**Thrombophilia**

**Definition**

*Thrombophilia* refers to a predisposition to thromboembolism. In practice, the term is used to describe patients who are at significantly increased long-term risk of venous thromboembolism (VTE). Heritable thrombophilia is an inherited tendency for venous thrombosis.[1]

**Epidemiology**[1]

Thrombophilia may be heritable, acquired or mixed.

**Heritable causes**[2]

- Heritable thrombophilias can be identified in 30-50% of VTE. Factor V Leiden, prothrombin 20210G>A, and deficiencies of antithrombin, protein C and protein S increase the risk of a first VTE.
- However, an individual's risk is determined by a combination of genetic, acquired and circumstantial risk factors.
- At least 50% of VTE events in thrombophilic individuals are provoked by predisposing factors such as immobility, surgery, trauma, cancer, hormonal therapy and pregnancy.
- Non-modifiable risk factors such as advancing age and family history also increase thrombotic risk.
- Factor V Leiden is the most common heritable thrombophilia in Caucasian populations. It is rare or absent in people of black African, Far East Asian, native Australian and native American origin[3].
- Individuals may have more than one inherited thrombophilia genotype, particularly in populations where the factor V Leiden and prothrombin 20210A alleles are common. Combined thrombophilias can multiply the VTE risk.

**Acquired causes**[4]

- Antiphospholipid syndrome:
  - Associated with both venous and arterial thrombosis.
  - May be primary (venous or arterial thrombosis, or recurrent first-trimester miscarriages) or secondary (linked to other conditions - eg, systemic lupus erythematosus, collagenosis).
- Acquired antithrombin deficiency:
  - Due to liver disease, nephrotic syndrome, disseminated intravascular coagulation or pregnancy.
- Myeloproliferative disorders, thrombocytosis or polycythaemia.
- Cancer.
- Certain inflammatory conditions - eg, inflammatory bowel disease.
- Haemolytic anaemias, including paroxysmal nocturnal haemoglobinuria.[5]
- Behçet's disease.
- Nephrotic syndrome.
- Heart failure, recent myocardial infarction or stroke.
- Possibly, HIV infection[6].
- The presence of a central catheter is the most important risk factor for thrombosis in children[7].
Mixed or uncertain causes\cite{4, 8}

- Hyperhomocysteinaemia:
  - May be inherited or acquired (deficiencies of folic acid, vitamins B12 and B6 may contribute).
  - Is a risk factor for VTE.
  - Mild hyperhomocysteinaemia is common in the general population; the severe form is rare.
  - The most common genetic hyperhomocysteinaemia involves the gene for methylene tetrahydrofolate reductase (MTHFR). Homocystinuria is a rare genetic cause.

- Clotting factor levels:
  - Raised factor VIIIc is now established as a risk factor for VTE.
  - Other clotting factors may be relevant - eg, raised levels of factors VII, IX and XI, or deficiency of factor XII. However, their role is uncertain.

- Other factors possibly involved in thrombophilia are plasminogen deficiency, plasminogen activator, plasminogen activator inhibitor, heparin cofactor II deficiency and histidine-rich glycoprotein.

Presentation

Possible presentations are:

- A strong family history of VTE.
- VTE which is spontaneous or with minimal provoking factors.
- VTE at a young age.
- Thrombosis in an unusual site (eg, mesenteric, portal vein, sagittal sinus thrombosis) or in multiple sites.
- Recurrent VTE.
- Recurrent miscarriage.
- Neonatal thrombosis (eg, neonatal purpura fulminans - rare).
- Warfarin-induced skin necrosis (rare) - see separate Protein C Deficiency article.

Assessment and screening

- Take a careful personal and family history, including VTE events and whether there were any provoking factors for the VTE event, such as immobility, surgery, oestrogens, etc.
- Selective screening based on prior VTE history is more cost-effective than universal screening\cite{9}.
- There is currently no strong evidence for the benefit(s) of testing for thrombophilia to determine the risk of recurrent VTE\cite{10, 11}.
  - One review found that universal screening of women prior to prescribing hormone replacement therapy (HRT) was the most cost-effective strategy but universal screening of women prior to prescribing combined oral contraceptives was the least cost-effective strategy. Selective thrombophilia screening based on previous personal and/or family history of VTE was more cost-effective than universal screening in all the patient groups evaluated\cite{12}.
  - It has been recommended that thrombophilia testing should not be performed in most situations and that, when performed, it should be used in a very selective manner and only in circumstances where the information obtained will influence a decision important to the patient and outweigh the potential risks of testing.
  - Testing should not be performed during acute thrombosis or during the initial (three-month) period of anticoagulation.

