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[redacted]

Re Official Information Request – Leiden Factor V Test

I refer to your official information request dated 29 June 2019 requesting the following information:

1. **What is the criteria to run the test for Leiden Factor V?**

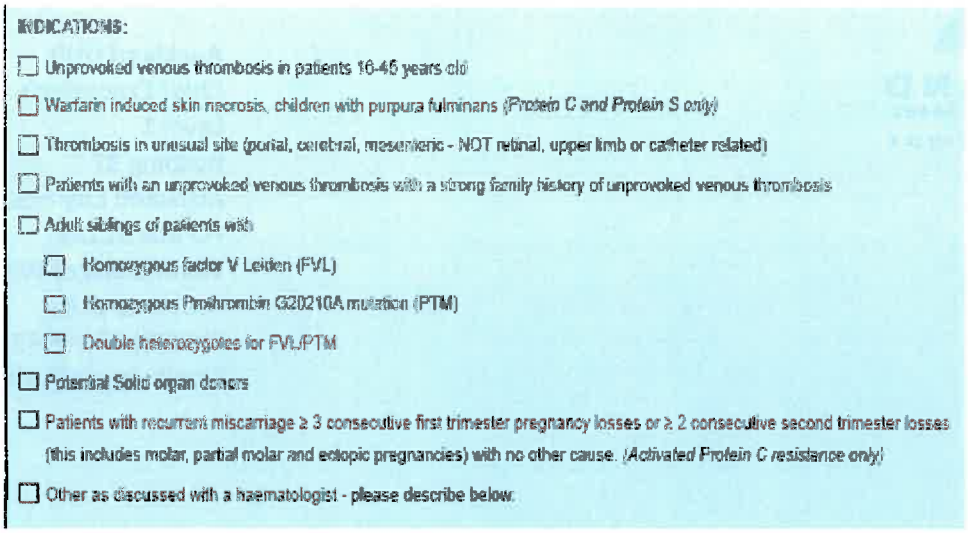
   Factor V Leiden is a point mutation in the Factor V gene which confers activated protein C resistance, meaning that activated Factor V is more resistant to being inactivated in the coagulation cascade. It is found in approximately 5% of Caucasian people. It is the most common of the genetic diagnoses which are commonly referred to as "thrombophilia": genetic causes of an increased tendency to venous thrombosis.

   Although a positive result is therefore common, there are only a limited number of scenarios where a positive result will change the way that a person is treated. These are primarily young patients with a venous thrombosis which is unprovoked, or in some situations where a woman is pregnant or planning pregnancy with a prior history of venous thrombosis.

   For reference, two articles are attached discussing the indications for thrombophilia testing, including factor V Leiden. Auckland City Hospital has not formally implemented these guidelines up to now but will institute them from 1 August 2019. In the meantime, the discretion of clinicians to follow the recommendations is required.

2. **When and why did the Leiden Factor V test criteria change?**

   On 1 August 2019 we will be introducing indications for thrombophilia testing (of which the factor V Leiden is part) to bring us in line with multidisciplinary national and international clinical guidelines. The indications will be:



INDICATIONS:

- ☐ Unprovoked venous thrombosis in patients 16-45 years old
- ☐ Warfarin induced skin necrosis, children with purpura fulminans (*Protein C and Protein S only*)
- ☐ Thrombosis in unusual site (portal, cerebral, mesenteric - NOT retinal, upper limb or catheter related)
- ☐ Patients with an unprovoked venous thrombosis with a strong family history of unprovoked venous thrombosis
- ☐ Adult siblings of patients with
  - ☐ Homozygous factor V Leiden (FVL)
  - ☐ Homozygous Prothrombin G20210A mutation (PTM)
  - ☐ Double heterozygotes for FVL/PTM
- ☐ Potential Solid organ donors
- ☐ Patients with recurrent miscarriage ≥ 3 consecutive first trimester pregnancy losses or ≥ 2 consecutive second trimester losses (this includes molar, partial molar and ectopic pregnancies) with no other cause. (*Activated Protein C resistance only*)
- ☐ Other as discussed with a haematologist - please describe below:

Please note the Factor V Leiden test would only be performed if the activated protein C resistance was abnormal (screening).

3. **How much money does it cost to run the test for Leiden Factor V?**

   The cost of the factor V Leiden test is approximately $100.

4. **In the past five years, how many of your patients have had blood samples taken for the Leiden Factor V test?**

   We have received 3325 samples for molecular testing for factor V Leiden over the last five years (this includes both community and hospital requests from our region).

5. **Out of those samples taken (as per the above question) how many have tested positive, how many have tested negative, and how many have not been processed?**

   Of those tested, 606 were heterozygous (mutation present on one allele) and 23 homozygous (mutation present on both alleles), the rest were normal (no mutation identified), we tested them all.

You are entitled to seek a review of the response by the Ombudsman under section 28(3) of the Official Information Act. Information about how to make a complaint is available at www.ombudsman.parliament.nz or freephone 0800 802 602.

Please note that this response, or an edited version of this response, may be published on the Auckland DHB website.

Yours faithfully

Ailsa Claire, OBE
Chief Executive

bjh guideline

Clinical guidelines for testing for heritable thrombophilia

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Introduction and methodology

The guideline group was selected to be representative of UK-based medical experts. The writing group met and communicated by email. The guideline was reviewed by a multidisciplinary sounding board, selected non-UK experts in thrombosis and thrombophilia, the British Committee for Standards in Haematology (BCSH) and the British Society for Haematology) (BSH and comments incorporated where appropriate. Criteria used to quote levels and grades of evidence are according to the GRADE system (Guyatt *et al*, 2006). As this guideline relates specifically to laboratory tests, reference is made to grading quality of evidence and strength of recommendations for diagnostic tests and strategies recognising that tests are only of value if they result in improved outcomes for patients (Schunemann *et al*, 2008). Strong recommendations (grade 1, 'recommended') are made when there is confidence that the benefits either do or do not outweigh the harm and burden and costs of treatment. Where the magnitude of benefit or not is less certain, a weaker grade 2 recommendation ('suggested') is made. Grade 1 recommendations can be applied uniformly to most patients whereas grade 2 recommendations require judicious application. The quality of evidence is graded as A (high quality randomised clinical trials), moderate (B) or low (C) (Guyatt *et al*, 2006; www.bcshguidelines.com).

The target audience for this guideline is healthcare professionals involved in the management of patients and families with venous thrombosis or pregnancy morbidity.

Summary of recommendations for testing for heritable thrombophilia

The summary recommendation of this guideline is that testing for heritable thrombophilias is not indicated in unselected patients presenting with venous thrombosis. Testing selected patients may give an indication of risk of recurrence following completion of anticoagulant therapy, for example those presenting with venous thrombosis at an early age (<40 years) and who are from apparent thrombosis-prone families (more than two other symptomatic family members). Analysis of the large Multiple Environmental and Genetic Assessment (MEGA) study showed that testing for inherited thrombophilia did not reduce recurrence of venous thrombosis (Coppens *et al*, 2008).

Other selected patient groups in whom the results of testing may influence treatment are children with purpura fulminans

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and 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.

