



# 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.<sup>1</sup> 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.<sup>3</sup>

#### 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,

**Table 1: Risk factors for VTE<sup>1</sup>**

#### 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)

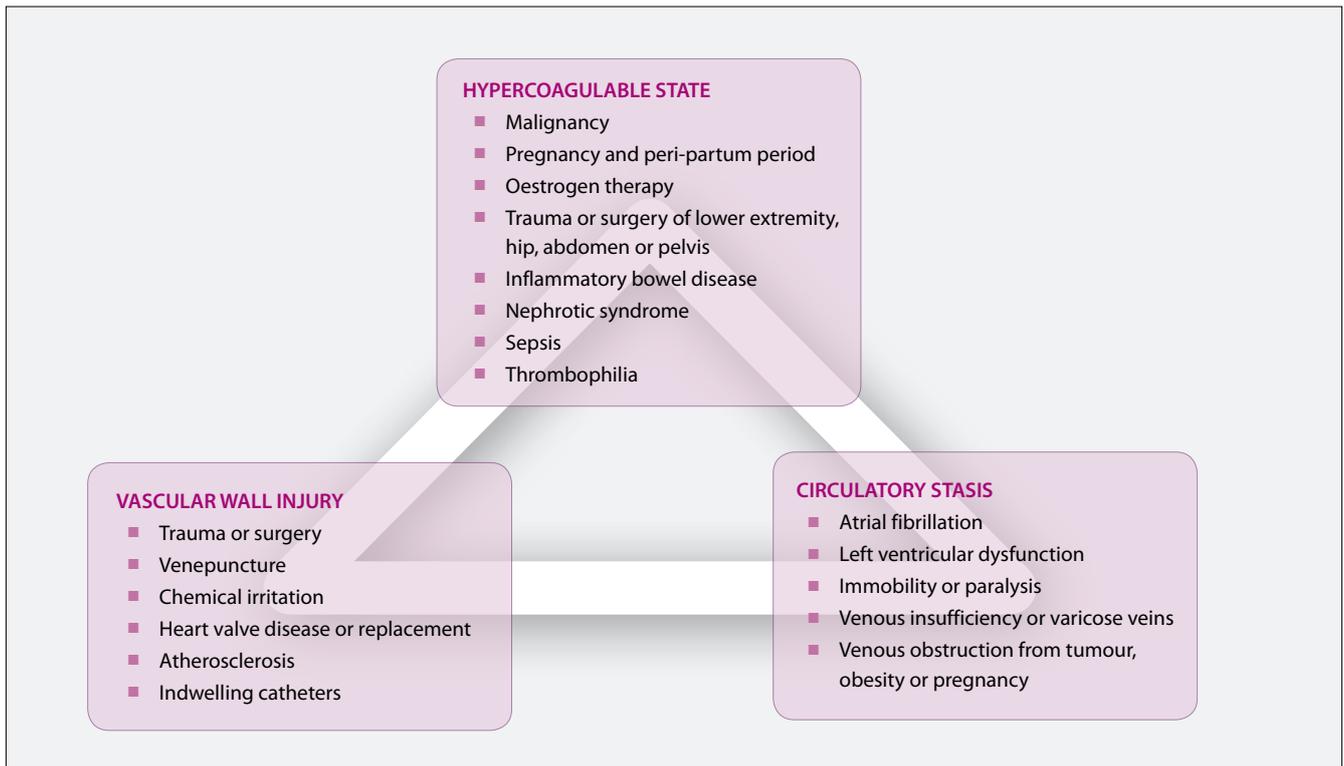
- Arthroscopic knee surgery
- Central venous lines
- Chemotherapy
- Congestive heart or respiratory failure
- Hormone replacement therapy
- Malignancy
- Oral contraceptive therapy
- Paralytic stroke
- Pregnancy/postpartum
- Previous venous thromboembolism
- Inherited thrombophilia

#### 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

rather than test results. There is a lack of evidence for indiscriminate screening,<sup>4</sup> 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.<sup>5</sup>

Although Factor V Leiden (3–7%) and Prothrombin gene (1–3%) are the most prevalent mutations,<sup>6</sup> 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.<sup>6</sup>



**Figure 1:** Virchow's triad (Adapted from Merli, 2006)<sup>2</sup>

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.<sup>7</sup> 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.<sup>8</sup>

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 purpura fulminans should be tested urgently for Protein C and S deficiency,<sup>8</sup> 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.<sup>8</sup> 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.<sup>8</sup>

### 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.<sup>8</sup>

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.<sup>8</sup>

### 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.<sup>9</sup>

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.<sup>9</sup>

### 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.<sup>10</sup> 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.<sup>10</sup>

## 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.<sup>8</sup> 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%).<sup>11</sup> Patients with DVT commonly present with pain, erythema, warmth and swelling of the affected limb.<sup>11</sup>

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).<sup>12</sup>

### 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)<sup>13</sup> 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)<sup>13</sup>

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
<b>Cut-off scores for considering DVT as absent</b>	<b>≤1</b>	<b>≤3</b>

rules can be safely used to reduce unnecessary referrals for compression ultrasonography, although the Primary Care Rule reduces unnecessary referrals slightly more.<sup>13</sup>

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.<sup>3</sup>

### 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:<sup>14</sup>

- 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.<sup>14,15</sup>

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