1. Background

- This document represents an updated version of guidance used in North Bristol NHS Trust since 2004. In April 2010 an updated version of BCSH guidance, incorporating newer evidence and expert opinion on the utility of thrombophilia tests was published.

- ‘Thrombophilia’ refers to a tendency to develop venous thrombosis. For some there may also be a risk of arterial thrombosis. When testing is performed, it is mostly for hereditary factors although a number of persistent acquired risk factors may be investigated. Laboratory features related to transient risk factors for VTE are not investigated although transient events may complicate interpretation of investigation for heritable thrombophilia.

2. Assessment of individuals with suspected thrombophilia

The following should be determined in all patients:

- Personal and family thrombotic history (more than two other family members symptomatic with VTE) including whether thrombotic episodes have been confirmed by objective investigations.

- General medical history and results of clinical examination to identify acquired pro-thrombotic risk factors. These include advanced age, immobility, trauma, surgery, inflammatory disorders, hormone use, tobacco smoking, pregnancy or post-partum state, obesity, nephrotic syndrome or malignant disease. About 4% of all patients presenting with an apparently idiopathic venous thrombosis subsequently receive a diagnosis of malignancy within 1 year of presentation, most frequently of pancreas, brain, ovary or lymphoma.

3. Indications for ‘thrombophilia screening’

Testing for heritable thrombophilia is not indicated in unselected patients presenting with venous thrombosis. Analysis of the large MEGA (Multiple Environmental and Genetic Assessment) study showed that testing for inherited thrombophilia did not reduce recurrence of venous thrombosis. Initiation and intensity of anticoagulant therapy following a diagnosis of acute venous thrombosis should be the same in patients with and without heritable thrombophilia. Decisions regarding duration of anticoagulation (lifelong or not) in unselected patients should be made with reference to whether or not a first episode of venous thrombosis was provoked or not, other risk factors, and risk of anticoagulant therapy-related bleeding, regardless of whether a heritable thrombophilia is known.
Selected groups where testing may give an indication of risk of recurrence of venous thromboembolism (VTE) or influence treatments are:

- those presenting with venous thrombosis at an early age (<40) and who are from apparent VTE prone families
- children with purpura fulminans
- pregnant women at risk of venous thrombosis.

The decision to test these selected patients should be based on whether or not test results are likely to influence treatment decisions.

**Thrombophilia screening is not indicated in the following situations:**

I. Testing for heritable thrombophilia in unselected patients presenting with a first episode of venous thrombosis.

II. Testing is not recommended in unselected patients with upper limb venous thrombosis.

III. Testing is not recommended in patients with central venous catheter (CVC)-related venous thrombosis.

IV. Testing is not indicated in patients with retinal vein occlusion.

V. Case finding of asymptomatic relatives with low risk thrombophilia, such as FVR506Q or F2G20210A, is not indicated.

VI. Case finding for very rare homozygosity or compound heritable thrombophilia is not indicated as these defects are so rare, they are not predicted by family history, and the risk of unprovoked thrombosis is low.

VII. COC or HRT when a first degree relative with venous thrombosis has not been tested. Suggest woman considers an alternative contraceptive or transdermal HRT. Testing for heritable thrombophilia will provide an uncertain estimate of risk and is not recommended.

VIII. COC or HRT if a first degree relative with venous thrombosis has been tested and the result is negative then suggest woman considers an alternative contraceptive or transdermal HRT. Testing for heritable thrombophilia will provide an uncertain estimate of risk and is not recommended.

IX. Women should be assessed for risk of pregnancy-associated venous thrombosis primarily in relation to clinical risk factors. Most women with a previous unprovoked venous thrombosis or pregnancy or COC-related thrombosis will qualify for thromboprophylaxis on clinical risk alone and so testing for heritable thrombophilia is not required. Asymptomatic women with a family history of venous thrombosis do not require testing if the clinical risks alone are sufficient to result in thromboprophylaxis during pregnancy. Women with a previous thrombosis due to a major risk factor e.g. surgery or major trauma, would not usually require prophylaxis during pregnancy or testing.

X. Antithrombotic therapy should not be given to pregnant women to prevent pregnancy morbidity (early and late pregnancy loss, pre-
eclampsia, IUGR) based on testing for heritable thrombophilia. Efficacy of LMWH/aspirin is proven for antiphospholipid syndrome. Outside antiphospholipid syndrome, a randomised controlled trial with a no treatment arm in women with a history of recurrent miscarriage showed no benefit in use of aspirin +/- LMWH in preventing recurrent miscarriage (Kaandorp SP, 2010). Only if studies indicate a benefit in some women with pregnancy complications and heritable thrombophilia, as compared with women without thrombophilia, would there be a rational basis for recommending that antithrombotic therapy is given to pregnant women with a history of pregnancy complications based on testing for heritable thrombophilia

XI. Testing asymptomatic women before assisted conception and in those with ovarian hyperstimulation syndrome is not indicated.

XII. Thrombophilia screening of hospitalised patients to identify patients at risk of hospital-acquired venous thrombosis is not indicated. All hospitalised patients should be assessed for risk of venous thrombosis regardless of heritable thrombophilia based on a clinical risk assessment. The presence of a previously known heritable thrombophilia may influence the assessment of risk.

XIII. Testing for heritable thrombophilia is not indicated in patients with arterial thrombosis.

XIV. It is suggested that testing for heritable thrombophilia is not indicated in children with stroke

Thrombophilia screening may be considered in the following situations:

I. Testing for heritable thrombophilia in selected patients, such as those with a strong family history of unprovoked recurrent thrombosis, may influence decisions regarding duration of anticoagulation. It is not possible to give a validated recommendation as to how such patients should be selected.

