# Risk factors for first and recurrent venous thrombosis : new insights from old concepts

Ribeiro, D.D.

*Chapter* 9

# *The influence of prothrombotic laboratory abnormalities on the risk of recurrent venous thrombosis*

Daniel D. Ribeiro
Willem M. Lijfering
Sandhi M. Barreto
Fabiane Dias Lopes
Giselli de Souza Pires
Frits R. Rosendaal
Suely M. Rezende

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Venous thrombosis (VT) is a disease that occurs in approximately 1-2 per 1000 persons per year [1]. Despite an appropriate treatment, up to one quarter of patients with VT will experience a recurrent event within the subsequent 5 years [2]. It has been recognized that the presence of a transient or reversible provoked risk factor at the time of VT is associated with a decreased risk of recurrence after stopping anticoagulant therapy [3]. Therefore, a relatively short period of anticoagulant treatment with vitamin K antagonists is advised for those with clear provoking risk factors for VT, such as oral contraceptive use, hospitalization, or surgery [4]. However, approximately 30%-50% of events occur without association with a provoking risk factor. Since the risk for recurrent VT is higher when the first event is unprovoked, such patients may need indefinite anticoagulant treatment. This approach could, however, lead to major side effects such as severe bleeding [5]. The challenge, therefore, is to identify patient groups who suffered an unprovoked event and still have a low risk of recurrence. These patients might benefit of anticoagulants for a fixed (shorter) time.

Since prothrombotic alterations can be demonstrated in at least 50% of patients with VT [6], testing patients with a first VT has gained great interest. Potential advances of testing patients might be the chance to elucidate the cause of the thrombosis and to track unaffected family members. However, there are also potential disadvantages. Although the presence of prothrombotic alterations is currently considered a weak predictor of recurrence in patients with a first episode of VT, [3,7,8] these results were mostly obtained in patients with either provoked and unprovoked first VT. Whether prothrombotic alterations have a predictive value for recurrence in patients who had a first unprovoked event is less well studied. Furthermore, most studies that were published on this issue [7,9], measured prothrombotic laboratory abnormalities (such as levels of factor VIII or homocysteine) only once, increasing the chance of a false positive (high) value and dilution of risk estimates.

We performed a prospective cohort study to assess the risk of recurrence in patients with provoked and unprovoked first VT, related to the presence or absence of prothrombotic alterations. In addition, these abnormalities were only considered present when they were confirmed in at least two consecutive measurements.

The subjects of the cohort and definitions of the study were described previously [10]. Briefly, subjects were patients with one previous venous thrombotic event followed from April 2000 to July 2011 at the University Hospital of Universidade Federal de Minas Gerais and at Hematológica, a specialized medical center in Hematology, Belo Horizonte, Brazil. All patients were attended by the same clinician (i.e. DDR) Patients were referred from anywhere in the State of Minas Gerais by their doctors who