- Initiation and intensity of anticoagulant therapy following a diagnosis of acute venous thrombosis should be the same in patients with and without heritable thrombophilia (1B).
- Indiscriminate testing for heritable thrombophilias in unselected patients presenting with a first episode of venous thrombosis is not indicated (1B).
- 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 (1B).
- Testing for heritable thrombophilias in selected patients, such as those with a strong family history of unprovoked recurrent thrombosis, may influence decisions regarding duration of anticoagulation (C). It is not possible to give a validated recommendation as to how such patients should be selected.
- Testing is not recommended in unselected patients with upper limb venous thrombosis (1B).
- Testing is not recommended in patients with central venous catheter (CVC)-related thrombosis (1C).
- Testing for heritable thrombophilia after a first episode of cerebral vein thrombosis (CVT) has uncertain predictive value for recurrence (C). Decisions regarding duration of anticoagulant therapy in relation to the results of testing are not evidence-based.
- Testing is not indicated in patients with retinal vein occlusion (1B).
- Testing for heritable thrombophilia after a first episode of intra-abdominal vein thrombosis has uncertain predictive value for recurrence (C). Decisions regarding duration of anticoagulant therapy in relation to the results of testing are not evidence-based.
- Neonates and children with purpura fulminans should be tested urgently for protein C and S deficiency (1B).
- A variety of functional methods may be required to identify specific severe type 2 functional defects when levels of protein C or S are not <5% (1B).
- It is suggested that adults who develop skin necrosis in association with oral vitamin K antagonists (VKAs) are tested for protein C and S deficiency after VKA treatment is withdrawn (2B).
- Case finding of asymptomatic relatives with low risk thrombophilia, such as *F5*G1691A (FVR506Q, factor V Leiden) or *F2*G20210A, is not indicated (1B).
- 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 (1B). 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.
- Case finding for very rare homozygosity or compound heterozygous 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 (2C).
- If a first-degree relative with venous thrombosis has not been tested then suggest that women consider an alternative contraceptive or transdermal hormone replacement therapy (HRT). Testing for heritable thrombophilia will provide an uncertain estimate of risk and is not recommended (1C).
- If a first-degree relative with venous thrombosis has been tested and the result is negative then suggest that a woman considers an alternative contraceptive or transdermal HRT. Testing for heritable thrombophilia will provide an uncertain estimate of risk and is not recommended (1C).
- If a first-degree relative with venous thrombosis has been tested and the result is positive then suggest that women consider 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 (C).
- Women should be assessed for risk of pregnancy-associated venous thrombosis primarily in relation to clinical risk factors (1B).
- Most pregnant women with a previous unprovoked venous thrombosis (1B) or pregnancy or combined oral contraceptive (COC)-related thrombosis (2C) will qualify for thromboprophylaxis on clinical risk alone and so testing for heritable thrombophilia is not required.
- Pregnant women with a previous event due to a major provoking factor, e.g. surgery or major trauma, would not usually require prophylaxis or testing (2B).
- Pregnant 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 (2C).
- In the asymptomatic pregnant woman with a family history of venous thrombosis, testing is not required if the clinical risks alone are sufficient to result in thromboprophylaxis (2C).
- It is suggested that asymptomatic pregnant 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 (2C). The result will be more informative if the first-degree relative has a known thrombophilia.
- Antithrombotic therapy should not be given to pregnant women with a history of pregnancy complications based on testing for heritable thrombophilia. Randomised controlled trials with a no-treatment or placebo arm in women with a history of pregnancy complications are in progress. If these

studies indicate a benefit in women with pregnancy complications and heritable thrombophilia, as compared with women without thrombophilia, only then 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.
- Testing asymptomatic women before assisted conception and those with ovarian hyperstimulation syndrome is not indicated (1B).
- Thrombophilia screening of hospitalised patients to identify patients at risk of hospital-acquired venous thrombosis is not indicated (1A).
- All hospitalised patients should be assessed for risk of venous thrombosis regardless of heritable thrombophilia based on a clinical risk assessment (1B). The presence of a previously known heritable thrombophilia may influence the assessment of risk.
- Testing for heritable thrombophilia is not indicated in patients with arterial thrombosis (1B).
- It is suggested that testing for heritable thrombophilia is not indicated in children with stroke (2C).

(Recommendations for laboratory practice are given toward the end of the document under the section on laboratory methodology and testing strategy).

The scope of the guideline and the concept of heritable thrombophilia as a risk factor for venous thrombosis

Heritable thrombophilia describes an inherited tendency for venous thrombosis (deep vein thrombosis, DVT, with or without associated pulmonary embolus, PE). Deficiency of the natural anticoagulant antithrombin was the first reported inherited risk factor for venous thromboembolism (Egeberg, 1965). Since then, deficiencies of the naturally occurring anticoagulants protein C (Griffin *et al*, 1981) and protein S (Comp *et al*, 1984) have been linked with familial venous thrombosis. In recent years, several other potential thrombophilic risk factors have been investigated but only the *F5*G1691A (FVR506Q, factor V Leiden) (Bertina *et al*, 1994) and the *F2*G20210A (Poort *et al*, 1996) gene mutations have been shown to be unequivocally associated with an increased risk of venous thrombosis (Reitsma & Rosendaal, 2007), i.e. odds ratio of 2 or greater. In the 1980s and 1990s thrombophilia testing became common in unselected patients and their relatives despite the fact that there was no evidence that testing had clinical utility. It is now apparent that testing for heritable thrombophilia typically does not predict likelihood of recurrence in unselected patients with symptomatic venous thrombosis (Baglin *et al*, 2003; Christiansen *et al*, 2005) and testing for inherited thrombophilia did not reduce recurrence of venous thrombosis in a large cohort study (Coppens *et al*, 2008). There is a low risk of thrombosis in affected asymptomatic relatives followed prospectively (Langlois & Wells, 2003) and the results of thrombophilia tests are frequently misinterpreted (Jennings *et al*, 2005).

The aim of this guideline is to provide recommendations to clinicians in relation to testing for heritable thrombophilia in the context of clinical management of venous thrombosis and pregnancy morbidity. This guideline is restricted to heritable thrombophilias shown to be associated with at least a two-fold increased risk of venous thrombosis, namely deficiencies of antithrombin, protein C and protein S due to mutations in the corresponding genes *SERPINC1, PROC, PROS1* and the two common mutations *F5*G1691A (FV R506Q, factor V Leiden) and *F2*G20210A (commonly referred to as the prothrombin gene mutation).

Since the publication of the previous BCSH (British Committee for Standards in Haematology) guideline 'Investigation and Management of Heritable Thrombophilia' in 2001 no randomised studies of treatment in relation to heritable thrombophilia have been published. A review of the clinical utility of thrombophilia testing was published in 2008 (Middeldorp & van Hylckama Vlieg, 2008) and several systematic reviews of the association of heritable thrombophilias with specific conditions have been published but the clinical utility of testing has not been assessed in these reviews.

Clinical utility

In situations where the clinical utility of testing is unproven, testing is clearly not mandatory (clinical utility defined as the ability of a test to influence or alter clinical outcome). However, many clinicians have used thrombophilia test results to determine clinical management. An example of this is the management of women at risk of pregnancy-associated venous thrombosis. The 2001 BCSH guideline classified pregnancy-associated venous thrombosis risk on the basis of thrombophilia test results and so testing was necessary in order to follow the guidance. However, all the recommendations were opinion-based on low quality evidence. It is unlikely that randomised studies would address the issue of risk of pregnancy-associated venous thrombosis and so guidance is given in this guideline recognising that there is only low level evidence and that careful assessment of clinical risk factors is required in all cases.

Definition of thrombophilic families and thrombosis-prone families

Criteria for defining thrombosis-prone families have not been validated. The association between family history of venous thrombosis and detection of inherited thrombophilia is weak (van Sluis *et al*, 2006). In addition, a family history of venous thrombosis is not a risk factor for recurrent venous thrombosis if patients with antithrombin, protein C or protein S deficiency are excluded (Hron *et al*, 2006). The influence of family history on recurrence risk in patients with deficiency of antithrombin, protein C or protein S requires study.

Treatment of lower limb deep vein thrombosis (DVT) and pulmonary embolus (PE)

There is no evidence that heritable thrombophilia should influence the intensity of anticoagulation with heparin or VKAs. In a review of 70 thrombotic events in 57 individuals with antithrombin deficiency, heparin resistance was infrequent and recurrence or extension of thrombosis while on treatment was no greater than ordinarily expected in patients treated for venous thrombosis (Schulman & Tengborn, 1992). Coumarin-induced skin necrosis is extremely rare, even in patients with protein C or S deficiency, such that most individuals with protein C or S deficiency do not develop skin necrosis; there is no indication that initiation of oral anticoagulant treatment whilst patients are receiving heparin should be different in patients known to have protein C or S deficiency. The intensity of maintenance therapy with warfarin should not be influenced by laboratory evidence of inherited thrombophilia. There is no evidence that recurrence on oral VKA treatment is more likely in patients with heritable thrombophilia (Kearon *et al*, 2008a).