Who should be investigated for heritable thrombophilia?\cite{1}

- In the 1980s-1990s thrombophilia testing became common in unselected patients and their relatives. However, it is now recognised that this approach is not clinically useful. It is reasonable to test where clinical management will be influenced by the results. For example, consider testing where the results will affect decisions about the duration of anticoagulation in VTE patients, or VTE prophylaxis during high-risk periods.
- Targeted case-finding of relatives of patients with 'severe' or 'high-risk' thrombophilia has been suggested, such as deficiency of antithrombin, protein C or protein S, although this remains an area of contention.
- There is no accepted definition of thrombosis-prone families. It is important to consider the circumstances of the VTE history - for example, the age of the patient and any provoking factors such as immobility, surgery or pregnancy.
- Before testing, patients should be counselled about the implications of a positive result.

The British Committee for Standards in Haematology (BCSH) guidelines on testing for heritable thrombophilia\cite{1}

Investigation is REQUIRED for:
Pregnant women with a previous non-oestrogen-related VTE provoked by a minor risk factor. They should undergo testing for thrombophilia, as this will influence management and decisions regarding thromboprophylaxis antenatally.  

**Note:** Thrombophilia testing is not recommended for pregnant women in the following cases, as it doesn't alter the proposed management:

- Women with a previous unprovoked or oestrogen-provoked VTE should be considered for thromboprophylaxis during pregnancy in any case, so testing for heritable thrombophilia is not required.
- Women with a previous VTE due to a major provoking factor (eg, surgery or major trauma) do not usually require prophylaxis or testing.

- Pregnancy affects the results of thrombophilia tests. In particular, protein S levels are reduced by pregnancy and protein S deficiency cannot be diagnosed in pregnancy.

**Purpura fulminans:**

- This is a rare syndrome comprising progressive haemorrhagic skin necrosis. It may occur in neonates with congenital severe protein C or protein S deficiencies, older children and adults with infections, or patients with protein C or protein S deficiency when treated with vitamin K antagonists (warfarin).
- Recommendations are:
  - Neonates and children with purpura fulminans require urgent testing for protein C and protein S deficiency (because specific treatment may be helpful).
  - Other patients with very severe skin necrosis - consider testing for acquired protein C or protein S deficiency (because plasma exchange may be beneficial).
  - Adults who develop skin necrosis while taking vitamin K antagonists (warfarin) - test for protein C and protein S deficiency when warfarin is withdrawn.

**CONSIDER investigation for:**

- Selected patients with VTE:
  - Testing for heritable thrombophilias in *selected* VTE 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.

- Asymptomatic relatives of patients with high-risk thrombophilia:
  - 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.
  - Counsel patients regarding the risks, benefits and limitations of testing.
  - It is not possible to give a validated recommendation as to how such patients and families should be selected.

- Female relatives of those with known thrombophilia who are considering taking oestrogen-containing contraception or HRT:
  - Testing for heritable thrombophilia may assist counselling of selected women, particularly if a high-risk thrombophilia has been identified in the symptomatic relative.
  - However, in many cases it is more appropriate to suggest alternative contraception/HRT than to test - see below.

- Cerebral vein (sinus) thrombosis:
  - It has become common practice to test patients for heritable thrombophilia after cerebral vein thrombosis. Some experts continue anticoagulation on a lifelong basis if there is a thrombophilic defect.
  - However, testing in this scenario is not evidence-based.

**Patients/scenarios NOT normally requiring investigation:**

- Unselected patients presenting with a first episode of VTE.
- To assess the risk of hospital-acquired VTE in patients admitted to hospital:\(^\text{[13]}\)
  - All hospitalised patients should be assessed for risk of VTE, regardless of heritable thrombophilia, based on a clinical risk assessment. The presence of a previously known heritable thrombophilia may influence the assessment of risk.

