

## Thrombophilia as a predictor of persistent residual vein thrombosis

**To compare the probability of leg vein recanalization between carriers and non-carriers of thrombophilia after an episode of deep vein thrombosis (DVT) of the lower extremities, we reviewed the clinical records of 472 patients with proximal DVT who were diagnosed with thrombophilia, and had long-term ultrasound scanning. One hundred and thirty-seven patients (29.0%) were carriers of thrombophilia. After adjusting for age, sex, DVT localization and modality of presentation, the hazard ratio of vein recanalization in thrombophilic compared with non-thrombophilic patients was 0.49 (95% CI, 0.38 to 0.63). These findings suggest that thrombophilia is an independent predictor of persistent residual vein thrombosis.**

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The persistence of residual thrombosis, as shown by repeat ultrasonography over time, is a predictor of recurrent venous thromboembolism (VTE) in patients with deep vein thrombosis (DVT) of the legs.<sup>1-3</sup> As persistent residual thrombosis predicts not only recurrent ipsilateral DVT, but also thrombotic events occurring in the initially non-affected leg and primary pulmonary embolism, this feature is generally considered a marker of hypercoagulability.<sup>1-3</sup> Since several thrombophilic abnormalities have been reported, though not consistently, to increase the risk of recurrent VTE,<sup>4,5</sup> we hypothesized that in carriers of thrombophilia the thrombotic mass would persist for a longer time than in non-carriers.

To compare the rate of leg vein recanalization between carriers and non-carriers of thrombophilia, we reviewed the clinical charts of 472 patients, who were admitted to our department for an episode of proximal DVT, were diagnosed with thrombophilia (antithrombin, protein C and S defects, lupus-like anticoagulants, factor V Leiden and prothrombin gene mutation), and had long-term follow-up scanning. All patients were treated with unfractionated or low-molecular-weight heparin followed by at least three months of warfarin therapy, targeted to achieve an International Normalized Ratio (INR) between 2.0 and 3.0.

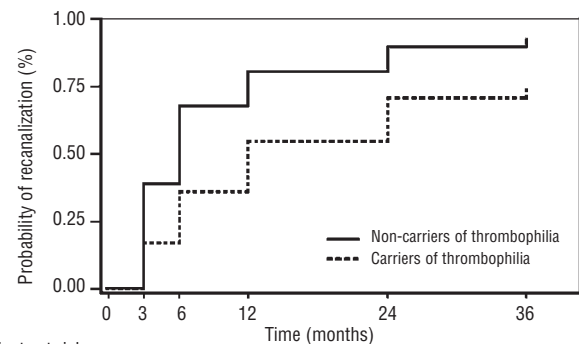
The first ultrasound assessment was performed at three months after the thrombotic episode. In patients with residual thrombosis, the test was repeated at six months, and then every six months up to the achievement of vein recanalization (maximum follow-up, three years). Veins were considered to be recanalized when vein diameter was < 2.0 mm in a single test, or < 3.0 mm in two consecutive tests.<sup>1</sup>

Kaplan-Meier estimates and their 95% confidence intervals (CI) were calculated to assess the cumulative probability of leg vein normalization in thrombophilic and non-thrombophilic patients. Time-dependent multivariate Cox proportional hazard ratio (HR) for vein recanalization was calculated in patients with and without thrombophilia after adjustment for age, sex, localization of DVT (popliteal only, common femoral vein only, or both) and modality of clinical presentation (idiopathic versus secondary to risk factors of thrombosis). Duration of oral anticoagulation treatment was used as a time-dependent covariate. Time spent in the targeted therapeutic

Table 1. Patients' demographic and clinical characteristics.

	With thrombophilia (n = 137)	Without thrombophilia (n = 335)
Age (median, range)	50 (11-86)	66 (18-91)
Male sex	70 (51.1)	153 (45.7)
Type of thrombophilia		
factor V Leiden	56 (40.9)	---
lupus-like anticoagulants	22 (16.1)	---
antithrombin defect	16 (11.7)	---
protein C defect	15 (10.9)	---
protein S defect	12 (8.8)	---
prothrombin mutation	11 (8.0)	---
combined abnormalities	5 (3.6)	---
DVT localization		
popliteal	58 (42.3)	160 (47.8)
common femoral	15 (11.0)	46 (13.7)
both	64 (46.7)	129 (38.5)
Symptoms of PE	18 (13.1)	60 (17.9)
Risk factors of DVT		
recent trauma or surgery	40 (29.2)	132 (39.4)
hormonal treatment, pregnancy or puerperium	16 (11.7)	24 (7.2)
medical diseases	4 (2.9)	20 (6.0)
idiopathic	77 (56.2)	159 (47.5)
Duration of anticoagulation		
up to 3 months	43 (31.4)	186 (55.5)
up to 6 months	38 (27.7)	80 (23.9)
longer than 6 months	56 (40.9)	69 (20.6)

Numbers in brackets indicate percentage unless otherwise indicated.



Patients at risk

Carriers	137	111	82	52	28
Non-carriers	335	200	102	58	24

Figure 1. Cumulative probability of vein recanalization in carriers and non-carriers of thrombophilia

range and beneath the lower limit of the therapeutic range was calculated using linear interpolation.

Table 1 shows the types of thrombophilia, and the main demographic and clinical characteristics of carriers and non-carriers of thrombophilia in the study group. Overall, in both patients' groups, approximately 60% of time was spent in the therapeutic range, and 33% was spent beneath this range.

The cumulative probability of normalized ultrasonography in carriers of thrombophilia was 0.17 (95% CI, 0.10 to 0.23) after three months, 0.37 after six months (0.29 to 0.45), 0.55 (0.47 to 0.64) after 12 months, 0.71 after 24 months (0.63 to 0.79), and 0.74 (0.66 to 0.82)

after 36 months. The corresponding figures in non-carriers were 0.39 (95% CI, 0.34 to 0.44) after 3 months, 0.68 (0.63 to 0.73) after 6 months, 0.81 (0.77 to 0.86) after 12 months, 0.90 (0.87 to 0.93) after 24 months, and 0.93 (0.91 to 0.96) after 36 months (Figure 1). The adjusted HR of vein recanalization in thrombophilic as compared to non-thrombophilic patients was 0.49 (95% CI, 0.38 to 0.63). The longer persistence of the thrombotic mass was consistently seen across all types of thrombophilia (*data not shown*).

These findings suggest that in carriers of thrombophilia who develop an episode of proximal DVT the thrombotic mass persists for a longer time period than in non-carriers. These findings could explain the higher risk for recurrent VTE seen in carriers rather than non-carriers of thrombophilia.<sup>4,5</sup> In addition, they support the view that persistent residual thrombosis is to be considered a marker of hypercoagulability.

This study improves our understanding of the mechanism behind the higher risk of recurrent VTE in carriers rather than non-carriers of thrombophilia, and offers new perspectives for future research. Further studies are needed to clarify the pathophysiology of this feature and to evaluate its clinical implications.

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