Recommendation

- **Initiation and intensity of anticoagulant therapy following a diagnosis of acute venous thrombosis should be the same in patients with and without heritable thrombophilia (1B).**

Long-term prospective cohort outcome studies have shown that finding a heritable thrombophilia does not typically predict recurrence (Baglin *et al*, 2003; Christiansen *et al*, 2005). An analysis of the MEGA study showed that testing for inherited thrombophilia did not reduce recurrence of venous thrombosis (Coppens *et al*, 2008). Systematic reviews of the risk of recurrent venous thromboembolism in patients heterozygous for the *F5*G1691A mutation indicate a risk of 1·4 and for the *F2*G20210A 1·2–1·7 (Ho *et al*, 2006; Marchiori *et al*, 2007). The authors concluded that the magnitude of the increase in risk was modest and by itself did not justify an extended duration of anticoagulation. In patients with deficiency of a natural anticoagulant (antithrombin, protein C, protein S deficiency) the risk of recurrence is uncertain but relative risks of recurrence appear to be <2·0 in patients who are not selected from thrombosis-prone families (Baglin *et al*, 2003; Christiansen *et al*, 2005; De Stefano *et al*, 2006a). In a retrospective analysis of patients selected on the basis of young age at time of first venous thrombosis and a family history of venous thrombosis, detection of deficiency of a natural anticoagulant predicted a risk of recurrence of 6·23%, compared to 2·25% in patients with *F5*G1691A or *F2*G20210A. Over a 10-year period this translated into a cumulative risk of recurrence of 55% (Lijfering *et al*, 2009). However, it is unclear what selection strategy would, in practice, enable identification of high-risk patients with thrombophilia. Furthermore, high-risk patients may be identified by clinical risk assessment alone, or possibly in association with tests of coagulability, such as D-dimer (Verhovsek *et al*, 2008). In principle, the duration of anticoagulant therapy should be determined by a clinical assessment of risk and benefit after an initial period of anticoagulant therapy (Kearon *et al*, 2008b). In the majority of patients this assessment will not require, or be informed by, testing for heritable thrombophilia.

Recommendation

- **Indiscriminate testing for heritable thrombophilia in unselected patients presenting with a first episode of venous thrombosis is not indicated (1B).**
- **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 (1B).**
- **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 (C). It is not possible to give a validated recommendation as to how such patients should be selected.**

Treatment of upper limb DVT

More than 60% of episodes of upper limb DVT are associated with central venous catheters (CVC) (Spencer *et al*, 2007), with CVCs and cancer being the predominant risk factors (Munoz *et al*, 2008). Thoracic outlet syndrome is less common. Heritable thrombophilias are found in one-third of patients without these factors and there is an interaction between common thrombophilias and oral contraceptive exposure (Martinelli *et al*, 2004). The risk of recurrence is either not higher or marginally higher in patients with heritable thrombophilias but the absolute risk of recurrence in the presence of thrombophilia is <5% per year and 80% of patients are recurrence-free 5 years after stopping anticoagulant therapy (Martinelli *et al*, 2004; Flinterman *et al*, 2008). One study demonstrated an increased risk of CVC-related thrombosis in patients with thrombophilia but the study was small and it is uncertain how treatment would be altered by knowledge of a defect in this situation.

Recommendation

- **Testing is not recommended in unselected patients with upper limb venous thrombosis (1B).**
- **Testing is not recommended in patients with CVC-related venous thrombosis (1C).**

Treatment of cerebral vein (sinus) thrombosis (CVT)

There is an association between thrombophilia and cerebral vein thrombosis with an interaction between common thrombophilias, particularly *F2*G20210A, and oral contraceptive use (Dentali *et al*, 2006; Wasay *et al*, 2008). Overall the risk of recurrence of CVT is lower than previously thought, affecting 2% to 3% of adults (Ferro *et al*, 2004). However, recurrence may be underestimated due to continuation of anticoagulant therapy in those patients thought to be at high risk. A study in children identified the *F2*G20210A mutation as an independent risk factor for recurrence (hazard ratio 4·1). It has become common practice to test patients for heritable thrombophilia after CVT and some experts continue anticoagulation lifelong if there is a thrombophilic defect. In all patients acquired risks should be removed or minimised, e.g. COC or HRT use, obesity.

Recommendation

- **Testing for heritable thrombophilias after a first episode of CVT has uncertain predictive value for recurrence (C). Decisions regarding duration of anticoagulant therapy in relation to the results of testing are not evidence-based.**

Retinal vein thrombosis

Retinal vein occlusion is associated with hypertension, hypercholesterolaemia and diabetes. An initial meta-analysis did not identify a statistically significant relationship with heritable thrombophilia but suggested that *F5*G1691A (OR 1·5) and *F2*G20210A (OR 1·6) mutations might be weak risk factors (Janssen *et al*, 2005). A more recent analysis confirmed an odds ratio of 1·5 for *F5*G1691A indicating a much weaker association than with lower limb DVT (Rehak *et al*, 2008). It is uncertain to what degree hypercoagulability is a material contributory factor in this condition and the risk of recurrence is low. Furthermore, there is no evidence that anticoagulant therapy is beneficial. Therefore, it is not recommended that decisions regarding treatment are made in relation to the results of testing for heritable thrombophilia.

Recommendation

- **Testing is not indicated in patients with retinal vein occlusion (1B).**

Intra-abdominal vein thrombosis

Myeloproliferative disorders, cirrhosis and surgery are strong risk factors for intra-abdominal venous thrombosis. The acquired *JAK2* V617F mutation is a risk factor even in the absence of an overt myeloproliferative disorder, being found in 17% of cases (Austin & Lambert, 2008). A meta-analysis of 12 studies of portal vein thrombosis found an odds ratio of 1·9 (1·2–2·9) for *F5*G1691A and 4·5 (3·1–6·5) for *F2*G20210A (Dentali *et al*, 2008). No studies have investigated how the finding of a heritable thrombophilia should influence management.

Recommendation

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

Purpura fulminans

Purpura fulminans is a rare syndrome characterised by progressive haemorrhagic skin necrosis that occurs in neonates with congenital severe protein C deficiency at birth or in the first few days of life, and rarely in association with infection in children and adults. The condition may occur in children without inherited anticoagulant deficiency following viral infection with an onset within 10 d of infection. Acquired severe protein S deficiency has been reported in purpura fulminans following chicken pox infection and is associated with a high morbidity and mortality without urgent treatment. With bacterial infections disseminated intravascular coagulation (DIC) is often present, for example in meningococcal infection. In patients with DIC or purpura fulminans due to sepsis, treatment with activated protein C should be considered. In patients with very severe skin necrosis testing for acquired protein C or S should be considered, as plasma exchange may be beneficial.

Neonates homozygous for protein C or S deficiency may be born with skin necrosis or DIC. Patients may be compound heterozygotes with a mixture of type 1 and 2 defects and so it may be necessary to perform different functional assays as well as antigen measurement to confirm almost complete deficiency. For example, a defect in the Gla-domain of protein C will not be detected by a chromogenic assay. Expert advice on testing should be obtained in all suspected cases. Patients heterozygous for protein C or protein S deficiency may develop skin necrosis when treated with oral VKAs but this is very rare and may be due to rapid initiation of anticoagulation in the absence of heparin.

