

Should adult patients be routinely tested for heritable thrombophilia after an episode of venous thromboembolism?

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Venous thromboembolism (VTE) is a multifactorial disease caused by heritable and acquired factors that lead to alterations in blood flow, endothelial injury and hypercoagulability of the blood. Patients with a first episode of VTE are generally treated with heparin for at least 5 days, followed by warfarin for 3–6 months.¹ Warfarin prevents recurrent VTE as long as treatment is continued but is inconvenient (regular anticoagulation monitoring is required) and risky (it may cause major bleeding). Thus, in deciding the duration of warfarin treatment, clinicians need to balance the risk of recurrent VTE when warfarin is discontinued against the inconvenience and risks of continuing treatment.

The risk of recurrent VTE can be quantified with reasonable precision by means of clinical assessment of the circumstances and likely cause of the index episode of VTE. If exposure to the cause of the VTE is transient (eg, recent surgery or hospitalisation) or can be “reversed” (eg, oestrogen therapy or pregnancy), then the long-term risk of recurrent VTE is likely to be low and long-term warfarin treatment is not required.

If, however, exposure to the cause of the VTE is permanent or irreversible (eg, paralysis after a stroke), then the long-term risk of recurrent VTE is likely to remain high. If the cause of the VTE is unexplained (idiopathic), the risk of recurrence is high but the optimal duration of anticoagulation remains unclear.

Laboratory testing for heritable thrombophilia, including factor V Leiden (FVL), the prothrombin (factor II) gene mutation (the substitution of A for G at position 20210 [FII20210A]), and deficiencies of the natural anticoagulants (antithrombin, protein C and protein S), has been proposed to help stratify patients' risk of recurrence (above and beyond clinical factors) and thereby inform the optimal duration of anticoagulation.²

However, testing practices seem to be highly variable, perhaps because Australian guidelines for thrombophilia testing are lacking. We believe that there is a need for local evidence-based guidelines that take into account the following issues.

How prevalent is heritable thrombophilia?

The prevalence of heritable thrombophilia (and the yield of thrombophilia testing) is influenced by the age and ethnic origin of the population. It is present in about a third of patients of European origin who have VTE, irrespective of whether the VTE is provoked or idiopathic,^{3–5} and is more common in younger patients (< 50 years) with VTE.⁴ FVL and FII20210A are the two most common types of heritable thrombophilia in people of European origin, but are much less common in some Asian populations and are rarely found in Indigenous Australians without European admixture.⁶

Is the test for heritable thrombophilia standardised?

Genetic testing for the gain-of-function mutations, FVL and FII20210A, is available in many routine clinical laboratories, but genetic testing for deficiencies of the natural anticoagulants is not

ABSTRACT

- The clinical usefulness of laboratory testing of adult patients with venous thromboembolism (VTE) for heritable thrombophilia needs to be critically evaluated. At present, some clinicians use testing to identify patients at higher risk of recurrence (who may benefit from an extended period of anticoagulation beyond the usual 3–6 months) and their relatives at risk of a first VTE episode.
- As prevalence of heritable thrombophilia is related to age and ethnic origin, the pretest probability of detecting heritable thrombophilia may be low in unselected populations.
- Interpretation of laboratory results may not be straightforward. Apparent deficiencies of a natural anticoagulant may be due to acute thrombosis and “consumption”, concomitant therapy with heparin and/or warfarin and other clinical factors.
- The predictive value of recurrent VTE conferred by the most common types of heritable thrombophilia (factor V Leiden and the G20210A prothrombin mutation) is limited. Risk of recurrence associated with deficiencies of a natural anticoagulant is less certain due to their rarity.
- Clinical risk factors (eg, the presence or otherwise of provoking factor(s) and whether or not the risk factor for VTE is reversible or permanent) appear to be the most important predictors of VTE recurrence. Duration of anticoagulation should be determined by clinical risk factors rather than the presence, or otherwise, of heritable thrombophilia.
- The benefit of identifying relatives who are carriers of thrombophilia is uncertain, as VTE is a multifactorial disease resulting from the interaction of various risk factors, some well recognised and others as yet unknown.

