially eligible for the study if confirmatory venography showed DVT. Patients were excluded from the study if they were referred because of recurrent venous thrombosis, were geographically inaccessible for follow-up, or if they refused to give informed consent.

### Baseline assessment

At the time of referral demographic details were recorded and a history was taken, including the period between onset of symptoms and presentation to the Thrombosis Service (patient-doctor delay), the presence of risk factors for thrombosis (i.e. malignancy, surgery, trauma or fracture, immobilization for more than seven days, pregnancy or childbirth and estrogen use) and symptoms of pulmonary embolism. In addition, information was obtained with regard to venous thromboembolism in first degree relatives. Subsequently, determinations of antithrombin III, protein C and S and lupus-like anticoagulants were carried out. Assays were performed and criteria for abnormality and deficiency were used as reported previously.[14-16]

The venograms obtained at baseline were subdivided into those representing proximal vein thrombosis (with or without concurrent calf vein thrombosis) and those indicating isolated calf vein thrombosis. Proximal vein thrombosis was defined as thrombosis above the trifurcation of the calf veins that involved at least the popliteal vein, the superficial femoral, common femoral or iliac veins. Furthermore, the location of proximal thrombi and their occlusiveness were determined. A patient was considered to have non occlusive DVT if contrast material was seen between the thrombus and the vessel wall along the entire thrombus.[17,18]

**Table 1. Standardized scale for the assessment of post-thrombotic syndrome.**

| *Subjective symptoms* | *Objective signs** |
|---|---|
| Heaviness | Pretibial edema |
| Pain | Induration of the skin |
| Cramps | Hyperpigmentation |
| Pruritus | New venous ectasia |
| Paresthesia | Redness<br>Pain during calf compression |
| *Definition of post-thrombotic syndrome* | |
| Absent | Score < 5 |
| Mild to moderate | Score 5 to 14 in two consecutive check-ups |
| Severe | Score ≥ 15 in two consecutive check-ups or ulceration in 1 occasion |

**Assign each sign and symptom a score between 0 (absent) and 3 (severe).*

### Treatment

Patients were admitted to the hospital and treated with an initial course of adjusted high-dose intravenous standard heparin or low molecular weight heparin.[7] Oral anticoagulants (OAC, coumarin) were started during the first week of treatment and continued for a period of at least 3 months. The dose of oral anticoagulant therapy was adjusted daily to maintain the international normalized ratio (INR) between 2.0 and 3.0. Treatment with (low molecular weight) heparin was discontinued on day 10 or later if the INR was less than 2.0.[7] Actual type and duration of treatments were recorded. Reasons for deviating from this treatment strategy included the presence of small isolated calf vein thrombosis (OAC alone), contraindications to anticoagulant treatment (no treatment or inferior caval vein filter), refusal of the patient to be hospitalized (low dose heparin and OAC), threatened viability of the leg (thrombolytic therapy). All patients were instructed to wear graduated elastic compression stockings (40 mmHg at the ankle) for at least two years.

### Follow-up

All patients were seen at three and six months afetr the initial referral and subsequently returned to the study center every six months for follow-up assessments. Patients were asked to return immediately to the Thrombosis Center if they developed symptoms indicative of recurrent venous thromboembolism. Follow-up was continued for a period of up to eight years. To avoid diagnostic suspicion bias, the medical history concerning general health, symptoms of recurrent venous thromboembolism and post-thrombotic syndrome were obtained with a standardized form. Patients who were not able to attend the follow-up sessions were examined at home. The date and cause of death were documented for all patients who died during follow-up.

