Investigating the patient with venous thromboembolic disease

In this series, we present authoritative advice on the investigation of a common clinical problem, specially commissioned for family doctors by the Board of Continuing Medical Education of the Royal Australasian College of Physicians.

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Venous thromboembolism (VTE) refers to deep venous thrombosis (DVT) and pulmonary embolism (PE), which have common pathophysiology. Clinical studies have focused on proximal lower limb thrombosis, which carries the greatest risk of PE, and therefore most clinical guidelines relate primarily to this group. However, 20 to 30% of calf vein (below the popliteal vein) thrombi will propagate proximally, and further investigation and treatment should be considered for symptomatic patients.

VTE is a common problem in clinical practice. It is very rare in childhood, except in children with major illness and central venous access devices. Rates are similar in men and women, and the incidence rises steeply with age, as shown in Figure 1.[1] It is a serious condition, with a reported 28-day case-fatality rate of 11%, which is in part a reflection of the association with serious underlying illness.[2]

The aims of investigation of patients with VTE are to identify occult predisposing conditions, estimate the probability of recurrence and direct further management. This article reviews investigation of patients with the condition; management will be reviewed in another article, to be published in a future issue of *Medicine Today*.

The importance of clinical evaluation

The patient's clinical history is essential to the evaluation of VTE. VTE may be idiopathic, where there is no temporal causative event, or secondary, where the thrombosis has occurred in relation to a known acquired risk factor. Factors predisposing to VTE are listed in Figure 2. True idiopathic VTE is associated with a higher incidence of recurrence, and longer treatment durations may be indicated.[3]

IN SUMMARY

- **Venous thromboembolism (VTE) is multifactorial, with both congenital and acquired risk factors.**
- **VTE may be the first presentation of systemic illness.**
- **It is not necessary to investigate patients who have VTE following recent major surgery or other identified temporal risk factors.**
- **Investigating for underlying systemic disease should be guided by careful history, examination and consideration of risk factors.**
- **Identifying single gene defects, such as factor V Leiden, usually does not change management.**
- **Specialist advice is suggested for multiple inherited defects or strongly thrombophilic defects, such as antithrombin deficiency.**

Idiopathic thrombosis can be the first presentation of malignancy or other serious medical illness, therefore a careful history and examination is necessary. A history of unexplained weight loss, bowel habit change, breast lumps and rectal or vaginal bleeding should be actively sought. A smoking and alcohol history is important, as is a history of combined oral contraceptive use or other hormonal therapy, and an obstetric history if appropriate. A family history with particular attention to possible thromboembolic events such as unexpected sudden death is essential.

Initial investigations

Before beginning anticoagulant therapy, initial tests should include a full blood count, prothrombin time and activated partial thromboplastin time (APTT), and renal and liver function tests. Abnormalities in these screening investigations may require exclusion of underlying causes such as malignancy or myeloproliferative disorders (Figure 3), and should prompt further investigation or referral.

Investigating for underlying malignancy

Approximately 20% of symptomatic venous thromboembolic events occur in patients with known malignancy. However, in a small proportion of patients, VTE may predate the diagnosis of malignancy.

Extensive screening is not usually warranted, and is seldom rewarding. It is our practice to perform age and sex appropriate cancer screening in patients with idiopathic VTE, including cervical, breast and colon cancer screening, and to request a chest x-ray in smokers and a PSA in men over the age of 50 years. Otherwise investigations should be guided by clues from the clinical evaluation.

In patients with thrombosis into the pelvis or inferior vena cava, abdominal imaging should be considered. The value of abdominal and pelvic imaging in otherwise asymptomatic patients with VTE remains the subject of continuing debate. Although there are low but improved rates of occult cancer detection with extensive investigation, there is no clear survival benefit. Recurrent or progressive thrombosis on anticoagulation is more likely in patients with malignancy or the antiphospholipid syndrome, and further investigation is likely to be appropriate in this group.