Recommendation

- **Neonates and children with purpura fulminans should be tested urgently for protein C and S deficiency (1B).**
- **A variety of functional methods may be required to identify specific severe type 2 functional defects when levels of protein C or S are not <5% (1B).**

- **It is suggested that adults who develop skin necrosis in association with oral VKAs are tested for protein C and S deficiency when VKA treatment is withdrawn (2B).**

Case finding as a means to prevent venous thrombosis in asymptomatic relatives of patients with a history of venous thrombosis

It has been suggested that testing for heritable thrombophilia in patients presenting with venous thrombosis allows case-finding of affected asymptomatic family members. The rationale is that this permits avoidance of environmental risks (such as use of combined oral contraceptive pills by females) or provides an opportunity for targeted thrombophylaxis at times of unavoidable high risk (such as surgery). However, individual risk is affected by multiple genetic and environmental factors, which will be different even amongst first-degree relatives. Four prospective cohort studies determined the annual risk of venous thrombosis in asymptomatic family members identified by testing unselected patients presenting with venous thrombosis (Pabinger *et al*, 1994; Sanson *et al*, 1999; Middeldorp *et al*, 2001; Simioni *et al*, 2002). These studies were included in a meta-analysis published in 2003 (Langlois & Wells, 2003). The studies included 3641 patient-years of observation. In the prospective studies the annual risk of venous thrombosis in asymptomatic family relatives of index patients was 0·6% for those with *F5*G1691A, 1·0–2·5% for protein C deficiency, 0·7–2·2% for protein S deficiency and 4% for antithrombin deficiency (Langlois & Wells, 2003). High risk periods contributed to approximately half of all events (provoked occurence) in patients with *F5*G1691A and thromboprophylaxis appeared to reduce risk. In a further prospective follow up of asymptomatic relatives with the *F2*G20210A mutation the annual incidence of venous thrombosis was 0·11% in carriers and 0·07% in non-carriers, a difference that was not significant (Tormene *et al*, 2004). In a prospective cohort study of asymptomatic carriers of deficiency of antithrombin, protein C or protein S the annual incidence of venous thrombosis was 1·5% [95% confidence interval (CI) 0·7–2·8] with approximately half being provoked with an incidence of 10% per period of acquired risk (Sanson *et al*, 1999). In summary, case finding of asymptomatic relatives of patients with venous thrombosis has not been shown to reduce the incidence of venous thrombosis and the annual risk of unprovoked thrombosis in affected family members is low.

In the European Prospective Cohort on Thrombophilia (EPCOT) registry patients were referred to specialist centres for thrombophilia testing if they had a personal or family history of venous thrombosis. The incidence of venous thrombosis on study entry was determined retrospectively in asymptomatic relatives. The risk of venous thrombosis was 16-times higher in affected relatives, with the greatest risk in relatives of patients with deficiency of a natural anticoagulant or multiple defects (Vossen *et al*, 2004). In a subsequent prospective follow-up over an average of nearly 6 years, 4·5% of 575 asymptomatic carriers suffered a first episode of venous thrombosis, compared to 0·6% in a control population. Nearly 60% of the episodes were unprovoked (Vossen *et al*, 2005). The incidence was 0·8% per year in carriers and 0·1% per year in controls. The highest incidence was in individuals with antithrombin deficiency (1·7% per year) or combined defects (1·6% per year).

In a separate study of families with type 1 antithrombin deficiency the incidence of venous thrombosis was 20-times greater in affected family members but was strongly dependent on acquired risks (van Boven *et al*, 1999). In this study the annual incidence of venous thrombosis in affected family members in any year in which they were exposed to surgery, trauma, plaster cast, hospitalisation or immobilisation was 20·3% but in any year in which there was no exposure the incidence of unprovoked venous thrombosis was only 0.3%, which is only slightly higher than the background 0·15% in an unselected general population (Naess *et al*, 2007). Targeted case-finding of relatives with 'severe' or 'high risk' thrombophilia, such as deficiency of antithrombin, protein C or protein S, has been suggested (De Stefano, 2004; Spencer & Goldberg, 2005) although there is still no evidence to support the clinical utility of such an approach and the issue remains contentious.

Given the uncertainty, some experts argue that it is reasonable to perform testing if it is anticipated that clinical management will be influenced, for example an intensified or extended period of prophylaxis during a high risk period. If a family history suggests a high degree of genetic penetrance then it might be reasonable to test a symptomatic patient and then their relatives, with a view to enhanced prophylaxis at times of high risk in affected members. For example in thromboprophylaxis in pregnancy when there is a family history of pregnancy-associated venous thrombosis, or intensified or extended surgical thromboprophylaxis when there is a history of thromboprophylaxis failure in affected members. In all cases the risks, benefits and limitations of testing should be discussed in the context of explained inheritance and disease risk (Varga, 2008). The importance of this is demonstrated by reported anxiety after testing positive (Hellmann *et al*, 2003; Bank *et al*, 2004; Cohn *et al*, 2008) and an overestimated perception of risk (Hellmann *et al*, 2003). At present the cost effectiveness of case-finding in thrombosis-prone families has not been demonstrated. Simple methods for quantifying a positive family history do not discriminate patients with and without thrombophilia and therefore the decision to test for inherited thrombophilia cannot be accurately guided by the presence or absence of a family history.

Recommendation

- **Case finding of asymptomatic relatives with low risk thrombophilia, such as *F5*G1691A or *F2*G20210A, is not indicated (1B).**

- **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 (1B). 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.**
- **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 (2C).**

Prevention of venous thrombosis associated with oestrogen-containing hormone preparations

In some women heritable thrombophilia has already been established whilst in others it is perceived that testing would enable informed decision making regarding use of a COC or HRT. However, the absolute risk of thrombosis is low and the fact that venous thrombosis has a polygenic basis with incomplete penetrance makes counselling in relation to genetic testing uncertain (Baglin, 2009). In many instances an alternative effective contraceptive is acceptable. Similar principles apply to HRT, although the baseline risk is higher as the population is older. Rarely is there a therapeutic indication for HRT and in most instances there is only a weak indication. If HRT is considered essential then non-oral formulations are associated with a significantly lower risk of venous thrombosis (Canonico *et al*, 2008). Of all the scenarios in which thrombophilia screening might be employed in decision making, a model for screening unselected women before prescribing oral HRT was calculated as the most cost-effective (Wu *et al*, 2005). A cost-effective model has also been reported for testing female relatives of *F5*G1691A carriers before prescribing oral contraceptives (Smith *et al*, 2008). However, the models rely on assumptions such as all women testing positive will not take a COC or HRT and that episodes of venous thrombosis are attributable to these low risk thrombophilias. Screening has not been implemented in the UK.

A first-degree relative with a history of venous thrombosis is a relative contraindication to an oestrogen-containing hormonal preparation. The risk is dependent on the circumstances of thrombosis in the relative. For example, a history of an elderly relative who developed venous thrombosis as a complication of cancer is not a contraindication. In contrast, a relative with unprovoked venous thrombosis, or specifically a sibling developing venous thrombosis whilst taking a COC, should be considered a strong contraindication. In families with known heritable thrombophilias, the risk of venous thrombosis can be increased in unaffected members as well as affected and so a negative thrombophilia result does not exclude an increased risk of venous thrombosis. Therefore, decisions regarding use of oestrogen-containing hormonal preparations and whether thrombophilia testing is likely to be informative should be made with reference to individual clinical risk factors and the circumstances associated with venous thrombosis in the family.

Recommendation

- **If a first-degree relative with venous thrombosis has not been tested 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 (1C).**
- **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 (1C).**
- **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 (C).**

Prevention of pregnancy-associated venous thrombosis

Reference to Green-top Guideline 37 from the Royal College of Obstetricians and Gynaecologists is recommended (Royal College of Obstetricians and Gynaecologists, 2004).

