

Point

Massimo Franchini*

The utility of thrombophilia testing

Abstract: In the past decades, the recognition of several inherited thrombophilic traits has greatly improved our knowledge of the pathogenesis of venous thromboembolism, explaining about half of all idiopathic cases. As a consequence, thrombophilia testing has enormously increased in the past years for various clinical conditions. In this paper, the current indications of the most commonly tested thrombophilic abnormalities (i.e., Factor V Leiden, prothrombin G20210A mutation, protein C, S and antithrombin deficiencies) are analysed. When used appropriately thrombophilia testing has a positive impact on the health care of the people tested and their relatives.

Keywords: Factor V Leiden; inherited thrombophilia; prothrombin mutation; testing.

*Corresponding author: Massimo Franchini, Department of Transfusion Medicine and Hematology, Carlo Poma Hospital, Mantua, Italy, Phone: +39 0376201234, Fax: +39 0376220144, E-mail: massimo.franchini@aopoma.it

In the past five decades our knowledge on the aetiology of venous thromboembolism (VTE) has dramatically improved [1–3]. Indeed, the recognition of a number of inherited coagulation abnormalities, first the deficiencies of natural anticoagulant proteins C and S and then the gain-of-function mutations Factor V Leiden and prothrombin G20210A [4–8], has allowed the identification of a thrombophilic defect in at least 50% of cases with idiopathic VTE. Accordingly, the number of patients tested for thrombophilia has exponentially increased in the last years, despite the usefulness and cost-effectiveness of testing still remains a matter of debate [9, 10].

Table 1 shows epidemiological data and association with risk of VTE of the most commonly tested thrombophilic defects. Overall, literature data shows that deficiencies of natural anticoagulant proteins are relatively rare (<0.5% in the general population), but are associated with a more severe thrombophilic tendency, with an increased risk of 5–10-fold and annual incidence of VTE >1% [11]. Conversely, Factor V Leiden and prothrombin G20210A polymorphisms are more common abnormalities, with

a prevalence of about 5% in the general population and up to 50% of patients with VTE, especially in studies on familial thrombophilia [12]. However, these mutations are associated with a lower increase of risk (2–5-fold) and incidence of VTE (<0.5% per year). Notably, patients carrying homozygous Factor V Leiden or combined defects show a more severe phenotype, with a 20–50-fold increased risk and an earlier onset of first VTE or recurrence. Interestingly, the different thrombotic risks associated with thrombophilic traits interplay in different manners with concomitant acquired conditions (see below) for development of VTE. Thus, a higher prevalence of unprovoked VTE (55%–60%) is observed in patients with natural anticoagulant deficiencies, who frequently show the first thrombotic event before 45 years of age. Globally, approximately 50% of subjects with antithrombin deficiency will have developed a VTE episode by 50 years of age. Conversely, patients with Factor V Leiden often develop the first VTE episode after 45 years of age, most frequently in association with acquired (triggering) risk factors such as trauma, surgery, pregnancy and oral contraceptives [13]. Among these well-established genetic factors, there is growing evidence that non-O blood group, which is associated with approximately 25% higher plasma von Willebrand factor and factor VIII levels (which are well-known thrombotic risk factors) than those in O blood type individuals, is associated with an approximately two-fold increased risk of VTE [14].

Clinical and epidemiological studies on prevalence of these thrombophilic traits, as well as on their association with development of VTE (Table 1), have led to defining the multifactorial nature of VTE, in which the thrombotic event is the result of multiple gene-gene and/or gene-environment interactions. In keeping with this model, inherited thrombophilia interacts with several other well-established acquired predisposing factors for VTE such as age, malignancy, inflammatory states, antiphospholipid antibodies, surgery, trauma, immobility, pregnancy-puerperium, use of oral contraceptives or hormone replacement therapy, elevated body mass index, severe infections and venous abnormalities. Overall, this model provides a dynamic concept of the thromboembolic risk, encompassing a genetic predisposition (one or more

Table 1 Epidemiological data and association with risk of VTE of the main thrombophilic defects.