- Asymptomatic relatives of those with low-risk thrombophilia - eg, factor V Leiden heterozygotes (FVR506Q) or prothrombin gene mutation (F2G20210A).
- Decisions about oestrogen-containing contraception or HRT, in relatives of those with VTE:
  - For women who have a first-degree relative with a history of VTE, testing for heritable thrombophilia is not indicated, as the results will not provide a clear estimate of risk. The actual risk to an individual depends not only on the thrombophilia but on other (unidentifiable) factors, even in family members with the same thrombophilia genotype.
  - Therefore, if a first-degree relative has a history of VTE, advise alternative contraception (or transdermal HRT, if HRT is required). This advice applies whether or not the relative has been tested for thrombophilia and even if their thrombophilia test result was negative.
  - However, testing for heritable thrombophilia may assist counselling of selected women, particularly if a high-risk thrombophilia has been identified in the symptomatic relative (as above).

- Unselected patients with upper limb VTE.
Central venous catheter-related VTE.
Retinal vein occlusion.
Assisted conception:
- Testing is not indicated for asymptomatic women before assisted conception and is not indicated in ovarian hyperstimulation syndrome.

Arterial thrombosis.
- It is suggested that testing for heritable thrombophilia is not indicated in children with stroke.

**Situations where the role of investigation is unknown:**
- Intra-abdominal vein thrombosis - there is not sufficient evidence to provide guidance in this area.

### Investigation[^1]

**Important points**
- Do not test for heritable thrombophilia at the time of acute VTE - because the results will not influence initial treatment, the usefulness of the test needs considering and patient counselling is needed.
- No single method of testing can detect all thrombophilic defects.
- Interpretation of the test results is complex; false positives and false negatives are common.
- The tests require supervision by experienced laboratory staff. The results require interpretation by an experienced clinician who is aware of all relevant factors of the individual case.
- Pre-test patient counselling and a physician with specialist knowledge are recommended.

**The initial tests**
- FBC and film - looking for myeloproliferative disorders, paroxysmal nocturnal haemoglobinuria, thrombocytosis, polycythaemia.
- Prothrombin time and activated partial thromboplastin time (aPPT).
- Assays for antiphospholipid antibodies, factor V Leiden, prothrombin G20210A, protein C, protein S and antithrombin. Details of which assays to use are given in published guidelines[^14].

**Other possible investigations**
- ESR, CRP, antinuclear antibodies - for connective tissue disorders or inflammation.
- Clotting screen - raised fibrinogen, raised prothrombin, raised factor VIII, plasminogen, factor XII.
- Homocysteine levels.
- Investigations for cardiac disease, liver disease, nephrotic syndrome, or other causes of acquired thrombophilia as appropriate.
- Consider occult malignancy and investigate appropriately.
- Consider tests for dysfibrinogenaemia:
  - It is very rare.
  - It should be considered when there is a severe familial thrombotic tendency in the absence of the other heritable thrombophilias mentioned above.
  - Test details are given in 2010 guidelines[^1].

### Management of thrombophilia

See also 'Pregnancy and postnatal' section, below.

### Management of acute VTE

See separate Deep Vein Thrombosis, Pulmonary Embolism and Venous Thromboembolism in Pregnancy articles.

### Minimising VTE risk

See also separate Prevention of Venous Thromboembolism article.

- Patients should be aware of their condition and how to recognise symptoms of VTE.
- Ensure mobility and adequate hydration.
- Extra precautions and short-term thromboprophylaxis may be needed at times of increased risk - eg, surgery, immobility, pregnancy and postnatally.
- Avoid oestrogen-containing contraceptives and HRT:
  - These increase VTE risk (the extent of risk depending on the nature of the thrombophilia) and should generally be avoided.
  - Progestogen-only contraceptives can be used.
- Pre-pregnancy counselling[^15].