### Diagnosis of (recurrent) venous thromboembolism and hemorrhage

Contrast venography of the symptomatic leg(s) was performed as described previously.[19,20] The criteria for DVT were a constant intraluminal filling defect confirmed in at least two different projections or non visualization of a vein or a segment thereof, despite adequate technique and repeated injections with contrast material. The presence or absence of venous thrombosis was assessed by a panel of independent observers who were unaware of other clinical features of the patient or prior test results.[10-13] If a patient presented with clinically suspected recurrent leg vein thrombosis, venography was performed. The criterion for recurrent leg vein thrombosis was a new intraluminal filling defect on the venogram.[21,22] If the venogram was not diagnostic, recurrent venous thrombosis was diagnosed on the basis of a positive $^{125}$I-fibrinogen leg scan or results of noninvasive tests that had changed from normal to abnormal.[21-24] Patients with suspected pulmonary embolism underwent venography if they presented concurrent leg symptoms, or perfusion lung scanning in the absence of leg symptoms. Pulmonary embolism was excluded if the perfusion scan was normal. Since ventilation lung scanning was not available during the first few years of the study and pulmonary angiography could not be performed routinely, we were unable to make a definitive diagnosis of pulmonary embolism in some patients. If a definitive diagnosis could not be made, patients were classified as not having recurrent venous thromboembolism. Perfusion lung scanning and pulmonary angiography were performed and interpreted according to standard procedures.[25,26] Hemorrhagic episodes were classified as major or minor as reported previously.[4-8,27] The documentation for all patients suspected of a recurrent venous thromboembolic or bleeding event was reviewed by a three-member adjudication committee that was unaware of other clinical details of the patient.

### Criteria for the post-thrombotic syndrome

Assessment of post-thrombotic syndrome was performed by

investigators who were unaware of previous post-thrombotic manifestations or other clinical details of the patient. The presence of leg symptoms (pain, cramps, heaviness, pruritus, and paresthesia) and signs (pretibial edema, induration of the skin, hyperpigmentation, new venous ectasia, redness and pain during calf compression) was scored (Table 1). For each item a score of 0 (= none or minimal) to 3 (= severe) was assigned. The presence of a lower limb venous ulcer was recorded. In patients with bilateral thrombosis the higher score was used. A total score of 15 or more on two consecutive check-ups or the presence of a venous ulcer indicated severe post-thrombotic syndrome, and a total score of 5 to 14 on two consecutive check-ups indicated mild post-thrombotic syndrome. This score has been demonstrated to have good reproducibility and correlates well with the patient's perception of the interference of leg complaints with daily life.[28]

*Analysis*

Kaplan Meier estimates and their 95% confidence interval (CI) were calculated for a visual assessment of survival, the risk of recurrent venous thromboembolism, mild and severe post-thrombotic syndrome. Then, using the stepwise Cox's proportional hazards model, the risk ratios for death, recurrent venous thromboembolism, mild and severe post-thrombotic syndrome were calculated for various clinical features. In each case, the duration of oral anticoagulant treatment was used as a time-dependent variable for recurrent venous thromboembolism and death. A recurrent event in the same leg was used as a time-dependent variable for mild and severe post-thrombotic syndrome. The results of these analyses were expressed as risk ratios with their 95% CIs.

## Results

A total of 528 consecutive patients with a first episode of venography confirmed DVT who gave informed consent were included in the study. The demographic and clinical characteristics and prevalence of potential risk factors are presented in Table 2.

*Recurrent venous thromboembolism*

Of the 528 patients, a total of 101 experienced one or more documented recurrent venous thromboembolic events. Of the first recurrences, 47 (46.6%) occurred in the initially involved leg, 33 (32.7%) in the contralateral leg and 21 (20.8%) were pulmonary emboli, which were fatal in 11 (10.9%) patients.

The cumulative incidence of recurrent venous thromboembolism after three and six months was 5.6 and 9.5%, respectively. This incidence gradually increased to 17.2% after two years, 24.3% after five years, and 29.7% after eight years of follow-up (Figure 1). Of the potential risk factors and clinical characteristics evaluated, malignancy and impaired coagulation inhibition increased the risk of recurrent venous thromboembolism (RR=1.48 and 2.0, respectively). In contrast, surgery and recent trauma or fracture were associated with a diminished risk of recurrent venous thromboembolism (RR=0.65 and 0.39, respectively).

*Post-thrombotic syndrome*

Of the 528 patients, a total of 119 developed post-thrombotic syndrome. Of these, 28 (23.5%) presented severe post-thrombotic manifestations.