Pregnancy is associated with a 5- to 10-fold increased risk of venous thrombosis compared to non-pregnant women of comparable age with an absolute risk of 1 to 2 per 1000 deliveries (James *et al*, 2006). The risk of venous thrombosis, compared to the general age-matched female population, is increased 100-fold in pregnancy in women with a previous thrombosis (De Stefano *et al*, 2006b). From an analysis of International Classification of Diseases (ICD) codes from almost 1 million pregnancy admissions in the USA the greatest risk factors for pregnancy-associated venous thrombosis were thrombophilia [odds ratio (OR) 52] and a history of thrombosis (OR 25) (James *et al*, 2006). However, details of thrombophilic conditions and accuracy of classification were not available. In contrast, in a retrospective study of women with previous venous thrombosis for whom detailed information on the thrombophilia was available, the rate of recurrence was similar in women with and without thrombophilia, but only eight women had high risk thrombophilias (anticoagulant deficiency, multiple defects) (De Stefano *et al*, 2006b). In this

study 88 women with a single episode of venous thrombosis became pregnant and did not receive thromboprophylaxis during 155 pregnancies. Thrombophilias were found in 40%. Venous thrombosis occurred in 12% of pregnancies. Recurrences did not occur in women whose initial event was provoked, a very similar finding to a previous study (Brill-Edwards *et al*, 2000). In a study of women with deficiency of antithrombin, protein C or protein S from families identified from testing consecutive patients with venous thrombosis the risk of pregnancy-associated venous thrombosis was determined retrospectively, after exclusion of the probands (Folkeringa *et al*, 2007). 29 of 101 (29%) deficient women and 5 of 121 (4%) non-deficient women had suffered venous thrombosis before 45 years of age. 7% of pregnancies in deficient women were complicated by venous thrombosis compared with 0·4% of pregnancies in non-deficient women.

In a systematic review of nine studies comprising 2526 pregnancies, considering all thrombophilias there was an associated increased risk of pregnancy-related venous thrombosis in those with thrombophilia (Robertson *et al*, 2006). The risk was greatest in *F5*G1691A homozygotes (OR 34, 95% CI 9–120) and *F2*G20210A homozygotes (OR 26, 95% CI 1–559) but remained significant in women who were heterozygous for the *F5*G1691A (OR 8, 95% CI 5 to12) or for the *F2*G20210A mutation (OR 6·8, 95% CI 2–18). The risk of pregnancy-related venous thrombosis in women with antithrombin deficiency was moderately increased (OR 4·6, 95% CI 1·3–17) and similarly for protein C deficiency (OR 4·8, 95% CI 2–10) and protein S deficiency (OR 3·2, 95% CI 1–7). Absolute risks as opposed to relative risks were not reported.

In general, the absolute risk of pregnancy-associated venous thrombosis in women with heritable thrombophilia with no previous history is small but women with antithrombin deficiency or those homozygous for the *F5*G1691A or the *F2*G20210A mutations or who are double heterozygotes should be regarded as being at higher risk. The number of women with these defects is very small.

In women with a previous history of venous thrombosis the major factor in determining whether prophylaxis should be given is if prior venous thrombosis was provoked or not. If the episode was unprovoked, prophylaxis should be considered and thrombophilia testing is not required if prophylaxis is given. In women with a first provoked event the decision to test or not should be influenced by the strength of the provocation, for example venous thrombosis associated with major trauma and subsequent immobility would not be an indication for prophylaxis or testing. In women with a first-degree relative with thrombosis the decision to test should be influenced by whether or not the event in the relative was unprovoked or provoked and the strength of the provocation. If the event in the first-degree relative was pregnancy or COC-associated, then testing and finding thrombophilia should prompt consideration of prophylaxis, particularly if the symptomatic relative was known to have the same defect, particularly deficiency of antithrombin or protein C. When testing in pregnancy it is necessary to interpret the results with reference to the effect of pregnancy on the tests.

Recommendation

- **Women should be assessed for risk of pregnancy-associated venous thrombosis primarily in relation to clinical risk factors (1B).**
- **Most women with a previous unprovoked venous thrombosis (1B) or pregnancy or COC-related thrombosis (2C) will qualify for thrombophylaxis on clinical risk alone and so testing for heritable thrombophilia is not required.**
- **Women with a previous event due to a major provoking factor, e.g. surgery or major trauma, would not usually require prophylaxis or testing (2B).**
- **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 (2C).**
- **In the asymptomatic woman with a family history of venous thrombosis testing is not required if the clinical risks alone are sufficient to result in thromboprophylaxis (2C).**
- **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 (2C). The result will be more informative if the first-degree relative has a known thrombophilia.**

Pregnancy morbidity

There is evidence of an association between heritable thrombophilia and pregnancy morbidity including early and late pregnancy loss, pre-eclampsia and intra-uterine growth restriction (Rey *et al*, 2003; Dudding & Attia, 2004; Robertson *et al*, 2006; Chan & Dixon, 2008). Therapeutic decisions should be based on clinical circumstances and not on the results of thrombophilia testing. For example, in the case of the older woman (e.g. aged >35 years) with a poor obstetric history a decision to treat with low dose heparin should not be determined by the results of testing for heritable thrombophilia.

Recommendation

- **Antithrombotic therapy should not be given to pregnant women based on tests for heritable thrombophilia. Randomised controlled trials with a no treatment or placebo arm in women with a history of pregnancy complications are in progress. If these studies indicate a benefit in women with pregnancy complications and heritable thrombophilia, as compared with women without thrombophilia, only then 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.**

Assisted conception and ovarian hyperstimulation syndrome

Ovarian hyperstimulation is associated with an increased risk of venous and arterial thrombosis. However, the overall risk of venous thrombosis in these women is small and estimated to be 0·1% per treatment cycle (Chan & Dixon, 2008), a similar incidence to that of pregnancy-associated venous thrombosis. Women who develop venous thrombosis in association with ovarian hyperstimulation frequently present with upper limb or internal jugular vein thrombosis for reasons that are unknown. The prevalence of thrombophilia is not increased in women with severe hyperstimulation syndrome. As the incidence of the condition is so low the predictive value of thrombophilia testing would be very low and testing should not be used to influence antithrombotic strategies in women commencing ovarian stimulation.

Recommendation

- **Testing asymptomatic women before assisted conception and those with ovarian hyperstimulation syndrome is not indicated (1B).**

Prevention of venous thrombosis in hospitalised patients

Thromboprophylaxis for hospitalised patients should be in accordance with a structured risk assessment based on procedural and personal risk factors for venous thrombosis. Screening for heritable thrombophilia is not indicated although a previously identified heritable thrombophilia may influence the assessment of risk.

Recommendation

- **Thrombophilia screening of hospitalised patients to identify patients at risk of hospital-acquired venous thrombosis is not indicated (1A).**
- **All hospitalised patients should be assessed for risk of venous thrombosis regardless of heritable thrombophilia based on a clinical risk assessment (1B). The presence of a previously known heritable thrombophilia may influence the assessment of risk.**

Coronary, cerebral and peripheral arterial thrombosis

Evidence of an association between heritable thrombophilia and arterial thrombosis is limited to case reports and small studies (Middeldorp & van Hylckama Vlieg, 2008). It is possible that heritable defects that result in increased coagulability increase the likelihood of atherothrombosis (Vossen & Rosendaal, 2006), particularly as there is an association between arterial and venous thrombosis risk (Prandoni *et al*, 2003). In patients presenting with venous thrombosis before the age of 40 years there is an increased risk of acute myocardial infarction (Spencer *et al*, 2008). However, the material contribution of heritable thrombophilia, as compared with established cardiovascular risk factors, is not sufficient to change therapy for primary and secondary prevention. Despite this, young patients are sometimes tested after an arterial occlusive event (Coppens *et al*, 2007). As there is no established causal relationship and as treatment and secondary prevention should be in relation to established cardiovascular risk factors, thrombophilia testing is not recommended.

Recommendation

- **Testing for heritable thrombophilia is not indicated in patients with arterial thrombosis (1B).**

Paediatric stroke

Testing may identify a material contributory factor but does not typically inform management decisions. For example, anticoagulant therapy is not usually considered and in many children there may be a significant time before a neurological deficit is recognised or the cause of stroke determined, particularly stroke occurring in the perinatal period.

