Risk Factors of Recurrent Venous Thromboembolism: The Role of Residual Vein Thrombosis

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Key Words
Venous thrombosis · Thrombophilia · Compression ultrasonography

Abstract
In 313 consecutive symptomatic outpatients with proximal deep vein thrombosis (DVT) who had a conventional anticoagulation, an ultrasound assessment of the common femoral and the popliteal vein was performed three months after the acute episode, and then at 6, 12, 24, and 36 months. Veins were considered as recanalized in case of a vein diameter < 2.0 mm in a single determination, or < 3.0 mm in two consecutive determinations. Of the 58 patients who experienced recurrent episodes, 41 occurred while the patient still had residual thrombosis. The hazard ratio of recurrent thromboembolism was 2.4 (95% CI, 1.3 to 4.4; p = 0.004) for persistent residual thrombosis versus early vein recanalization. In conclusion, residual venous thrombosis should be regarded as an important risk factor of recurrent thromboembolism.

Introduction
In contrast with the extensive documentation on the short-term outcome of deep vein thrombosis (DVT) of the lower extremities [1,2], few studies are available that have addressed the risk of late recurrent venous thromboembolic complications. These studies suggest that this risk persists for years and is related to patient's characteristics at the time of presentation.

The absolute incidence of recurrent venous thromboembolism decreases over years [3,5]. Likewise residual thrombus mass decreases over time in patients with proximal vein thrombosis [6,7]. To estimate whether the risk of recurrent venous thromboembolism is higher in patients with than in those without residual thrombosis, repeat ultrasound was performed in a large number of patients with proximal-vein thrombosis who were followed prospectively for up to six years [8].

Patients and Methods
All consecutive outpatients who referred to the Department of Medical and Surgical Sciences of the University of Padua between 1993 and 1996 with the clinical suspicion of the first episode of DVT were eligible for this investigation, provided that they had a proximal-vein
thrombosis as shown by compression ultrasound. Patients who completed the initial 3-month treatment without experiencing a recurrent thrombotic episode were recruited.

On the basis of laboratory results and clinical characteristics, recruited patients were divided in three categories (i.e., thrombophilia, secondary DVT or idiopathic DVT). Patients without thrombophilia were further classified as having an idiopathic DVT or a DVT episode secondary to transient risk factors based on a standardized clinical data collection form completed at referral.

All patients underwent the first ultrasound assessment three months after the initial event. Subsequently, the test was scheduled 6, 12, 24 and 36 months after the initial event only for patients with residual thrombosis. Only the common femoral vein at the sapheno-femoral junction and the popliteal vein in the mid-popliteal fossa were scanned for the presence of residual vein thrombosis. Vein compression was performed in the transverse plane. The vein diameter was measured during maximal compression and expressed in millimeters. Veins were considered as recanalized in case of a vein diameter < 2.0 millimeters in a single determination or in case of a diameter < 3.0 millimeters in two consecutive determinations.

All recruited patients were instructed to interrupt oral anticoagulant therapy at the time of inclusion into the current investigation. They were followed-up to document the incidence of symptomatic recurrent DVT or pulmonary embolism. The diagnosis of recurrent thromboembolism was done according to standardized procedures (9,10).

**Results**

Three hundred thirteen patients agreed to participate in the current investigation, and were enrolled in the study. In 265 patients (85%) a search for thrombophilia was performed, leading to the demonstration of abnormalities in 80 (30.2%). Of the remaining 233 patients, 109 had a thrombotic event that was associated with one or triggering risk factors, and 124 were classified as idiopathic.

The first ultrasound assessment, performed three months after the initial event, showed normalization in 61 (19.5%) patients. The cumulative incidence of normalized ultrasonography was 38.8% at six months, 58.1% at 12 months, 69.3% at 24 months, and 73.8% at 36 months.

Of the 313 patients, 110 presented during follow-up with clinically suspected recurrent venous thromboembolism, which was confirmed in 58 (53%). The cumulative incidence of recurrent venous thromboembolism was 4.2% at six months, 7.4% at 12 months, 12.7% at 24 months, 16.2% at 36 months, and 21.1% at five years.

Of the 58 patients with recurrent events, 29 occurred in the 80 (36.2%) patients who were carriers of a thrombophilic status. Of the remaining 29 events, 20 occurred in the 124 (16.1%) patients with idiopathic DVT, and 9 in the 109 (8.3%) patients with secondary thrombosis. The hazard ratio of recurrent venous thromboembolism was 2.8 (95% CI, 1.5 to 5.0; p = 0.001) for idiopathic thrombosis, and 3.3 (95% CI, 2.0 to 5.5; p = 0.001) for patients with thrombophilia as compared with those with secondary thrombosis.

Of the 58 recurrent episodes, 41 occurred while patients still had residual thrombosis, while the remaining 17 occurred after the ultrasonographic normalization of the affected veins. The hazard ratio of a recurrent event was 2.9 (95% CI, 1.6 to 5.2; p= 0.004) during the time that residual thrombosis was present. Using a multivariate stepwise Cox Proportional Hazards model with persistent residual thrombosis as a time-dependent variable, the hazard ratio of a recurrent event was 2.4 (95% CI, 1.3 to 4.4; p= 0.004) for residual thrombosis, while it was 2.5 (95% CI, 1.4 to 4.4; p=0.003) for idiopathic thrombosis, and 3.1 (95% CI, 1.8 to 5.2; p<0.001) for thrombophilia versus secondary thrombosis.

**Discussion**

The results of our study confirm that the lack of an identifiable etiology and the presence of thrombophilic conditions in patients at their first episode of symptomatic proximal-vein thrombosis are both associated with an increased risk of recurrent venous thromboembolism [1-5]. In addition, they strongly suggest that the risk of recurrence in patients with residual vein thrombosis, as shown by repeat ultrasonography, is considerably higher than that observed in patients with early vein recanalization. Therefore, the persistence of residual vein thrombosis should be regarded as a powerful and independent risk factor for recurrent thromboembolism. In this respect, ultrasound testing performed at fixed intervals to monitor for thrombus evolution may help individually tailor the duration of anticoagulant therapy.

In conclusion, the results of this investigation suggest that patients with proximal-vein thrombosis whose veins do not recanalize are likely to develop recurrent thrombotic events following interruption of oral anticoagulant therapy. These conclusions apply to all categories of investigated patients, i.e., patients with idiopathic venous thrombosis, patients with thrombosis secondary to transient risk factors, and carriers of thrombophilic abnormalities. Assessing the thrombotic burden, therefore, opens new perspectives for the management of patients with venous thrombosis based on individual basis rather than broad guidelines alone.
References