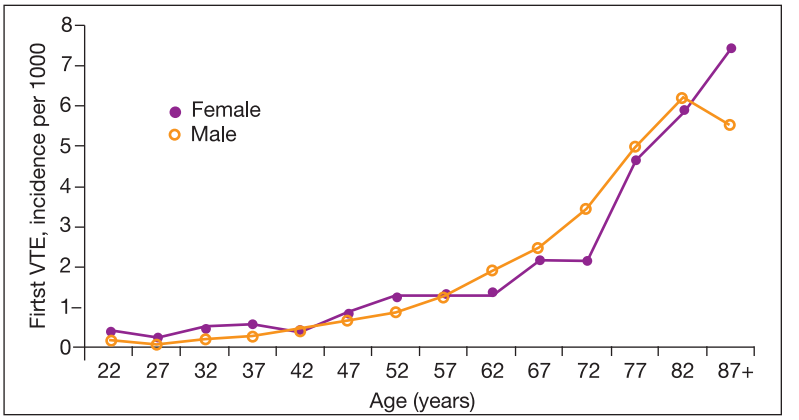

Figure 1. Age-related incidence of first venous thromboembolism (VTE) event in a Norwegian population.[1]

When to test for a hypercoagulable state

Conditions that predispose to a higher risk of initial VTE can be categorised as inherited or acquired (Figure 2). These conditions are often referred to as 'thrombophilic states', and frequently more than one is present in a given patient. There is continuing controversy regarding the utility of, and indications for, testing for thrombophilic disorders and there is no consensus on which tests should be used, or in which patients. Identification of predisposing thrombophilia generally does not change initial therapy or the length of anticoagulation therapy. However, prolonged anticoagulation may sometimes be considered in younger patients with strong thrombophilic factors, such as homozygosity for factor V Leiden, antithrombin III deficiency or multiple risk factors.

There are a number of factors related to acute VTE that can interfere with testing, and which may lead to difficulties in interpretation of the results, particularly if samples are taken at the time of acute thrombosis or while on anticoagulant therapy. Hence, it may be best to delay screening for a thrombophilia until after the completion of initial anticoagulant therapy.

Given these uncertainties, a practical clinical approach that considers the prevalence and risk of thrombophilic disorders has been suggested as a framework for making decisions on further investigation.[4] This classifies patients into either 'weakly' or 'strongly' thrombophilic groups and directs testing appropriately. The approach is summarised in the Table.[4]

Our own practice is to target thrombophilia testing to:

- patients younger than 50 years with idiopathic

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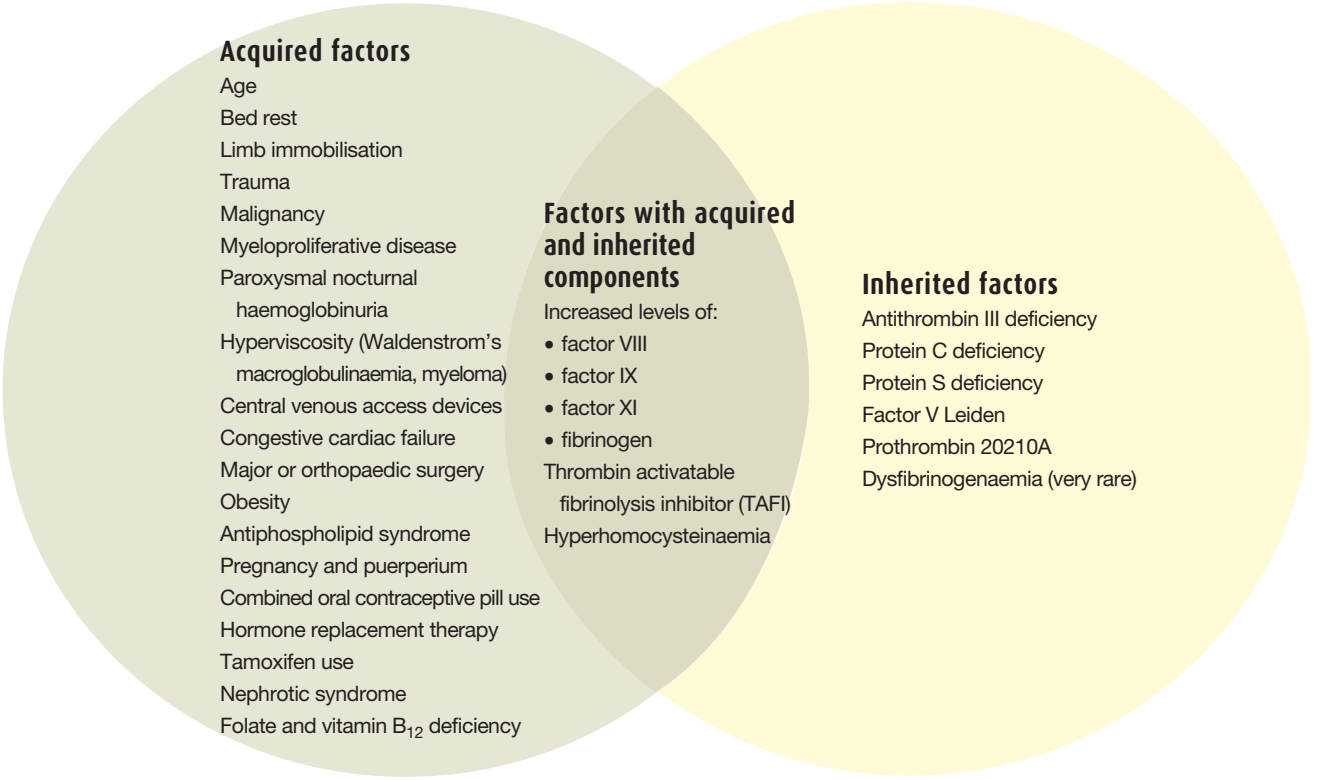