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routinely available; these require antigenic and/or functional assays to establish the diagnosis. However, in the Quality Assurance Program for Haematology of the Royal College of Pathologists of Australasia, the coefficients of variation for such assays range from 5% to 40%, with protein S assays showing the greatest variability.⁷ Blood levels of protein C and protein S, measured by clot-based functional assays, are often lower in patients with raised blood levels of factor VIII and in those with concomitant FVL.⁷ Therefore, interpreting results of blood tests for the natural anticoagulants requires consideration of both patient factors and laboratory methods.

Are there population norms to guide interpretation of test results?

Population studies have provided reference ranges for blood levels of the natural anticoagulants. However, these blood levels are influenced by health and sickness, potentially complicating inter-

pretation of results. This is especially the case for protein S, 40%–50% of which circulates as the free form, with the remainder bound to the complement component, C4b-binding protein. Only the free fraction of protein S is physiologically active and normal ranges differ between the sexes, and between pre- and postmenopausal women. A low blood level of any of the natural anticoagulants requires confirmation by retesting and interpretation in the light of clinical circumstances. Testing of relatives may be necessary to confirm a heritable deficiency.

Protein S deficiency appears to significantly increase the risk of VTE when the free antigen level is < 30%,⁸ whereas the lower limit of the reference range (based on healthy blood donors) is much higher at about 65%. With protein C, thrombotic risk appears to correlate with the level: using protein C activity \geq 85% as a reference, for every 10% decrease in level, thrombotic risk increases progressively.⁹

Although population norms are available, the interpretation and predictive value of a reduced level of the natural anticoagulants are often uncertain.

Is the test result valid?

Heparin therapy affects antithrombin levels whereas warfarin lowers blood levels of protein C and protein S. Thus, testing for deficiencies of the natural anticoagulants should ideally be undertaken when the patient is not receiving anticoagulation medication. Despite this, a recent audit of investigation for heritable thrombophilia in an Australian institution reported that the result in 40%–90% of the cases with apparent deficiencies in natural anticoagulants was attributable to concomitant anticoagulant therapy.¹⁰ Testing at the time of VTE diagnosis may also give falsely low levels of the natural anticoagulants, because of acute thrombosis and “consumption”.

Further, in the Royal College of Pathologists of Australasia Quality Assurance Program for Haematology, errors occurred in 2%–8% of assays for the natural anticoagulants (false normal interpretation for deficient samples and false abnormal interpretation for normal plasma).⁷ Genetic testing is generally considered diagnostic but inaccuracies arise when reagents or samples become contaminated, or when errors occur in sample matching or transcription of results. Genetic testing for FVL and FII20210A gives average error rates of 1%–2% in Australasia, although a patient with homozygous FVL was incorrectly diagnosed by as many as 15% of laboratories.¹¹

As with all tests, results of laboratory testing for heritable thrombophilia are not always accurate.

Does testing provide clinically significant prognostic value?

In a meta-analysis of about 3000 patients with a first episode of VTE (not associated with malignancy), heterozygous carriage of FVL or FII20210A conferred a modest 1.4-fold or 1.7-fold increase in recurrence risk, respectively, compared with non-carriage of these mutations.¹² Cohort studies have reported that heterozygous natural anticoagulant deficiencies collectively conferred a 1.5–1.8-fold increased recurrence risk when compared with patients having normal levels.^{13,14} Of the natural anticoagulants, antithrombin deficiency appears to be associated with the greatest risk (1.9–2.6-fold increased risk) of recurrent VTE.^{3,13}