**Table 2. Demographic and clinical characteristics of the study population (n=528).**

| | |
|---|---|
| *Age (yrs) (median, 5 to 95% percentile)* | 63 (29 to 83) |
| *Sex (M/F)* | 294/234 |
| *Patient-doctor delay (days)(median, 5 to 95% percentile)* | 7 (1 to30) |
| *Side of DVT (Left/Right/Bilateral)* | 208/130/17 |
| *Extent of DVT* | |
| Isolated calf | 34 (6.4%) |
| Calf and popliteal vein | 47 (8.9%) |
| Calf, popliteal and femoral | 183 (34.6%) |
| All proximal veins | 217 (41.1%) |
| Femoral and/or iliac | 47 (8.9%) |
| *Occlusive thrombi* | 432 (81.8%) |
| *Concomitant suspected pulmonary embolism* | 78 (14.7%) |
| *Potential risk factors for DVT* | |
| Malignancy | 100 (18.9%) |
| Surgery < 3 months ago | 101 (19.1%) |
| Trauma or fracture | 92 (17.4%) |
| Positive family history for deep vein thrombosis | 116 (21.9%) |
| Impaired coagulation inhibition | 69* (13.1%) |
| Immobilization > 7 days | 77 (14.6%) |
| Varicosities | 128 (24.2%) |
| Smoking | 184 (34.8%) |
| Obesity | 58 (11.0%) |
| High dose estrogens | 11 (2.1%) |
| Pregnancy or childbirth | 10/234° (4.3%) |
| Contraceptives | 26/234° (11.1%) |
| *Treatment* | |
| Adjusted-dose heparin + OAC | 353 (66.8%) |
| Low molecular weight heparin + OAC | 128 (24.2%) |
| Low-dose heparin + OAC | 19 (3.6%) |
| OAC alone | 16 (3.0%) |
| Thrombolytic therapy | 7 (1.3%) |
| Caval vein filter | 6 (1.1%) |
| None | 3 (0.6%) |

**protein S deficiency=19; antithrombin III deficiency=15; protein C deficiency=15; lupus-like anticoagulants=20.*
*°Proportion calculated for females only. OAC= oral anticoagulants.*

The cumulative incidence of post-thrombotic syndrome was 18.0% after one year, and 24.5% after two years of follow-up. The cumulative incidence increased gradually up to 29.6% after five years. Thereafter it did not change substantially (29.8% at eight years) (Figure 2). Considering only severe post-thrombotic manifestations, a different pattern is seen in the first five years of follow-up, since the cumulative incidence increased gradually from 2.7% after one year to 8.1% after five years. Thereafter the cumulative incidence of severe post-thrombotic manifestations did not increase (Figure 2).

The development of ipsilateral recurrent DVT was associated with a strong increase in risk for post-thrombotic syndrome (RR=2.4). There were no significant associations between the occurrence of post-thrombotic syndrome and the presence of thrombi in the popliteal vein (RR=1.2), occlusive thrombi (RR=0.8), or the extent of thrombosis