Figure 2. Inherited and acquired factors predisposing to venous thromboembolism.

VTE, particularly where there is a family history
- patients younger than 50 years with thrombosis due to a single minor provoking factor
- patients with thrombosis in unusual sites.

Screening family members for an identified inherited thrombophilic state is also controversial. Anticoagulant prophylaxis may be offered to cover high-risk situations in those family members. As with any genetic testing, family members should receive appropriate counselling before testing, and as the evidence on which this is based is sparse, testing is best targeted towards families with strong thrombotic risk.

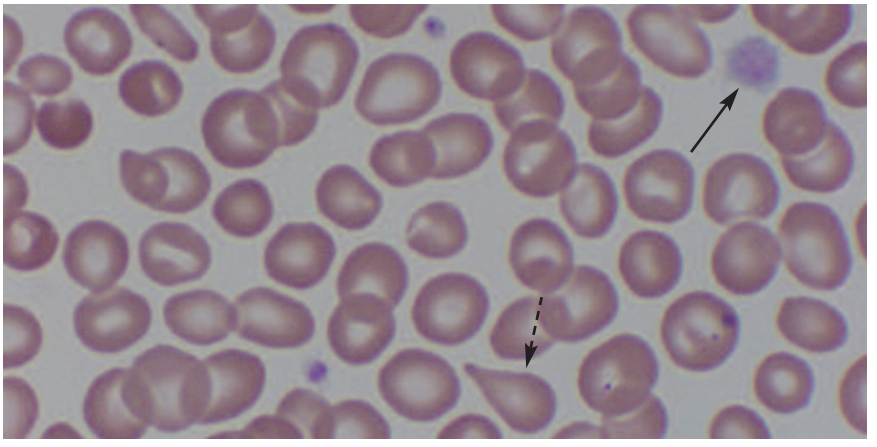

Figure 3. A blood film from a 45-year-old woman with splenic vein thrombosis (100 x magnification). Blood counts showed erythrocytosis and neutrophilia. The blood film shows large platelets (solid black arrow) and occasional tear drop poikilocytes (dashed black arrow), markers of the underlying myeloproliferative disorder as a cause of the thrombosis.

When not to screen for thrombophilic states

There are several clinical settings in which inherited prothrombotic disorders have not been found at increased frequency, and in which screening is therefore not indicated. These include thrombotic events following recent major surgery, trauma or immobilisation, and active malignancy, systemic lupus erythematosus, inflammatory bowel disease, myeloproliferative disorders, heparin-induced thrombocytopenia with thrombosis, retinal vein thrombosis and pre-eclampsia at term.