II. Testing for heritable thrombophilia after a first episode of cerebral vein thrombosis has uncertain predictive value for recurrence. Decisions regarding duration of anticoagulant therapy in relation to the results of testing are not evidence based.

III. Testing for heritable thrombophilia after a first episode of intra-abdominal vein thrombosis has uncertain predictive value for recurrence. Decisions regarding duration of anticoagulant therapy in relation to the results of testing are not evidence based.

IV. Neonates and children with purpura fulminans should be tested urgently for protein C and S deficiency.

V. Adults who develop skin necrosis in association with oral vitamin K antagonists should be tested for protein C and S deficiency when VKA treatment is withdrawn.
VI. Case finding of asymptomatic relatives with high risk thrombophilia, such as deficiency of antithrombin, protein C or protein S, should only be considered in selected thrombosis-prone families. If testing is performed the risks, benefits and limitations of testing should be discussed in the context of explained inheritance and disease risk. It is not possible to give a validated recommendation as to how such patients and families should be selected.

VII. If a first degree relative with venous thrombosis has been tested and the result is positive then suggest woman considers an alternative contraceptive or transdermal HRT before offering testing as a negative test result does not exclude an increased risk of venous thrombosis. Testing for heritable thrombophilia may assist counselling of selected women particularly if a high risk thrombophilia has been identified in the symptomatic relative.

XV. In assessing women for risk of pregnancy-associated venous thrombosis. Women with a previous event due to a minor provoking factor, e.g. travel, should be tested and considered for prophylaxis if a thrombophilia is found.

XVI. Prevention of pregnancy associated venous thrombosis. It is suggested that asymptomatic women with a family history of venous thrombosis be tested if an event in a first degree relative was unprovoked, or provoked by pregnancy, COC exposure or a minor risk factor. The result will be more informative if the first degree relative has a known thrombophilia.

4. Sample collection

- 12 ml blood (3x 4.3ml citrate) is required for each thrombophilia screen. A serum sample (1x 7.5ml serum-gel) is required to investigate anti-cardiolipin and β2-glycoprotein 1 antibodies. A full blood count and plasma viscosity (1x 4.3ml EDTA blood) should be included in the investigation of thrombophilia to identify patients with myeloproliferative disorders or paraproteins. A serum sample (1x 7.5ml serum-gel) is required to assay CRP, U&E, LFTs.

- The request form should include the clinical indication for thrombophilia screen as indicated in section 3 and should indicate the presence of acquired risk factors for thrombosis, particularly intercurrent illness.

- Samples should not be submitted from patients in the acute phase of a thrombosis, during anticoagulation therapy, within 1 month of finishing warfarin, during pregnancy or within 1 month post-partum without discussion with a Haematology Consultant.
5. **Investigations performed**

Coagulation laboratories in North Bristol NHS Trust offer the following investigations as part of investigation for venous thrombosis:

Assays performed on all requests (venous and arterial thrombosis) with appropriate samples:
- I. Prothrombin time
- II. Activated partial thromboplastin time
- III. Fibrinogen
- IV. Lupus anticoagulant screen
- V. Anti-cardiolipin antibodies (anti β2-glycoprotein 1 antibodies when clinically indicated and requested)
- VI. FBC
- VII. CRP
- VIII. PV
- IX. LFT
- X. U+Es

Assays for hereditary thrombophilia performed only on requests matching BCSH criteria:
- XI. Antithrombin activity
- XII. Protein C activity
- XIII. Free protein S antigen
- XIV. Factor VIII activity
- XV. Activated Protein C Resistance
- XVI. Factor V R506Q (Factor V Leiden) genotype
- XVII. Prothrombin G20210A genotype

6. **Interpretation of results and suggested referral practice**

- Approximately 50% of patients presenting with venous thrombosis have no identifiable laboratory abnormality yet still have an appreciable lifelong risk of further thrombosis. Conversely, many individuals with a documented heritable thrombophilia never suffer thrombosis.

- Before thrombophilia screening is performed, facilities must be in place for the provision of informed and detailed advice based on an appreciation of the limitations of laboratory tests and an understanding of the pro-thrombotic risk associated with positive and negative results.

- Investigation of thrombophilia in children is rarely indicated and should always be discussed with a Haematology Consultant or Specialist Registrar.

- There is no evidence to suggest that heritable thrombophilia increases the risk of arterial thrombosis. However, antiphospholipid syndrome is a
risk and requests for ‘lupus anticoagulant and anti-cardiolipin antibodies’ will be considered in young patients with arterial thrombosis. These should be requested as part of a wider screen for arterial thrombosis risk factors.

- The Department of Haematology will supply a coded advice comment for every thrombophilia screen request and offers telephone guidance for the interpretation of results and clinical advice. In the event of an inappropriate request, the specimen will be retained by the haemostasis laboratory for 4 weeks pending discussion.

- Referral to a Haematology outpatient clinic should be considered for patients with:
  1. Deficiency of antithrombin, protein C or protein S
  2. Homozygosity for Factor V R506Q or the Prothrombin G20210A mutation
  3. Persistent lupus anticoagulant or significant elevation of IgG anticardiolipin antibody (or Rheumatology clinic)
  4. Multiple abnormalities.

7. References


Kaandorp SP & others (2010) Aspirin plus heparin or aspirin alone in women with recurrent miscarriage. New England Journal of Medicine, 362(17); 1586-1596.