

EDUCATIONAL ARTICLE

Hereditary Thrombophilia and Venous Thromboembolism: Critical Evaluation of the Clinical Implications of Screening

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Venous thromboembolism is a complex disease resulting from the interactions of several risk factors from diverse origins: genetic, environmental and behavioral. Numerous studies have evidenced an association between genetic thrombophilia defects and venous thromboembolism. However, the clinical relevance of genetic thrombophilia to recurrent venous thromboembolism is not clear and the risks of long-term anticoagulant treatment usually outweigh any benefits of hereditary thrombophilia screening. Therefore, in everyday clinical practice (outside of research protocols) hereditary thrombophilia screening should be performed only in cases where such testing is likely to influence patient management.

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Keywords: Thrombophilia; FV Leiden; Screening; VTE recurrence.

Introduction

Venous thromboembolism (VTE) is a major source of morbidity and mortality affecting an estimated 1/1000 people annually, with prevalence increasing with age (in young individuals incidence of VTE is 1/100,000 people; by middle age it is approximately 1/1,000 and thereafter it increases steeply approaching 1%/year in older age).¹ VTE is a complex multifactorial disease where genetic, environmental and other risk factors participate in determining an individual predisposition to thrombotic events. Within the last 15 years several genetic risk factors have been described and investigated. This has led to diagnostic techniques, mostly molecular, becoming used more widely. However, despite the overwhelming observational evidence of the association between hereditary thrombophilia and VTE, the implications of thrombophilia screening for everyday clinical practice remain uncertain. The most common inherited thrombophilias (FV Leiden mutation, prothrombin G20210A mutation; deficits in protein C, S and antithrombin III)

are a group of genetic conditions that predispose to thrombotic events by influencing several factors participating in the coagulation cascade (Table 1).

Why Performing an Inherited Thrombophilia Screening ?

In this review we focus on some common situations for which thrombophilia testing is usually requested but where such testing may not actually be useful for the management of patients. There are several reasons why in every day practice doctors request a genetic thrombophilia screen for their patients: (1) To provide an explanation for VTE, (2) To assess risk of VTE recurrence and therefore offer guidance in determining duration of anticoagulation, (3) To predict risk in asymptomatic relatives.

1. To provide an explanation for VTE

In clinical practice one of the most frequently advocated reasons for thrombophilia testing is to provide an explanation for the venous thromboembolic event. However, VTE is a complex multifactorial disease resulting from the interaction of genetic, environmental, and behavioral risk factors. Usually for VTE to

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Table 1. Most frequent hereditary thrombophilia defects

		Pro-thrombotic mechanism
Loss of function	Deficiency in antithrombin-III, protein C, protein S	Deficiency of natural occurring anticoagulants
Gain of function	FV Leiden mutation	FV Leiden is relatively resistant to inactivation by activated protein C
	Prothrombin (G20210A) mutation	Leads to increased levels of prothrombin

develop, several risk factors, genetic and acquired, need to occur simultaneously. Additionally, complexity of VTE etiology is exacerbated by the dynamic influence of age. In fact, for a patient with a FV Leiden mutation, the risk of developing a VTE will vary with age. Absolute risk at early age is relatively low, even in the presence of several predisposing factors. As an example, risk is 1/10,000/year at 25–30 years of age, it increases with the use of oral contraceptives (3–4/10,000/year) and is further increased if concomitant FV Leiden mutation is present, but remains at an absolute level of only 3/1,000/year. Since aging is a risk factor for venous thrombosis by itself^{2,3} at a later age fewer risk factors will be needed to develop similar levels of absolute risk of VTE. Based on these observations and the complexity of VTE etiology, the relative contribution of hereditary thrombophilia when generalized to a whole patient population is questionable. Epidemiological studies have shown that only 50% of patients with VTE have a positive genetic thrombophilia screen, but this percentage varies when selected patient populations are screened.

Evaluation of a link between a potential risk factor and VTE occurrence is not always easy although a number of risk factors are known, new risk factors are being described continually. However, some large published trials have added to the knowledge of VTE occurrence and single hereditary thrombophilias: i) LETS is a European case-control study of unselected patients aged <70 years without cancer who experienced a first deep vein thrombosis (DVT),⁴ and ii) LITE is an USA prospective cohort study of 21,680 individuals aged >65 years in which baseline risk factors were assessed in relation to future VTE.^{5,6} Results from these two studies are similar (Fig. 1). From these trials we gather the information that for patients with the two most common hereditary thrombophilias (FV Leiden mutation and prothrombin G20210A mutation) the relative risk of VTE, in absence of concomitant risk factors, increases 3.7–7.9 fold for the heterozygous FV Leiden mutation and 1.9–2.8-fold for the prothrombin mutation (G20210A). These increases are modest, given the