Thrombophilia	Prevalence, %		First VTE		Recurrent VTE
	General population	VTE cases	Relative risk	Annual incidence	Relative risk
Antithrombin deficiency	0.02–0.2	1–2	5–8	1–4	0.5
Protein C deficiency	0.2–0.4	2–5	5–8	1–2	2.5
Protein S deficiency	<0.5	1–3	1.7–8	0.7–2	2.5
Factor V Leiden heterozygous	3–7	12–20	4.9–9.7	0.19–0.67	1.3
Factor V Leiden homozygous	0.02	1.5	40–80	–	–
Prothrombin G20210A	1–3	3–8	1.9–3.8	0.13	1.4
Factor V Leiden+prothrombin G20210A	0.01	–	20–58.6	0.57	2.5

VTE, venous thromboembolism.

co-inherited thrombophilic abnormalities) and a variable contribution of environmental factors (possibly modifiable or preventable) during different ages, which may lead to overcome a threshold and trigger the VTE episode [3]. Therefore, inherited thrombophilia should be evaluated in the framework of coexisting risk factors for first or recurrent VTE when assessing the need and modalities of primary or secondary prophylaxis.

Thus, taking into account these considerations, it appears evident that universal population screening for thrombophilia is unjustified and that screening should be performed only in well-selected cases [15]. The current indications for thrombophilia screening include (Table 2): idiopathic thrombosis and/or age <50 years and thrombosis, venous thrombosis in unusual sites (such as hepatic, mesenteric and cerebral veins), recurrent VTE, first VTE and a strong family history of VTE, VTE during pregnancy, postpartum or in women taking oral contraceptives or under hormone replacement therapy, women with unexplained pregnancy loss and asymptomatic adult family members of relatives with documented inherited thrombophilia. Importantly, testing for thrombophilia in

patients during the thrombotic episode is not indicated as many of those laboratory tests are functional and can hence result abnormal as a consequence of the inflammatory state rather than of the inherited defect.

In general, screening for thrombophilia is only reasonable when it may influence the future management of affected patients. However, whether the presence of thrombophilia is able to predict VTE recurrence is still a matter of debate [16]. The estimated risk of recurrence for VTE is approximately 5% per year, although idiopathic cases tend to recur more frequently (approx. 20% in the first 2 years) than unprovoked cases [1]. Several follow-up studies have compared the prevalence of thrombophilia in patients with recurrent VTE with those without recurrence with conflicting results [16]. For instance, two large prospective trials found that carriers of a thrombophilic defect (Factor V Leiden, prothrombin G20210A, protein C, S and antithrombin deficiencies) did not show a highly increased risk of developing a recurrent venous thrombotic event [17, 18]. Two meta-analyses analysed the risks of recurrence in patients with the common thrombophilias, i.e., FVL and prothrombin G20210A mutation. The risk of recurrence was found consistently to be 1.3–1.4-fold higher in patients with FVL and 1.4–1.7-fold higher in patients with the prothrombin mutation [19, 20]. Data on natural anticoagulant deficiencies are less extensive, because only a few studies with a limited number of patients have assessed the risk of VTE recurrence associated with these thrombophilic abnormalities, suggesting limited effects on the risk of recurrent VTE [16]. However, a recent study reported a higher risk of VTE recurrence during follow-up in patients with deficiencies of natural anticoagulants compared with the risk of recurrence in the general VTE population [21]. Inherited thrombophilia has also been implicated in pregnancy complications, such as recurrent miscarriage, foetal death, preeclampsia and intra-uterine

Table 2 Current indications for thrombophilia testing.

- Idiopathic thrombosis and/or age ≤50 years with thrombosis
- Venous thrombosis in unusual sites (hepatic, mesenteric, splenic, portal, cerebral)
- Recurrent VTE
- First VTE and a strong family history of VTE
- VTE during pregnancy, postpartum or in women taking oral contraceptives or under hormone replacement therapy
- Women with unexplained pregnancy loss
- Asymptomatic adult family members of relatives with documented inherited thrombophilia

VTE, venous thromboembolism.

growth retardation, although a causal association is still controversial [22]. Thus, thrombophilia testing appears more useful for the identification of asymptomatic family members of thrombophilic patients. Indeed, identifying a thrombophilic trait in the latter cases is very helpful since these individuals, who have a 2–10-fold increased risk for VTE as compared with non-carriers [1], may benefit from targeted thromboprophylaxis in high-risk situations (e.g., pregnancy, puerperium, surgery, immobilisation and trauma), and the avoidance of acquired risk factors, most notably oral contraceptives.