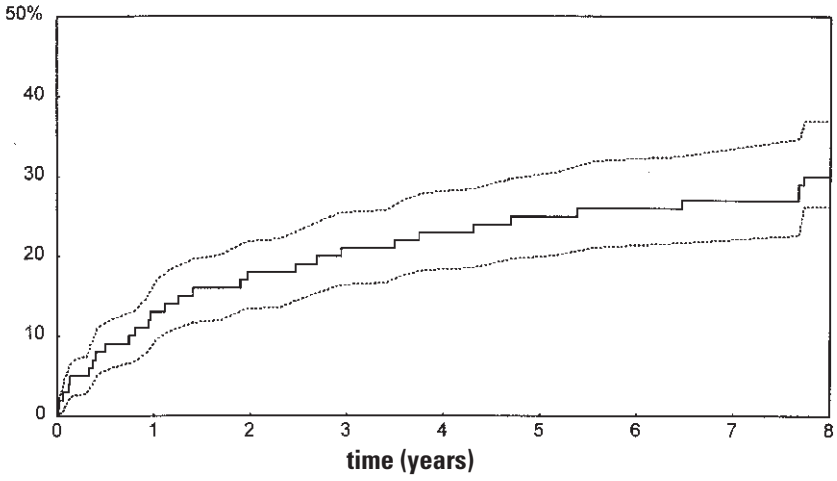


**Figure 1. Cumulative incidence of recurrent venous thromboembolism after the first episode of symptomatic DVT**

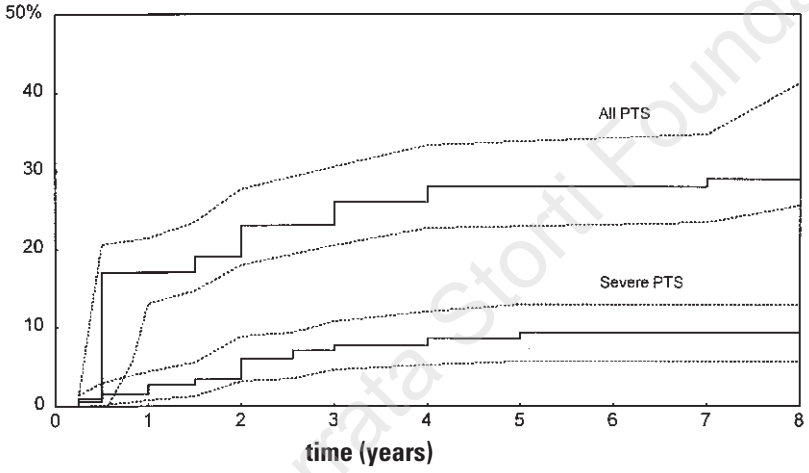


**Figure 2. Cumulative incidence of post-thrombotic syndrome (PTS), separated for all PTS and severe PTS, after the first episode of symptomatic DVT**

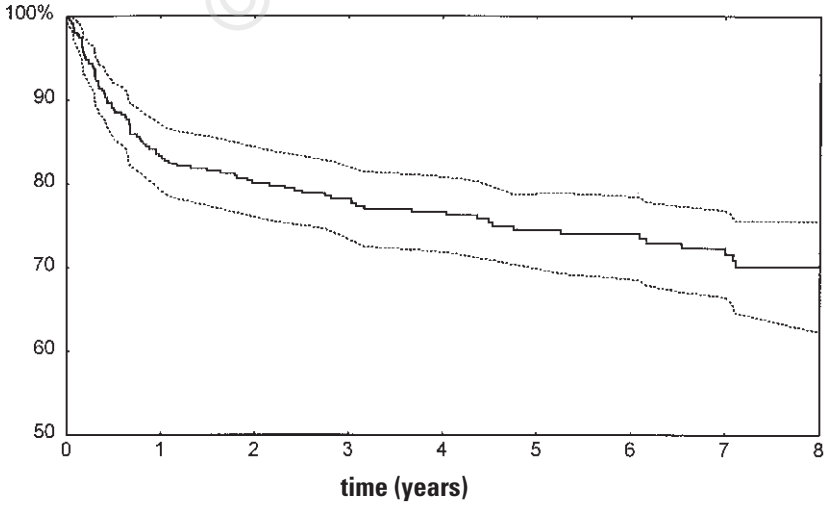


**Figure 3. Proportion of patients surviving after the first episode of symptomatic DVT**

(RR=1.1). If ipsilateral recurrent DVT was included in the analysis, then none of the other clinical features showed a significant association with the risk of post-thrombotic syndrome.

*Other clinical events*

Sixty-one patients developed a hemorrhagic complication, which was major in 28 of them (fatal in six).

Malignant disease became apparent during follow-up in 29 of the 428 patients without a malignancy at baseline. This occurred mainly in patients with an unexplained DVT at baseline, as reported previously.[29]

Sixteen patients developed an ischemic stroke during follow-up, which was fatal in 8 of them.

*Mortality*

Of the 528 patients, 130 died during follow-up. The causes of death included malignancy (n=78), pulmonary embolism (n=12), acute myocardial infarction or heart failure (n=10), ischemic stroke (n=8), anticoagulant related hemorrhage (n=6), miscellaneous (n=6), while in 10 patients who died suddenly a definite diagnosis could not be made.