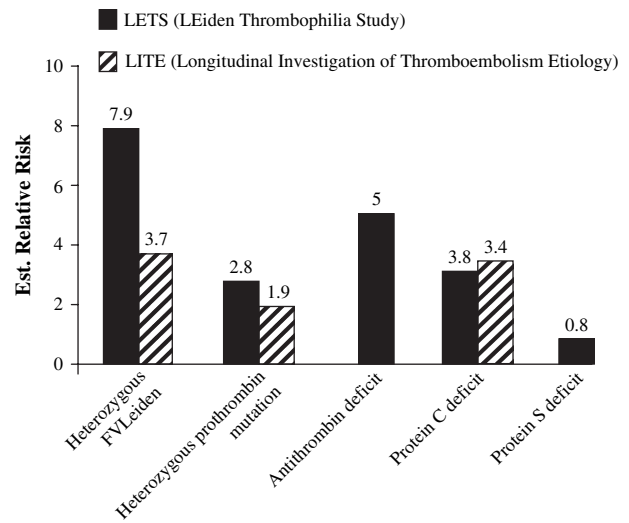


Fig. 1. Estimated relative risk of first time VTE in patients with hereditary thrombophilia.^{4–6}

high prevalence of these defects in the general population and the true incidence of VTE. Such observations suggest that the mere presence of one or more hereditary thrombophilic factors is not a sufficient explanation for VTE development per se. This may be explained partially by the fact that clinical penetrance of hereditary thrombophilias is highly variable even within a single family. Therefore, phenotypic expression is variable and, as already mentioned, depends not only on the presence of one or multiple genetic defects but also on the interaction with other concomitant risk factors.

2. To assess risk of VTE recurrence and determine duration of anticoagulation

Another common reason for thrombophilia testing is to assess risk of VTE recurrence thus offering guidance to determine duration of anticoagulation. Indeed, the main goal of anticoagulant treatment after VTE is to prevent recurrence, and if the risk of recurrence is considered high then long term anticoagulation may be offered to the patient. Does the presence of genetic thrombophilia increase significantly this risk of recurrence in a patient experiencing VTE? The answer to this question is not straightforward. In fact, data presented in the literature are often contradictory and studies conducted so far are mainly retrospective. Moreover, some of the genetic defects (i.e. protein C, protein S, and antithrombin-III deficits) are rare and therefore it is difficult to determine accurately their impact on VTE recurrence. However,

despite all these limitations, some studies have provided insight as to the risk of VTE recurrence in the presence of hereditary thrombophilia. In the LETS study 474 unselected patients experiencing a first episode of VTE were followed for many years.⁷ The cumulative recurrence rate in these patients was 16.5% at 7 years. Recurrence rate for each genetic thrombophilia was low, after adjustment for sex, age, and anticoagulation, with mean estimated relative risks always < 2 (Fig. 2). This also was true for combined thrombophilic defects. Overall risk of recurrence was not significantly increased in patients with hereditary thrombophilias compared with patients without known such abnormalities. Similar results were obtained in the CVTE study (Cambridge Venous Thromboembolism Study) where 570 patients of all ages with a first episode of VTE, no cancer, and no antiphospholipids syndrome, were followed for 2 years after stopping anticoagulant treatment.⁸ Interestingly, in the CVTE study, patients with post surgical VTE had a very low risk of VTE recurrence, and patients with non-surgical risk factors had a significantly lower risk of recurrence (8%) than patients with an idiopathic VTE (20%). In both groups of patients, idiopathic VTE and non-surgical risk factor VTE, no significant difference in recurrence rates was observed between patients with and without genetic evidence of thrombophilia. Homozygous thrombophilic mutations also can be present. Such homozygous mutations have been hypothesized to increase further the risk of VTE recurrence. However, data from the

literature have suggested that this may not always be relevant. The Procare group recently reported a relative risk of VTE recurrence of only 1.8 in those patients homozygous for the FV Leiden mutation compared to those heterozygous for the mutation.⁹

These observations strongly suggest that in unselected patients with a first episode of VTE hereditary thrombophilia screening does not help to predict VTE recurrence and therefore should not be used to guide decisions on duration of anticoagulant treatment. On the contrary, clinical risk factors seem to play a major role in risk prediction.

When deciding about long-term anticoagulation benefits and risks have to be balanced, the principal risk being an hemorrhagic event. This risk should be substantially lower than the risk of VTE recurrence. A recent trial, the European Prospective Cohort on Thrombophilia (EPCOT), followed, for about 6 years, patients with hereditary thrombophilia who experienced a first VTE.¹⁰ Among these patients 44 of 180 patients not on long-term anticoagulation experienced a recurrent VTE (5%/year) compared to 7 of 124 patients on long-term anticoagulation (1.1%/year). In this latter group, the benefit of long-term anticoagulation was offset by an 0.8%/year risk of major hemorrhage.