In conclusion, thrombophilia tests represent an important tool for assessing the subjects' thrombotic risk and their recognition allows physicians to individualise

treatment strategies and preventative measures in selected groups of patients.

Conflict of interest statement

Author's conflict of interest disclosure: The author stated that there are no conflicts of interest regarding the publication of this article.

Research funding: None declared.

Employment or leadership: None declared.

Honorarium: None declared.

Received July 18, 2013; accepted July 19, 2013; previously published online August 14, 2013

References

- Coppola A, Tufano A, Cerbone AM, Di Minno G. Inherited thrombophilia: implications for prevention and treatment of venous thromboembolism. *Semin Thromb Hemost* 2009;35:683–94.
- Favaloro EJ, McDonald D, Lippi G. Laboratory investigation of thrombophilia: the good, the bad, and the ugly. *Semin Thromb Hemost* 2009;35:695–710.
- Lippi G, Franchini M. Pathogenesis of venous thromboembolism: when the cup runneth over. *Semin Thromb Hemost* 2008;34:747–61.
- Egeberg O. Inherited antithrombin deficiency causing thrombophilia. *Thromb Diath Haemorrh* 1965;13:516–30.
- Griffin JH, Evatt B, Zimmerman TS, Kleiss AJ, Wideman C. Deficiency of protein C in congenital thrombotic disease. *J Clin Invest* 1981;68:1370–3.
- Comp PC, Esmon CT. Recurrent venous thromboembolism in patients with a partial deficiency of protein S. *N Engl J Med* 1984;311:1525–8.
- Dahlback B, Carlsson M, Svensson PJ. Familial thrombophilia due to a previously unrecognized mechanism characterized by poor anticoagulant response to activated protein C: prediction of a cofactor to activated protein C. *Proc Natl Acad Sci USA* 1993;90:1004–8.
- Bertina RM, Koeleman BP, Koster T, Rosendaal FR, Dirven RJ, de Ronde H, et al. Mutation in blood coagulation factor V associated with resistance to activated protein C. *Nature* 1994;369:64–7.
- Franchini M. Utility of testing for factor V Leiden. *Blood Transfus* 2012;10:257–9.
- Favaloro EJ. Futility of testing for factor V Leiden. *Blood Transfus* 2012;10:260–3.
- Rosendaal FR, Reitsma PH. Genetics of venous thrombosis. *J Thromb Haemost* 2009;7(Suppl 1):301–4.
- Middeldorp S, Levi M. Thrombophilia: an update. *Semin Thromb Hemost* 2007;33:563–72.
- Heit JA. Venous thromboembolism: disease burden, outcomes and risk factors. *J Thromb Haemost* 2005;3:1611–7.
- Dentali F, Sironi AP, Ageno W, Turato S, Bonfanti C, Frattini F, et al. Non-O blood type is the commonest genetic risk factor for VTE: results from a meta-analysis of the literature. *Semin Thromb Hemost* 2012;38:535–48.
- Wu O, Robertson L, Twaddle S, Lowe G, Clark P, Walker I, et al; Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) Study. Screening for thrombophilia in high-risk situations: a meta-analysis and cost-effectiveness analysis. *Br J Haematol* 2005;131:80–90.
- Kyrle PA, Rosendaal FR, Eichinger S. Risk assessment for recurrent venous thrombosis. *Lancet* 2010;376:2032–9.
- 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;362:523–6.
- Christiansen SC, Cannegieter SC, Koster T, Vandenbroucke JP, Rosendaal FR. Thrombophilia, clinical factors, and recurrent venous thrombotic events. *JAMA* 2005;293:2352–61.
- Vink R, Kraaijenhagen RA, Levi M, Buller HR. Individualized duration of oral anticoagulant therapy for deep vein thrombosis based on a decision model. *J Thromb Haemost* 2003;1:2523–30.
- 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;166:729–36.
- Brouwer JL, Lijfering LM, ten Kate MI, Kluin-Nelemans HC, Veeger NJ, van der Meer J. High long term absolute risk of recurrent venous thromboembolism in patients with hereditary deficiencies of protein S, protein C, or antithrombin. *Thromb Haemost* 2009;101:93–9.
- Robertson L, Wu O, Langhorne P, Twaddle S, Clark P, Lowe GD, et al; Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) Study. Thrombophilia in pregnancy: a systematic review. *Br J Haematol* 2006;132:171–96.