looked after them during the first episode of VT. There was no control over these referrals. Patients were included consecutively, but certainly they were not consecutive patients with thrombosis in the State. Throughout the study, patients' data were collected using a standardized form with questions related to first and recurrent VT. Venous thrombosis (either first or recurrent) was defined as provoked if it had occurred at or within 3 months after exposure to exogenous risk factors including surgery (with more than 30 minutes of duration), trauma leading to hospitalization, immobilization for more than 3 days (hospitalization for clinical reasons), limb immobilization in a plaster cast for more than 7 days, pregnancy, post-delivery period (2 months), the use of oral contraceptives or hormonal replacement therapy (at the time of thrombosis), presence of autoimmune diseases, or active malignancy. In the absence of these risk factors, venous thrombosis was classified as unprovoked. Despite efforts to follow-up all included patients, 42 patients (10%) were only seen at the time of enrolment. These patients were excluded from the analysis, which resulted in 378 eligible patients. All but 62 patients who had incomplete follow-up (16%) were contacted by phone or had a clinical evaluation at July 1st 2011. The last consultation of the 62 patients with incomplete follow-up was between 09.03.2005 and 30.03.2011 (2 in 2011, 41 in 2010, 7 in 2009, 5 in 2008, 5 in 2007 and 1 in 2005). At that moment they were questioned about recurrent VT and included in the analysis up to this date. Recurrence was considered established if it was demonstrated by objective techniques at another site than the first event, or at the same site if previously repeated tests showed no residual venous thrombosis. If the recurrence of DVT was at the same site and we had not previously repeated tests to analyze if there was residual venous thrombosis, we only considered recurrence when the compressive ultrasound showed new thrombus formation together with clinical symptoms that were absent previously. Only the objectively demonstrated PE was considered a recurrence. If these criteria were not fulfilled, anticoagulant treatment was withheld and the event was not classified as a recurrent venous thrombosis. We had access to all discharge letters. Laboratory test information was available for factor VIII activity, homocysteine, factor V Leiden, (rs6025), prothrombin G20210A (rs1799963) and blood group. We analysed these risk factors individually and grouped. We considered high factor VIII as levels > 150 IU/dL in two occasions after at least three months apart. Similarly a high level of homocysteine (> 20 μmol/L) was only considered when confirmed in a subsequent testing. All eligible patients for this study provided written informed consent, and the study was approved by the local ethical committee. Observation time started after vitamin K antagonists were withdrawn and ended at time of recurrence or at the last consultation. Incidence rates of recurrent thrombotic events were calculated as the number of events over the accumulated observation time in different

groups of patients with specific prothrombotic alterations. The incidence rate ratio was calculated and patients without prothrombotic alterations were considered as the reference group. Incidences and 95% confidence intervals (95% CI) were calculated under the Poisson distribution assumption.

Statistical analyses were performed using SPSS software, version 17.0 (SPSS Inc., Chicago ILL).

The study cohort included 378 patients; 291 (77%) were women, 253 (67%) had a provoked VT, the median age at time of the first event was 36 years, 109 (29%) had a distal VT, 175 (46%) had a proximal VT, 71 (19%) had a PE and 22 (6%) had DVT and PE (these patients were analyzed in the PE group). The total follow-up was 1573 person-years, for a median follow-up of 43 months. Recurrent VT occurred in 35 (9%) patients, for an incidence of 22 per 1000 person-years. The median age at recurrence was 49 years. At a median of 7 months after their initial first event, patients were consulted by one physician (DDR). Only two patients died during the follow up and the causes were not related to VT. In patients with elevated factor VIII, 5 (11%) out of 47 had a second event of VT. Recurrence was also identified in 1 (8%) out of 13 with high levels of homocysteine. The presence of factor V Leiden or prothrombin 20210A mutation were associated with VT recurrence in 2 (5%) out of 37 and 3 (15%) out of 20, respectively. Among the 190 patients with blood group non O 19 (10%) had a second event of VT (Table 1). The broad confidence interval of some groups reflects the small numbers. Despite this, the relative risk estimates are approximately 1 for all comparisons showing no association between VT recurrence risk and prothrombotic laboratory abnormalities (Table 1). A stratified analysis showed no increase in the risk for VT recurrence by sex and for patients with a provoked first event. However, in patients with an unprovoked first event there was a 4-fold increase in the recurrence risk in those with abnormal prothrombotic tests, albeit again with wide confidence intervals.

It has been suggested that the identification of prothrombotic abnormalities could lead to reduced VT recurrence due to changes in clinical management, such as prolongation of initial anticoagulant treatment or intensified prophylaxis during high-risk situations. However, no different recurrence risk was found when tested patients were compared with patients who were not tested [11]. Despite a slightly different study question, the presence of prothrombotic abnormalities did not increase the risk for recurrence in our study, corroborating the findings of Coppens *et al* and others [11]. However, these latter studies did not stratify on type of first event (if provoked or unprovoked). In the present study, we observed that patients with a first unprovoked event and prothrombotic abnormalities had a 4.4-fold increased risk of recurrence. Although numbers were small, and therefore a chance result cannot be ruled out, this finding can be supported by taking the