Often for those patients who already have experienced one or more VTE, genetic thrombophilia screening is proposed in order to assess the need for prophylaxis in future high-risk thrombotic situations. A large amount of data appearing in the literature over the last 15 years has clearly shown that there is a need for antithrombotic prophylaxis in future high risk situations for all patients who experienced VTE, especially if idiopathic, even without the knowledge of the presence of a hereditary thrombophilia.¹¹

3. To predict risk in asymptomatic relatives

Screening of asymptomatic family members of patients with hereditary thrombophilia who experienced VTE is a controversial topic. In a large recent prospective study, the European Prospective Cohort on Thrombophilia (EPCOT), 575 asymptomatic carriers of genetic thrombophilia were followed for about 6 years.¹² Incidence of first VTE was higher in individuals with thrombophilia than in controls (0.8% year vs. 0.1% year) with a relative risk of 9 after adjustment for age and sex. Annual incidence of first VTE was highest for individuals with antithrombin-III deficit (1.7% year) or with combined thrombophilic defects (1.6% year) and lowest in individuals carrying the FV Leiden

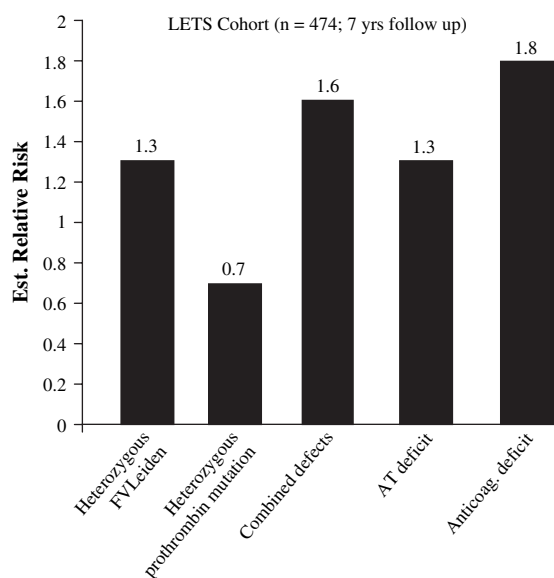


Fig. 2. Estimated relative risk of VTE recurrence in patients with hereditary thrombophilia.⁷

mutation (0.1% year). Interestingly, first VTE event occurred at an earlier age in thrombophilic individuals than in controls. Mean age of onset was 40 years for those with protein C, protein S, antithrombin-III deficiencies or combined defects as compared to 63 years of those individuals carrying the FV Leiden mutation and control subjects. This interesting study shows that the risk of first VTE is increased in carriers of genetic thrombophilia, but that this risk remains still low and does not outweigh the risk of major hemorrhage associated with prolonged anticoagulation [(1–3% year), providing that the INR remains within the therapeutic range of 2–3.^{10,13,14} These observations suggest that long-term prophylactic anticoagulation is not warranted for asymptomatic carriers of genetic thrombophilias. Consequently, unselected genetic testing of individuals with a positive familial history is not fully justifiable. Additionally, one has to be aware of the consequences that genetic screening results may have on patients: anxiety in asymptomatic carriers and false reassurance in negative ones.¹⁵ A reason for genetic testing in individuals with a family history of VTE is to offer appropriate prophylaxis in high-risk situations. However, one has to remember that: i) general recommendations on VTE prophylaxis already include antithrombotic treatment for all those patients experiencing high risk thrombotic situations, regardless of the presence or absence of detectable genetic thrombophilia,¹¹ and ii) these recommendations are even more stringent for those patients with a positive family history of VTE.¹¹

When is Hereditary Thrombophilia Testing Useful?

In the preceding section of the review we have discussed situations where hereditary thrombophilia screening is not appropriate. On the other hand, there are clinical situations where such tests may be useful and their indication should be discussed. Hereditary thrombophilia testing may be appropriate in young women desiring to use oral contraceptives (OCP) and who have a family history of VTE, particularly if idiopathic. Oral contraceptives may be considered if screening is negative. On the contrary, careful counselling should be provided if screening is positive. Such patients should be aware of the increased thrombotic risk, alternative contraception methods may be proposed or the use of a less thrombogenic OCP. Another situation in which thrombophilia testing may be useful for patient management is the case of a woman desiring a first pregnancy who experienced a proximal DVT following a lower limb fracture treated with

immobilization with a cast while on OCP 5 years previously. In this case, VTE risk factors were the use of OCP (although she had been using it safely for 5 years) and concomitant transient risk factors (immobilization and traumatism) that are no longer present. If thrombophilia screening is positive the patient doctor may want to discuss antithrombotic prophylaxis throughout pregnancy and during the 6 weeks post partum. On the contrary, if screening is negative only post partum anticoagulation may be considered. In a 60 year old man (with two daughters) developing an idiopathic proximal DVT genetic thrombophilia testing is unnecessary for the patient, since results would not change therapeutic approach or future prophylaxis. However, thrombophilia screening may be performed and if this is positive, testing of the daughters may be appropriate to evaluate the need for antithrombotic prophylaxis during a future pregnancy or offer counselling in case of OCP use. In this latter case, the cost of such tests should be discussed since in some countries testing for prevention may not be covered by health insurance.