Recommendation

- **It is suggested that testing for heritable thrombophilia is not indicated in children with stroke (2C).**

Laboratory methodology and testing strategy

Recommendations for laboratory practice remain relatively unchanged (British Committee for Standards in Haematology 2001). Functional assays should be used where accuracy and imprecision are acceptable. However, no single method will detect all defects. For example, a protein C chromogenic assay will not detect a dysfunctional protein C molecule with impaired phospholipid binding due to a mutation in the Gla domain. Whilst, a clot-based protein C assay would be sensitive to this defect the imprecision of the assay would result in reduced sensitivity for other defects, as compared to a chromogenic assay. Similarly the performance of antithrombin assays will be influenced by heparin and the pre-incubation time with heparin as well as the source of thrombin and the endpoint detection method employed. For example an assay utilising a short heparin incubation time will detect heparin binding site defects, which may not be associated with an appreciable increased risk of venous thrombosis.

Even in families with characterised defects a phenotypic assay may fail to accurately discriminate affected and non-affected individuals (Allaart *et al*, 1993). The interpretation of

thrombophilia test results is difficult and errors in interpretation are frequent, which results in both reduced sensitivity and specificity (Jennings *et al*, 2005). Thus, genuine deficiencies and abnormalities may not be detected and false positive diagnoses are common.

Familial thrombosis due to dysfibrinogenaemia is very rare. This diagnosis should be considered when there is a severe familial thrombotic tendency in the absence of one of the five heritable thrombophilias covered by this guideline. Functional and antigenic levels of fibrinogen, thrombin time and reptilase and ancrod times will detect the majority of patients with abnormal fibrinogens. Dysfibrinogenaemia is indicated by disparity between functional and antigenic levels, while the pattern of clotting time results varies depending on the type of defect.

Recommendations for laboratory tests and interpretation

- **Testing at the time of acute venous thrombosis is not indicated as the utility and implications of testing need to be considered and the patient needs to be counselled before testing. As treatment of acute venous thrombosis is not influenced by test results, testing can be performed later if indicated.**
- **The prothrombin time (PT) should be measured to detect the effect of oral VKAs, which will cause a reduction in protein C and S levels.**
- **Functional assays should be used to determine antithrombin and protein C levels.**
- **Chromogenic assays of protein C activity are less subject to interference than clotting assays and are preferable.**
- **Immunoreactive assays of free protein S antigen are preferable to functional assays. If a protein S activity assay is used in the initial screen, low results should be further investigated with an immunoreactive assay of free protein S.**
- **If an APC (Activated protein C) resistance assay is performed to detect the *F5*G1691A then the modified APC sensitivity test (predilution of the test sample in factor V-deficient plasma), as opposed to the original APC sensitivity test should be used. If positive the mutation should be confirmed by a direct genetic test. An APC resistance assay is unnecessary if a direct genetic test for *F5*G1691A is used initially.**
- **Repeat testing for identification of deficiency of antithrombin, protein C and protein S is indicated and a low level should be confirmed on one or more separate samples. Deficiency should not be diagnosed on a single abnormal result.**
- **Rigorous internal quality assurance and satisfactory participation in accredited external quality assessment schemes are mandatory.**
- **Thrombophilia testing must be supervised by experienced laboratory staff and the clinical significance of the results must be interpreted by an experienced clinician who is aware of all relevant factors that may influence individual test results in each case.**

Audit

The recommended (grade 1) and suggested (grade 2) indications for testing or not testing can be used as standards to audit local requesting for thrombophilia testing. It is also suggested that clinicians audit clinical management decisions in patients for whom thrombophilia testing was requested to ensure that inappropriate decisions regarding intensity and duration of anticoagulation are not made on the basis of the thrombophilia test results, e.g. recommending lifelong anticoagulation after a first episode of venous thrombosis on the basis of testing and finding the *F5*G1691A mutation. Performance in external quality assurance schemes should be continuously monitored.

Disclaimer

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On behalf of the British Committee for Standards in Haematology.

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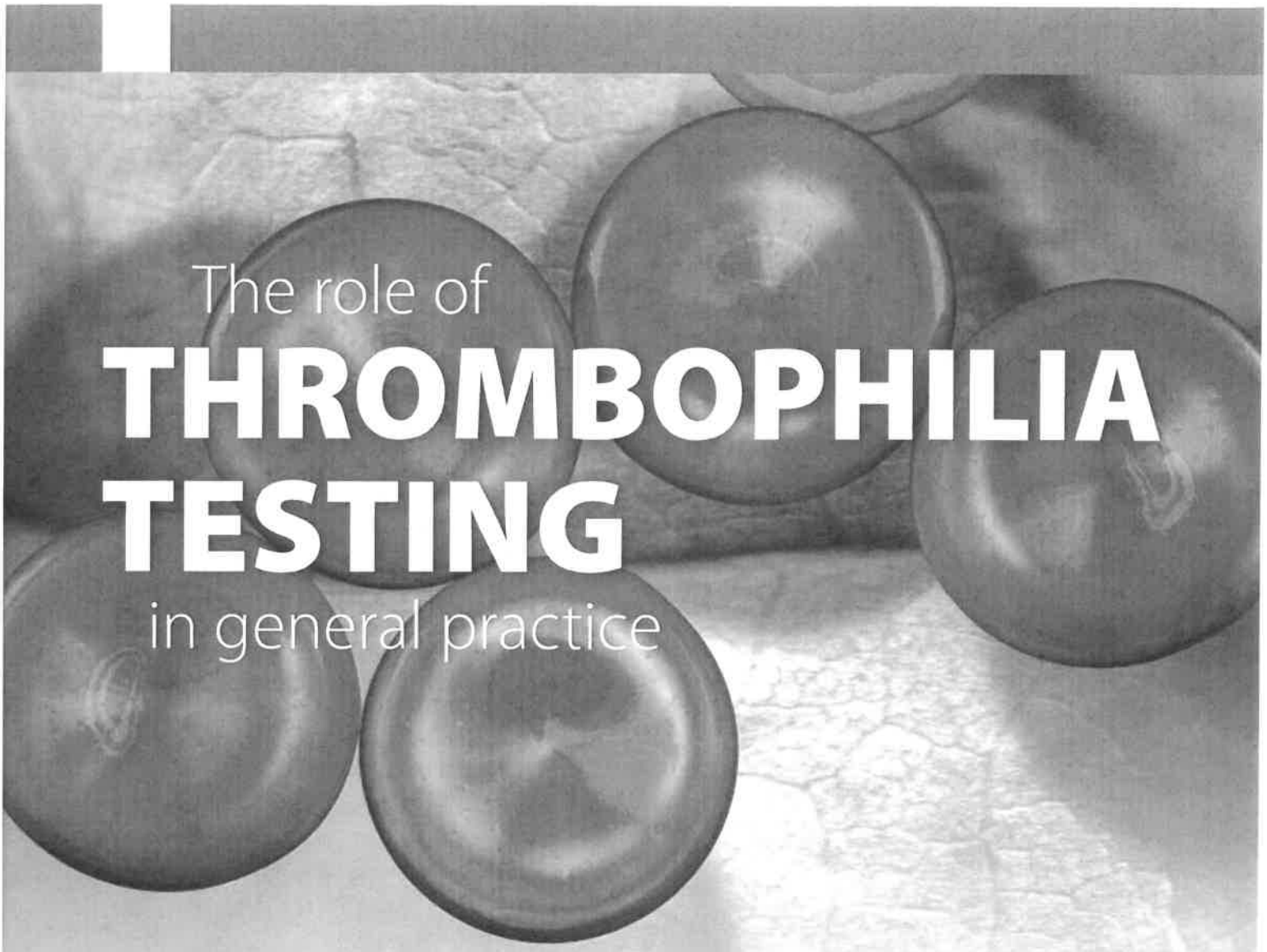

The role of THROMBOPHILIA TESTING in general practice

Key concepts:

- Thrombophilia testing is rarely indicated
- Thrombophilia testing should only be performed in specific situations when the results will alter management
- Situations in which thrombophilia testing may be appropriate include: people presenting at a young age with an unprovoked venous thrombosis and with a positive family history, children with purpura fulminans and some pregnant women (Page 4)

Thrombophilia is the increased tendency for a person to develop blood clots. There are a number of factors that contribute to increased thrombotic risk, many of which are well recognised and some of which are unknown. In most cases, the presence of one or more risk factors is thought to contribute to a thrombotic event. However, in some cases, described as idiopathic or unprovoked, a patient has no clear triggering event. Although over the last few years there has been increased interest in laboratory tests for investigating thrombophilia, their role in general practice is limited, their use is controversial and the results in most cases will not influence management. Testing may also lead to unnecessary anxiety and psychological distress, given that some inherited thrombophilic traits are very common but are of limited clinical significance.