thrombosis potential model into account [12]. Unprovoked events are those events of which we do not know the underlying cause. However, there may be several reasons why patients with unprovoked thrombosis had their event. If these reasons were in some part transient, such as an infection [13], or a flare of inflammatory bowel disease [14], and in some part chronic (e.g., prothrombotic abnormalities), one would expect the risk of recurrence to be increased in patients with prothrombotic abnormalities. In this case, the thrombosis potential in the latter (chronic causes) is not altered after the first event, but the thrombosis potential in the former group (transient causes) significantly drops after the first event. These patients will have a lower risk for recurrence than those with lasting prothrombotic abnormalities [12].

Our study has limitations including small sample size and the selection of referred patients, as our Hospital is a tertiary care center. Patients were on average nearly 30 years younger than the average age of first VT in the community [15]. In addition, only 0.5% of 378 patients died during follow-up, but as 16% of patients were lost to follow up, it is likely that at least some of these patients died, possibly due to thrombosis. However, because thrombophilia is not associated with a reduced life expectancy in previous studies [16,17], it is not likely that mortality of patients who were lost to follow-up biased our results.

We conclude from our study that thrombophilia testing in all patients with a first VT is neither clinically feasible nor useful. Future studies are required to further elucidate if patients with a first unprovoked event and a negative result for prothrombotic abnormalities are at reduced risk for VT recurrence and could, therefore, benefit from a shorter period of anticoagulant treatment.

# REFERENCE LIST

1. Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrom J. Incidence and mortality of venous thrombosis: a population-based study. J Thromb Haemost 2007; 5(4): 692-9.
2. Prandoni P, Noventa F, Ghirarduzzi A, Pengo V, Bernardi E, Pesavento R et al. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. Haematologica 2007; 92(2): 199-205.
3. Baglin T, Luddington R, Brown K, Baglin C. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. Lancet 2003; 362(9383): 523-6.
4. Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133(6 Suppl): 454S-545S.
5. Veeger NJ, Piersma-Wichers M, Tijssen JG, Hillege HL, van der Meer J. Individual time within target range in patients treated with vitamin K antagonists: main determinant of quality of anticoagulation and predictor of clinical outcome. A retrospective study of 2300 consecutive patients with venous thromboembolism. Br J Haematol 2005; 128(4): 513-9.
6. Bauer KA. The thrombophilias: well-defined risk factors with uncertain therapeutic implications. Ann Intern Med 2001; 135(5): 367-73.
7. Christiansen SC, Cannegieter SC, Koster T, Vandenbroucke JP, Rosendaal FR. Thrombophilia, clinical factors, and recurrent venous thrombotic events. JAMA 2005; 293(19): 2352-61.
8. Ho WK, Hankey GJ, Quinlan DJ, Eikelboom JW. Risk of recurrent venous thromboembolism in patients with common thrombophilia: a systematic review. Arch Intern Med 2006; 166(7): 729-36.
9. Kyrle PA, Eichinger S. The risk of recurrent venous thromboembolism: the Austrian Study on Recurrent Venous Thromboembolism. Wien Klin Wochenschr 2003; 115(13-14): 471-4.
10. Ribeiro DD, Lijfering WM, Barreto SM, Silva IB, Chalup MM, Rosendaal FR, Rezende SM. Past provoking venous thrombosis risk situations on the risk of a recurrent thrombotic event: a cohort study. Thromb Res 2011; 128(3): 227-32.

11. Coppens M, Reijnders JH, Middeldorp S, Doggen CJ, Rosendaal FR. Testing for inherited thrombophilia does not reduce the recurrence of venous thrombosis. J Thromb Haemost 2008; 6(9): 1474-7.

12. Lijfering WM, Rosendaal FR, Cannegieter SC. Risk factors for venous thrombosis - current understanding from an epidemiological point of view. Br J Haematol 2010; 149(6): 824-33.

13. Smeeth L, Cook C, Thomas S, Hall AJ, Hubbard R, Vallance P. Risk of deep vein thrombosis and pulmonary embolism after acute infection in a community setting. Lancet 2006; 367(9516): 1075-9.