Survival was 83.3% after one year and 79.9% after two years of follow-up. After five and eight years the survival was 73.5 and 69.3%, respectively (Figure 3). The presence of malignancy increased the risk of death remarkably (RR=7.1). Other clinical features showed no associations with mortality.

## *Discussion*

In contrast to the extensive documentation on the short-term outcome of patients with acute DVT of the lower extremities, little is known about the long-term clinical course of this disease.[9] Our study assessed the incidence of complications after a first episode of documented DVT in a large cohort of consecutive patients during long-term follow-up. The results of this investigations on the long-term follow-up of 528 symptomatic patients confirm those from a smaller cohort of 355 patients recently published.[9] A surprisingly high risk of recurrent venous thromboembolic disease that persisted after the treatment period was found and resulted in a cumulative incidence of these complications of about 30% after eight years of follow-up. It is noteworthy that one of every five recurrent episodes was a pulmonary embolism (which was fatal more than half the time), and that more than 30% of the recurrent leg vein thromboses were in the previously asymptomatic leg. Patients with underlying malignancy or defects that impaired coagulation inhibition were at a statistically significant higher risk for recurrences than patients without these features. As expected, a considerable number of patients in our cohort developed DVT following surgery or trauma. Our finding that these patients were at a significantly lower risk for recurrent venous thromboembolism indicates that these conditions are transient risk factors for DVT.

Post-thrombotic syndrome occurred in approximately 30% of patients. However, the cumulative incidence of severe post-thrombotic manifestations after eight years of follow-up was less than 10%. This is in contrast with the results of small studies, in which post-thrombotic sequelae were observed in 60 to 90% of patients.[30-37] However, the systematic use of elastic compression stockings in our study could have contributed to this relatively low incidence, as suggested by a recent controlled trial.[38]

In more than 80% of patients, post-thrombotic syndrome manifestations became apparent within the first two years following the acute thrombosis. These findings, which challenge the general view that such manifestations require a long time to appear,[37] suggest that the duration of follow-up in our patients might be adequate to give a valid estimate of the overall incidence of post-thrombotic syndrome.

Although we expected that the extent of the initial DVT and its degree of occlusiveness would be related with the risk of developing post-thrombotic syndrome,[3,37,39] we could not demonstrate such a relationship. However, patients with recurrent ipsilateral DVT showed a highly significant increased risk for developing post-thrombotic syndrome. Mortality was high (30% after 8 years) and occurred mainly during the first year in patients with underlying malignancy. These data are fully consistent with the results of a similar study among patients suffering from pulmonary embolism, and suggest that venous thromboembolism is a strong predictor of death in patients with cancer.[40]

We believe that our observations reflect the true clinical course of symptomatic DVT. Diagnosis of DVT was made in all patients by contrast venography, the reference standard.[21] The demographic and clinical characteristics of our patients are comparable to those in other large series of patients with symptomatic DVT.[4-8,15,23,24,27,38] Patients were treated according to standard practice. Furthermore, follow-up was carried out prospectively and there were few patients lost during it. Finally, predefined criteria were strictly applied to diagnose recurrent venous thromboembolism[21-24] and a validated scale was used to assess post-thrombotic syndrome.[28]

What do our findings imply for the management of patients with DVT? The high incidence of recurrent venous thromboembolism after cessation of anticoagulant therapy suggests that prolongation of this treatment could be considered in selected patients, depending on the presence of risk factors for recurrent venous thromboembolism.[41] However, the recommendation to use prolonged anticoagulation therapy in these patients can only be based on

the results of a large trial addressing the reduction of venous thromboembolism relative to the increased risk of warfarin-related bleeding. Since recurrent venous thrombosis strongly predicted the development of post-thrombotic syndrome, the prevention of recurrent DVT might be the key to lowering its incidence.

We conclude that DVT carries a high risk for recurrent venous thromboembolism which persists for many years, especially in patients without transient risk factors for DVT. Post-thrombotic syndrome occurs in almost one-third of patients and is strongly related to recurrent ipsilateral DVT. Our findings challenge the widely adopted short course of anticoagulation in patients with symptomatic DVT.

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