Thrombotic risk is an accumulation of a number of factors. Virchow's triad demonstrates this risk in terms of physiological states that promote thrombosis, including; circulatory stasis, hypercoagulability and vascular wall injury (Figure 1, Page 4). Predisposing factors or current

health status can alter one or more components of this triad. Most patients presenting with venous thromboembolism (VTE), will have more than one recognised risk factor, with overall risk increasing as the number of risk factors increase.[1] Risk factors for VTE are listed in Table 1.

Clinical assessment of patients at increased thrombotic risk

When a patient presents to primary care with a VTE or a family history of VTE, it is important to perform a thorough clinical assessment to determine the presence of risk factors (Table 1), and to collect a personal and family medical history. This assessment can help to determine if the event was provoked, i.e. whether risk was exacerbated by external risk factors, or unprovoked, i.e. occurred for no apparent reason. The thrombotic load (large or small thrombosis) and the site (proximal or distal) should also be noted.

What is included in a "thrombophilia screen?"

The tests included in a thrombophilia screen generally include:

- Factor V Leiden
- Prothrombin gene mutation
- Antithrombin
- Protein C and Protein S
- A lupus anticoagulant screen will sometimes be included

It is recommended that all requests for thrombophilia tests are first discussed with a haematologist. In addition, requests should be accompanied by all relevant clinical information. Laboratories may reject the specimen unless there is sufficient clinical information to justify testing.

The choice of tests will depend on clinical information. For example, antithrombin, Protein C or Protein S deficiency is more likely in a younger person with a spontaneous VTE, and less likely in an older person with other risk factors for a VTE.[3]

Testing principles

Thrombophilia testing should only be performed when the test results will alter management. In most cases management **will** be determined by clinical presentation, rather than test results. There is a lack of evidence for indiscriminate screening,[4] and instead it is recommended that careful and selective testing should be done only if the results would affect the patient's medical management or provide useful information for the health care of the family.[5]

Although Factor V Leiden (3–7%) and Prothrombin gene (1–3%) are the most prevalent mutations,[6] they only increase an individual's risk of a first VTE by approximately five-fold and have little effect on the risk of recurrence after a first VTE. Antithrombin, Protein C and Protein S are relatively rare mutations, but the presence of these mutations increases an individual's risk of a first VTE by approximately ten-fold and risk of recurrence by approximately two-fold.[6]

Table 1: Risk factors for VTE[1]

Strong risk factors (odds ratio > 10)
Fracture (hip or leg)
Hip or knee replacement
Major general surgery
Major trauma
Spinal cord injury
Moderate risk factors (odds ratio 2–9)
Arthroscopic knee surgery
Central venous lines
Chemotherapy
Congestive heart or respiratory failure
Hormone replacement therapy
Malignancy
Oral contraceptive therapy
Paralytic stroke
Pregnancy/postpartum
Previous venous thromboembolism
Inherited thrombophilia
Weak risk factors (odds ratio < 2)
Bed rest > 3 days
Immobility due to sitting, e.g. prolonged car or air travel
Increasing age
Laparoscopic surgery, e.g. cholecystectomy
Obesity
Pregnancy/antepartum
Varicose veins

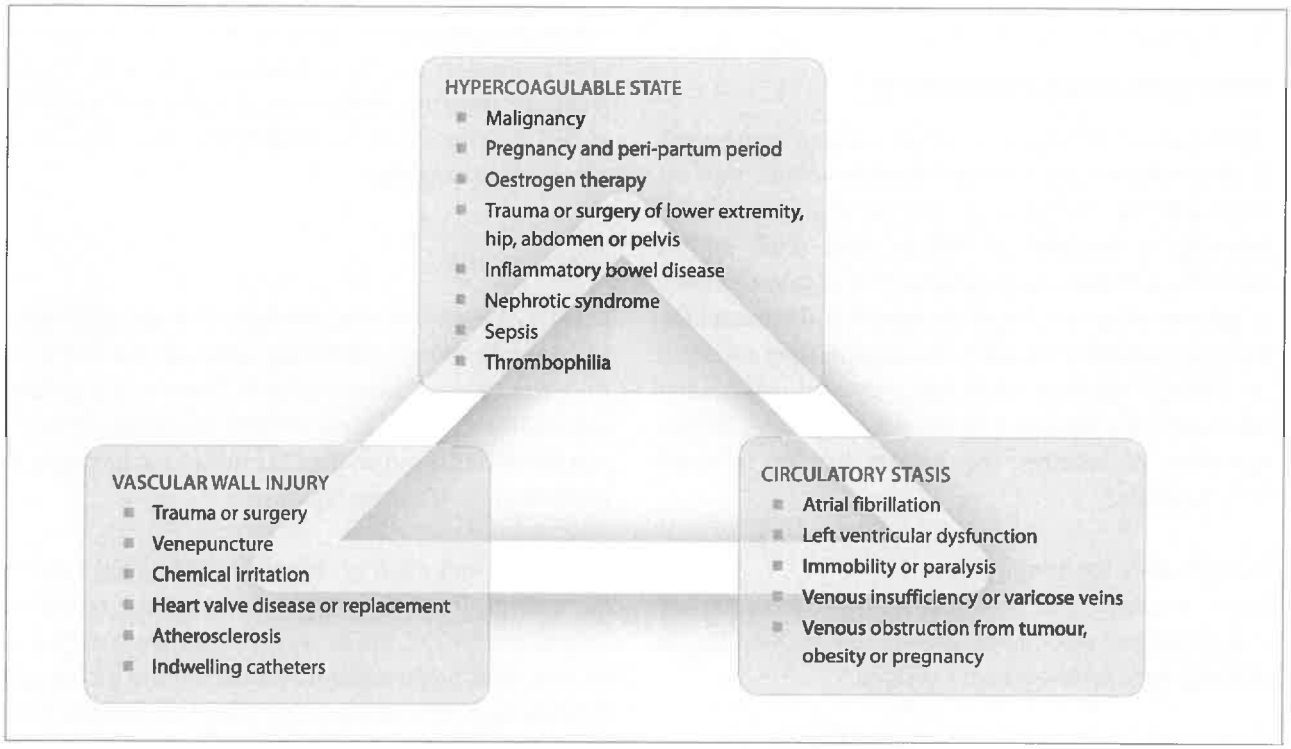

Figure 1: Virchow's triad (Adapted from Merli, 2006)[2]

There are a number of other markers that may be implicated in increasing risk of VTE, however, they have currently not been demonstrated to be independent risk factors.[7] In addition, it is likely that a number of other yet to be identified mutations exist.

Who should be tested?

Although there has been increased interest in thrombophilia testing over the last few years, the role of testing for determining thrombotic risk is likely to have been overstated. Recent guidelines indicate that in most cases thrombophilia testing will not influence management or determine individual risk.[8]

Thrombophilia testing is therefore only recommended in specific situations for selected patients where the results will influence management. These situations include:

- **People presenting with unprovoked venous thrombosis at an early age (<40 years), with a family history of thrombosis (more than two other symptomatic first degree family members).** The yield of testing and the significance of positive results are likely to be increased in this group of patients. However, strong clinical history should be taken into account when making future decisions such as contraceptive options, pregnancy management and prophylaxis in high-risk situations, irrespective of the results of thrombophilia testing. Negative results in an individual with a strong personal or family history of VTE does not necessarily mean that they are at low risk of VTE.
- **Children with purpura fulminans.** This is a rare condition presenting as a progressive haemorrhagic skin necrosis. It may be either inherited (as congenital Protein C deficiency) or acquired (Protein S deficiency). All infants and children with purpua fulminans should be tested urgently for Protein C and S deficiency,[8] since this result will alter management in this situation.
- **Pregnant women at risk of venous thrombosis.** Pregnant women who have had a previous VTE due to a minor provoking factor, i.e. a less significant risk factor, or who have a first degree relative with a previous VTE due to minor provoking factor, should be tested.[8] Most pregnant women with a previous unprovoked VTE will be given anticoagulation treatment based on clinical risk alone, and testing is not required.