14. Grainge MJ, West J, Card TR. Venous thromboembolism during active disease and remission in inflammatory bowel disease: a cohort study. Lancet 2010; 20;375(9715): 657-63.

15. Heit JA, Silverstein MD, Mohr DN, Petterson TM, Lohse CM, O'Fallon WM, Melton LJ, III. The epidemiology of venous thromboembolism in the community. Thromb Haemost 2001; 86(1): 452-63.

16. Heijmans BT, Westendorp RG, Knook DL, Kluft C, Slagboom PE. The risk of mortality and the factor V Leiden mutation in a population-based cohort. Thromb Haemost 1998; 80(4): 607-9.

17. Pabinger I, Vossen CY, Lang J, Conard J, Garcia-Dabrio MC, Miesbach W et al. Mortality and Inherited Thrombophilia: results from the European Prospective Cohort on Thrombophilia (EPCOT). J Thromb Haemost 2011; 10-7836.

Table 1: Risk for venous thrombosis recurrence in subgroups based on laboratory findings

| | Number (%) | Patients with VT recurrence (%) | IR per 100 PY (95% CI) | IRRatio (95% CI) |
|---|---|---|---|---|
| **Thrombophilia** | | | | |
| **Factor VIIIc** | | | | |
| Normal | 298(86) | 27(8) | 1.98 (1.31-2.88) | Reference |
| Elevated (>150%) | 47(14) | 5(1) | 2.82 (0.92-6.59) | 1.4 (0.6-3.7) |
| **Homocysteine** | | | | |
| Normal | 340(96) | 31(9) | 2.03 (1.38-2.88) | Reference |
| Elevated (>20 mMol/L) | 13(4) | 1(0.3) | 2.13 (0.05-11.85) | 1.1 (0.1-7.7) |
| **Factor V Leiden** | | | | |
| Wild type | 329(90) | 31(9) | 2.20 (1.50-3.13) | Reference |
| Heterozygote | 37(10) | 2(0.5) | 1.04 (0.13-3.76) | 0.5 (0.1-2.0) |
| **Protrombin mutation** | | | | |
| Wild type | 337(94) | 29(8) | 1.92 (1.29-2.76) | Reference |
| Heterozygote | 20(6) | 3(0.8) | 4.41 (0.91-12.89) | 2.3 (0.7-7.5) |
| **Blood group** | | | | |
| O | 71(27) | 5(2) | 1.62 (0.53-3.79) | Reference |
| Non-O | 190(73) | 19(8) | 2.27 (1.37-3.55) | 1.4 (0.5-3.7) |
| **All thrombophilia** | | | | |
| No | 52(19) | 3(6) | 1.31 (0.28-4.00) | Reference |
| Any ‡ | 224(81) | 22(10) | 2.27 (1.41-3.42) | 1.6 (0.5-5.5) |

‡ Presence of at least one of the following: high factor VIII or homocysteine, presence of factor V Leiden or prothrombin mutation and blood group non-O

IR denotes, incidence rate; PY, patient years; CI, confidence interval; VT, venous thrombosis

**Table 2. Risk for venous thrombosis recurrence for laboartory thrombophilias in subgroups**

| | IRRatio 95% (CI) | IRRatio 95% (CI) | IRRatio 95% (CI) | IRRatio 95% (CI) | IRRatio 95% (CI) |
|---|---|---|---|---|---|
| | **Overall** | **Unprovoked** | **Provoked** | **Male** | **Female** |
| **Thrombophilia** | | | | | |
| No | Reference | Reference | Reference | Reference | Reference |
| Any ‡ | 1.6 (0.5-5.5) | 4.4 (0.6-33.3) | 0.7 (0.1-3.2) | 1.4 (0.3-6.3) | 1.8 (0.3-14.7) |

‡ Presence of at least one of the following: high levels of factor VIII, elevated homocysteine, presence of factor V Leiden, presence of prothrombin mutation or blood group non-O

IR denotes, incidente rate; CI, confidence interval