Main Pitfalls In Hereditary Thrombophilia Testing

During the last 20 years the number of laboratory tests for the detection of hereditary thrombophilia has been constantly increasing. In this article we briefly pointed out situations for which genetic testing is not clinically relevant for the future management of patients. Once doctors decide to perform a thrombophilia screening this should be done in the most appropriate conditions to avoid misinterpretation of results, which

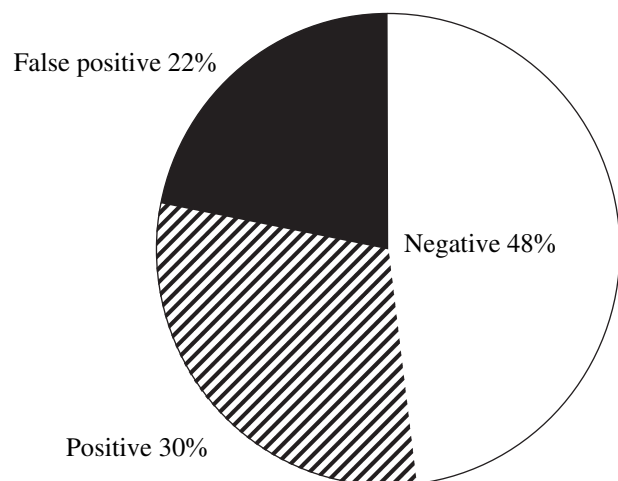


Fig. 3. «Real world» laboratory testing results for patients presenting with VTE. False positive results include deficits in protein C and S and accounted for about 1/5 of all tests. Adapted from ref 16.

Table 2. Most common pitfalls in hereditary thrombophilia testing

Laboratory test	When to avoid testing	Type of test
FV Leiden mutation	Avoid performing the activated protein C resistance test during pregnancy, and in presence of anti-phospholipid antibodies.	- Genotyping (PCR) - Activated protein C resistance (aPTT-based assay, indirect evidence)
Prothrombin G20210A mutation		- Genotyping (PCR)
Deficit in protein C	Acute phase, ongoing vitamin K antagonist treatment, liver dysfunction	- Protein C activity - Antigenic assays*
Deficit in protein S	Acute phase, ongoing vitamin K antagonist treatment, liver dysfunction, pregnancy, ongoing oral contraception or hormonal substitution	- Free protein S - Antigenic assay*
Deficit in antithrombin-III	Acute phase, liver dysfunction, ongoing heparin treatment, nephrotic syndrome, pre-eclampsia	- Antithrombin-III activity - Antigenic assay*

* does not detect all deficiencies.

could bring more harm than benefit to the patient. An interesting paper published in 2006 evaluated the use of thrombophilia screening in a large urban academic tertiary care center.¹⁶ The results show the excessively high number of false positive tests (Fig. 3). This was mainly due to either inappropriate timing of testing (acute phase of VTE) or testing while the patient was on oral anticoagulants or pregnant.

In Table 2 the main pitfalls of hereditary thrombophilia screening are indicated, emphasising when to avoid testing to limit false positive results. Another aspect to consider when interpreting results is the wide normal ranges for protein C, S and antithrombin-III. How should a slightly diminished protein level be interpreted? In some situations repeated testing may be necessary to confirm a true deficiency.

Conclusion

Hereditary thrombophilia testing is commonly performed in routine clinical practice for patients with VTE or asymptomatic individuals from families with a history of VTE. A number of studies have shown associations between genetic thrombophilic defects and VTE however, the clinical relevance of this association remains to be fully demonstrated. Recent data from the literature show rather convincingly that in general

hereditary thrombophilia: i) does not increase risk of a first VTE in such a way to outweigh the hemorrhagic risk of long term anticoagulation; ii) does not increase significantly the risk of VTE recurrence; iii) is a worst predictor for future recurrent VTE events than clinical risk factors; iv) screening should be reserved to subgroups of individuals for whom results are susceptible to influence management. Moreover, tests should be performed under optimal conditions to avoid false positive results and consequently false diagnosis which is potentially harmful to the patient. Care should be taken to avoid testing in an acute setting, to ensure patients are not on conflicting anti-coagulants, taking concomitant oral contraception, hormonal substitution or are pregnant.

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Accepted 25 April 2007

Available online 27 June 2007