Who should not be tested?

Anticoagulation following acute VTE

Thrombophilia testing is not recommended in the acute phase of a thrombotic event, or in patients on anticoagulant treatment. The intensity and duration of anticoagulation following a diagnosis of VTE is most often initially determined in secondary care, but it is usually the same in patients with or without an inherited thrombophilia. Decisions regarding duration of anticoagulation are based on whether the first event was provoked, what other risk factors are present and the risk of anticoagulation, regardless of whether the patient has an inherited thrombophilia.[8]

Family history for thrombosis

Factor V Leiden and Prothrombin gene mutation are considered low risk thrombophilias, and case finding in asymptomatic relatives is not indicated.[8]

Antithrombin, Protein C and Protein S deficiencies are considered high risk thrombophilias, but testing should only be considered in thrombosis-prone families after careful explanation of inheritance and disease risk.[8]

Oestrogen containing hormone preparations and thrombosis

If a patient has a history of VTE, or a current VTE, then oestrogen-containing hormonal preparations should not be prescribed. If there is a family history of VTE in a first degree relative under 45 years of age, the use of such preparations is not usually recommended unless other methods are not available or not acceptable.[9]

For patients with known thrombogenic mutations (e.g. Factor V Leiden, Prothrombin mutation, Protein C, Protein S and Antithrombin deficiencies) oestrogen containing preparations should be avoided. However routine screening is not appropriate.[9]

Thrombophilia and flying

VTE is a relatively uncommon event among healthy travellers on long-haul flights, with approximately one event occurring per 4500 flights. Thrombophilia testing is unhelpful and, instead, risk should be assessed based on the presence of clinical risk factors.[10] Those at particular risk include people with a history of VTE, active cancer or recent surgery, especially orthopaedic surgery to the lower limbs. It is recommended that air travellers with a high risk of DVT be considered for prophylaxis with knee-length compression stockings.[10]

Case studies

Case 1: A well-informed, intelligent 22-year-old female has been on the combined oral contraceptive (COC) pill since age 18 years. She is a smoker. There is no significant past medical or family history of VTE. She has read that she is at risk of DVT being on the COC and asks to be tested for thrombophilia. Is testing indicated?

There is no indication to request thrombophilia tests for this patient. There is a slightly increased risk of VTE for women on the COC, but because she has been on the COC for more than a year without incident she is at a lower risk. Most patients who develop DVT with COC tend to do so in the first year. Any concern would be best managed by reducing other contributing risk factors such as obesity, and recommending smoking cessation, where relevant.

Case 2: A 50-year-old male presents prior to a long distance flight. His mother died from a PE two years ago. He is also obese and has very bad varicose veins. Is testing indicated?

This patient has a positive family history of VTE and testing is not going to determine management. Prophylaxis is advisable in view of the patient's risk factors and the patient's anxiety about his mother's death.

Case 3: A healthy 33-year-old female presents in her first pregnancy. She tells you she has previously had VTE when she flew to England ten years ago. Is testing for hereditary thrombophilia indicated?

Recent clinical guidelines recommend that this patient should have thrombophilia testing.[8] Travel is considered a minor risk factor for VTE, and on its own would be unlikely to contribute to the thrombotic event. Therefore, it is likely there are other provoking factors present. If clinical assessment does not identify any other contributing factors, thrombophilia testing would be indicated.

Acute presentation of venous thromboembolism (VTE)

Although patients may present with the classic symptoms of deep vein thrombosis (DVT) or pulmonary embolism (PE), they can also pose a diagnostic challenge if the classic signs and symptoms are absent. In patients with symptomatic VTE, PE manifests in one-third and DVT alone in two-thirds.

The most common symptoms of PE are dyspnoea (73%), pleuritic pain (66%) and cough (37%), and the most common signs are tachypnoea (70%), lung crepitation (51%) and tachycardia (30%).[11] Patients with DVT commonly present with pain, erythema, warmth and swelling of the affected limb.[11]

The incidence of VTE in the general population is approximately ten cases per 10 000 people, per year. However, this estimate is dependent on age as there is a significant increase in VTE incidence particularly after age 40 years. The risk of VTE for a person aged 25–35 years is approximately three cases per 10 000 people, whereas for a person aged in their 70's the risk is more than ten times higher than this (30–50 cases per 10 000 people).[12]

D-dimer can be used to confirm absence of VTE

D-dimer is a fibrin degradation product, and is elevated in nearly all patients with VTE, but can also be elevated in patients with infection, malignancy or recent surgery. Because of the low specificity of D-dimer for VTE, its key role is as a negative predictor of VTE, i.e. a low or normal D-dimer level with a low pre-test probability makes VTE an unlikely diagnosis.

D-dimer can be used in conjunction with the Wells Rule or the Primary Care Rule (Table 2)[13] to determine the probability of a DVT. Historically, the Wells Rule has predominantly been used in New Zealand, but more recently the Primary Care Rule has become popular. Both

Table 2. Wells Rule and the Primary Care Rule Scoring to rule out deep vein thrombosis (DVT) (Adapted from van der Velde et al, 2011)[13]

Variables	Wells Rule	Primary Care Rule
Male gender	n/a	1
Oral contraceptive use	n/a	1
Presence of active malignancy (within last 6 months)	1	1
Immobilisation paresis/plaster lower extremities	1	n/a
Major surgery (within last 3 months)	1	1
Absence of leg trauma	n/a	1
Localised tenderness of deep venous system	1	n/a
Dilated collateral veins (not varicose)	1	1
Swelling, whole leg	1	n/a
Calf swelling > 3 cm	1	2
Pitting oedema confined to the symptomatic leg	1	n/a
Previously documented DVT	1	n/a
Alternative diagnosis at least as likely as DVT	−2	n/a
Positive D-dimer result	n/a	6
Cut-off scores for considering DVT as absent	≤1	≤3

rules can be safely used to reduce unnecessary referrals for compression ultrasonography, although the Primary Care Rule reduces unnecessary referrals slightly more.[13]

Patients with a high probability of DVT should be referred for ultrasound irrespective of the results of the D-dimer test. Using this approach, only approximately 0.5% of patients with an initially negative assessment, i.e. a low Clinical Probability Score and negative D-dimer, are likely to be later diagnosed with DVT.[3]

Differentiating between DVT and SVT

It can sometimes be difficult to differentiate between DVT and superficial vein thrombosis (SVT). SVT or superficial thrombophlebitis, is often associated with conditions that increase thrombotic risk, e.g. surgery or trauma, immobilisation, malignancy. A patient with SVT will often present complaining of a painful, red, firm lump in the lower leg. Clinical examination will usually confirm the diagnosis, but in some cases further investigation may be required as SVT and DVT can co-exist (because a superficial thrombus can move into the deep veins).

The presence of clot within a vein may be palpable as an indurated (hardened) nodular cord, however in some cases the clot may only be accurately diagnosed with ultrasound.

DVT should be suspected if:[14]

- The superficial thrombosis is in the upper medial third of the thigh*
- The swelling in the lower leg is more than would be expected with SVT alone
- The SVT is extending
- The diagnosis of SVT is uncertain
- There are risk factors for DVT, e.g. history of DVT, malignancy, oestrogen therapy or thrombophilia

N.B. Clots that occur in the main deep vein of the thigh ("superficial" femoral vein) should be classified and treated as a DVT as the femoral vein is part of the proximal deep venous system.

* When SVT occurs close (within 3 cm) to the sapheno-femoral there is an increased risk of DVT (+/- PE) therefore treatment should be as for DVT.[14, 15]

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