One study found that after a first episode of VTE, patients who are compound heterozygous for FVL/FII20210A have a 2.7-fold higher risk of recurrence compared with non-carriers.¹⁵ In another study, however, carriers of FVL and another thrombophilia did not have a higher risk of recurrence compared with carriers of FVL alone, even if the first episode of VTE was idiopathic.¹⁴ A more recent study also showed that patients who were homozygous carriers of FVL or FII20210A and those who were compound FVL/FII20210A heterozygote carriers did not have a higher recurrence risk than non-carriers.¹⁶

These data suggest that laboratory testing for FVL and FII20210A has limited prognostic value. Natural anticoagulant deficiencies may be associated with a higher risk of recurrence than FVL and FII20210A, but are much less common and estimates of recurrence risk are less certain.

Have clinical risk factors been evaluated and appropriately modified?

Patients with a reversible risk factor for VTE have a low rate of recurrence: in one cohort, those with an episode of VTE provoked by recent surgery or pregnancy who received 6 months of anticoagulation had a negligible risk of VTE recurrence at 2 years. When VTE was provoked by other reversible risk factors (eg, oral contraceptive use, limb immobilisation in a plaster cast), the 2-year recurrence rate was 8.8% compared with 19.4% for idiopathic cases.³ VTE associated with a permanent risk factor (eg, malignancy) has a high risk of recurrence regardless of thrombophilia status.

Thus, clinical risk factors appear to be the most important predictors of recurrence and should be modified where possible. There are no studies evaluating the predictive value of heritable thrombophilia after modification of a transient risk factor.

Will test results alter clinical management and does intervention (eg, prolonged anticoagulation) provide clinical benefit?

No randomised controlled trials have examined the impact of thrombophilia testing (and altered management based on test results) on the risk of recurrent VTE.¹⁷ An uncontrolled study showed that testing and presumably any subsequent management did not reduce recurrence risk.¹⁸

There is some evidence to suggest that anticoagulation for the standard 6 months (or longer) ameliorates the effect of heritable thrombophilia on recurrence risk. A retrospective cohort study of 714 patients with a first episode of VTE found a higher risk of recurrence among carriers of FVL and/or FII20210A, compared with patients with neither mutation, when anticoagulation was given for only 3 months. However, after 6 months or more of anticoagulation, there was no difference in recurrence risk between carriers and non-carriers.⁵ Likewise, a substudy of 195 patients with a first episode of idiopathic VTE reported that patients with thrombophilia (heritable and acquired) had an increased recurrence risk, compared with those without thrombophilia, when anticoagulation was given for 3 months, but this difference in risk was no longer evident when treatment was extended to 12 months.¹⁹ The benefit of a longer duration of anticoagulation was not confirmed in another retrospective analysis of 496 patients with a first episode of VTE who were allocated at random to either 6 weeks or 6 months of anticoagulation.²⁰

Examples of clinical situations in which testing for heritable thrombophilia may be considered²²⁻²⁷

Clinical situation	Possible argument for testing
Preventing VTE during pregnancy in a patient with a previous episode of VTE	Tailoring of prophylaxis especially when a "higher risk" thrombophilia (eg, antithrombin deficiency) is found ²²
Case finding of asymptomatic carriers, especially in families with a strong history of VTE	
<ul style="list-style-type: none"> Prevention of pregnancy-related VTE in asymptomatic women with heritable thrombophilia 	Pregnant women with no previous VTE who have antithrombin deficiency may benefit from prophylaxis (including peripartum antithrombin replacement) ²³
<ul style="list-style-type: none"> Prevention of VTE through avoidance of oral oestrogen-containing hormone preparations among asymptomatic women with heritable thrombophilia 	Testing of female relatives of FVL carriers was reportedly cost-effective; however, the modelling assumed complete abstinence from oral contraceptive use among those found to be carriers ²⁴
Development of skin necrosis with warfarin	Identification of patients with protein C or protein S deficiency ^{25,26}
Heparin resistance	Identification of patients with antithrombin deficiency (rare) ²⁷

VTE = venous thromboembolism. FVL = Factor V Leiden. ◆

A survey of clinicians reported that, in almost 80% of patients for whom heritable thrombophilia testing was requested, the test results did not influence their decisions on subsequent patient management.²¹ Nevertheless, some clinicians test selected patients and extend the duration of anticoagulation beyond 3–6 months in those with a natural anticoagulant deficiency or with multiple thrombophilia (Box).²²⁻²⁷

Does the overall benefit of testing outweigh the adverse consequences and costs?