**Consider thromboprophylaxis**
The use of short- or long-term anticoagulation should be considered, weighing up the reduction of VTE risk against the risk of serious haemorrhage. This depends on the individual diagnosis and any other medical conditions. Guidelines suggest that, as a general rule:

- All patients with known thrombophilia or previous VTE - consider short-term thromboprophylaxis at times of increased VTE risk.
- Patients with a first VTE event - long-term anticoagulation is not indicated (the risks outweigh the benefits).
- Patients with ≥2 spontaneous VTEs - consider indefinite anticoagulation.
- Patients with recurrent VTEs linked to a provoking factor (e.g., surgery, pregnancy, oestrogen use) may not require long-term anticoagulation but do require prophylaxis during any further high-risk situations.
- Asymptomatic family members found to have a thrombophilic genotype - the risk of long-term anticoagulation outweighs the benefits. Consider short-term prophylaxis to cover periods of high VTE risk.

Pregnancy and postnatal period\cite{15}

**Background**

- Pregnancy and the puerperium confer increased risk of VTE.
- Pulmonary embolism is a leading and often preventable cause of maternal mortality in the UK (although the absolute risk is low).
- The risk begins in the first trimester and is greater postpartum than antenatally, particularly during the first postnatal week.
- Women with thrombophilia have a further increased risk (the magnitude of increased risk depending on the specific diagnosis).

Royal College of Obstetricians and Gynaecologists (RCOG) Green Top Guidelines give detailed guidance for reducing VTE risk in all pregnant and postnatal women, including those with known or suspected thrombophilia or a past/family history of VTE\cite{15}. See the ‘Prevention: prophylaxis’ section in the separate Venous Thromboembolism in Pregnancy article.

**Potential complications of thrombophilia**

- Complications of VTE.
- Complications of anticoagulation, if used.
- Pregnancy complications:
  - Antiphospholipid syndrome is associated with pregnancy loss.
  - Heritable thrombophilia may be linked with pregnancy complications, including an increased risk of late fetal loss, pre-eclampsia and intrauterine growth restriction. However, this remains an area of debate\cite{16,17}.

- Warfarin-induced skin necrosis in patients with protein C or protein S deficiency:
  - This is extremely rare, and may be due to rapid initiation of warfarin in the absence of heparin\cite{1}. See separate Protein C deficiency article.

- Possible association with arterial thrombosis:
  - There may be a link between thrombophilia and arterial thrombosis, although the evidence is limited\cite{18}. As a contributor to arterial disease, thrombophilia is probably less important than the established cardiovascular risk factors\cite{1}.

- Anxiety resulting from thrombophilia testing and results\cite{19}.

**Prognosis\cite{3}**

VTE is a multifactorial disease. The VTE risk depends not only on the specific thrombophilia but also on other factors such as:

- Family history and previous history of VTE.
- The presence of any additional thrombophilia (heritable or acquired).
- Other VTE risk factors (age, immobility, surgery, obesity, hormone use and pregnancy/postpartum states).

VTE risks multiply; for example, the relative risk of VTE for women heterozygous for factor V Leiden is 3-8; however, this increases to 35-50 when taking oestrogen-containing contraception and then to several hundred for homozygous factor V Leiden women taking such contraceptives.

With thrombophilia testing, interpretation of results and predictions about the prognosis are difficult because:

- The incidence of thrombosis in those with heritable thrombophilia is variable - from none to recurrent VTE at an early age.
- Many individuals with heritable thrombophilia diagnosed only by laboratory investigation will not have a thrombotic event.
- Failure to identify a thrombophilic defect on laboratory testing does not prove that no thrombophilia exists.
- Clinicians may overestimate the risk of thrombosis and underestimate the risks of anticoagulation.

Further reading & references

- Guideline for the diagnosis and management of the rare coagulation disorders; A United Kingdom Haemophilia Centre Doctors’ Organization guideline on behalf of the British Committee for Standards in Haematology (Oct. 2014)
Clinical guidelines for testing for heritable thrombophilia; British Committee for Standards in Haematology (January 2010)


Venous thromboembolism in adults admitted to hospital: reducing the risk; NICE Clinical Guideline (January 2010)


Thrombosis and Embolism during Pregnancy and the Puerperium, the Acute Management of; Royal College of Obstetricians and Gynaecologists (April 2015)


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