Testing positive for heritable thrombophilia can generate anxiety and distress for affected patients and their families and the potential exists for discrimination by insurers based on the test results. In contrast, individuals who test negative for heritable thrombophilia may be falsely reassured that they are not at an increased risk of recurrence. Testing can also reveal unanticipated deviations from normal patterns of inheritance and raise unwelcome questions concerning parentage (eg, a homozygous parent with an unaffected child).

Testing of female relatives of FVL carriers for their FVL status before oral contraceptive use was found to be cost-effective,²⁴ but the decision-tree model used assumed that none of the carriers identified would take oral contraceptives, and that all episodes of VTE were attributable to FVL. Furthermore, as VTE is a multifactorial disease, a negative test in an asymptomatic relative in a family with a strong history of thromboses does not exclude an increased risk of VTE in that individual (due to other as yet unrecognised genetic or environmental risk factors).^{25,28}

In the 2009–10 financial year alone, Medicare Australia paid more than \$2.3 million in benefits for laboratory testing of patients with VTE for heritable thrombophilia (and lupus anticoagulant).²⁹ This amount does not include testing for heritable thrombophilia in public hospital laboratories and testing of relatives, so that the cost to taxpayers may be several times higher. Moreover, the propriety of requests for thrombophilia testing is called into question by a recent audit of FVL testing at a tertiary institution in Australia.¹⁰ Consistent with published data on cohorts of consecutive patients with VTE, FVL was identified in about 25% of cases 15 years ago, whereas, more recently, the mutation was found in fewer than 10% of requests, a prevalence that is closer to that of the general (European origin) population.¹⁰ This low level of detection implies that increasingly, the test is being ordered as a screening tool.

If the results of testing do not influence management in most patients, routine testing is unlikely to be cost-effective and, taking into account the potential adverse psychosocial impact, we believe it may cause net harm.

Are there alternative tests to guide clinical decision making?

Preliminary data indicate that raised blood levels of D-dimer after cessation of anticoagulation, and residual lower-limb venous thrombosis detected by ultrasonography, have a high positive predictive value for VTE recurrence.³⁰ These tests may serve as alternatives to testing for heritable thrombophilia to predict VTE recurrence, but their clinical usefulness also remains unproven.

Conclusion

We believe that, in the absence of evidence demonstrating benefit, routine testing for heritable thrombophilia is unwarranted. This is consistent with recent guidelines in the United Kingdom and some European countries.^{25,28,31} Moreover, the duration of anticoagulation after an episode of VTE is determined by clinical risk factors.^{25,28,32} Long-term anticoagulation should be considered for patients with recurrent VTE, regardless of their heritable thrombophilia status.³³

However, an argument can be made for thrombophilia testing in selected clinical situations where the result may influence clinical management of a patient or his or her relatives. These are highlighted in the Box.²²⁻²⁷ The yield (ie, the likelihood of a positive test) in such settings might be increased by restricting testing to younger patients (eg, <50 years at the time of the first episode of VTE) and those with a strong family history of VTE (eg, two or more affected family members),^{26,34} although a strongly positive family history appears to be more predictive of risk than known common heritable thrombophilia. However, a selective testing strategy has not been validated, and clinicians ordering thrombophilia testing need to have a clear idea about how to deal with the results.

Competing interests

None relevant to this article declared (ICMJE disclosure forms completed).

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