Inherited risk factors

Factor V Leiden and prothrombin gene mutations

Following their description as risk factors for VTE in the 1990s, there has been widespread (and perhaps premature) adoption

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Table. Suggested testing for thrombophilic states[4]

Condition tested for	'Strongly thrombophilic' First idiopathic VTE before 50 years of age, OR History of recurrent VTE, OR First-degree relatives with documented VTE before age 50	'Weakly thrombophilic' First episode of idiopathic VTE at age 50 years or younger AND Negative family history of VTE
Factor V Leiden mutation/activated protein C resistance	+	+
Prothrombin gene mutation	+	–
Antiphospholipid antibodies	+	+
Antithrombin III deficiency	+	–
Protein C deficiency	+	+
Protein S deficiency	+	–

of testing for the factor V Leiden (G1691A) mutation, which results in activated protein C (APC) resistance, and the prothrombin (G20210A) gene mutation, which results in higher plasma levels of prothrombin. Both of these mutations are independent risk factors for venous thrombosis, and are the most common causes of inherited thrombophilia in western populations. The factor V Leiden mutation is present in about 5 to 7% of Caucasian populations, and leads to an estimated five- to sevenfold increased risk of thrombosis. The prothrombin gene mutation is present in about 2% of Caucasian populations, and leads to a three- to fourfold increased risk of thrombosis.

Although there is very good concordance between coagulation assays for APC resistance and molecular testing for the factor V Leiden mutation, it is common practice in Australia to screen for both factor V Leiden and prothrombin gene mutations together in a polymerase chain reaction (PCR) assay. Because of this, it is usually unnecessary to perform both PCR and coagulation assays initially in the same patient. Although APC resistance may be due to causes other than factor V Leiden, these other causes are uncommon and we prefer to use the coagulation assay for APC resistance only when other testing, including factor V Leiden, is negative and there remains a high clinical suspicion of a thrombophilia.

Protein C, protein S and antithrombin III deficiencies

Congenital deficiencies of the natural coagulation pathway inhibitors protein C, protein S and antithrombin III are potent contributors to an increased risk of thrombosis. Although relatively less common than factor V Leiden and prothrombin gene mutations, there is a higher lifetime thrombotic risk with these deficiencies.[5] As these conditions are usually inherited in an autosomal dominant pattern, there is often a significant family history of VTE, frequently with the first episode at a relatively young age. Diagnosis of these conditions requires expensive, labour-intensive assays, and consequently should only be performed in patients with a strongly thrombophilic presentation.

Other risk factors

The antiphospholipid syndrome is a strong acquired risk factor for venous thrombosis. The key clinical clues are an unexplained prolongation of the APTT, thrombocytopenia or recurrent fetal loss. Other features that may be present include symptoms of a systemic connective tissue disorder, arterial thrombotic events, livedo reticularis and autoimmune haemolytic anaemia. Not all clinical features need be present, but repeated identification of antiphospholipid antibodies, by either lupus anticoagulant or anticardiolipin assays, is required to make the diagnosis. We generally recommend testing for antiphospholipid antibodies in all patients with idiopathic VTE.

A wide variety of other coagulation factors have been reported to be risk factors for venous thrombosis (see Figure 2). Factor VIII is an instructive example where both congenital and acquired factors determine levels in an individual. Blood group O is associated with significantly lower levels of factor VIII than other blood groups, and confers a decreased risk of thrombotic events. Factor VIII may be increased by acute inflammation, trauma, liver disease, malignancy and pregnancy, and may be a contributing factor to the increased risk of thrombosis in some of these conditions. Given this complexity, the clinical utility of testing for these coagulation factors has yet to be determined, and routine testing is not advised.

Hyperhomocysteinaemia has been shown to be a risk factor for vascular, particularly arterial, thrombotic events. However, evidence for an association of hyperhomocysteinaemia with a significantly increased risk of VTE is conflicting because hyperhomocysteinaemia may be a marker of thrombotic disease rather than a cause. The most common genetic cause of hyperhomocysteinaemia is a mutation in the methylene tetrahydrofolate reductase (MTHFR) gene, but most evidence suggests that such mutations lead to minimal, if any, increase in the risk of DVT.

In addition, results of a recently published trial of supplementation with folic acid, pyridoxine and vitamin B_{12} (the Vitamins and Thrombosis [VITRO] study) indicate that such treatment did not significantly reduce the incidence of recurrent VTE events in patients with elevated homocysteine concentrations.[6] Therefore, routine measurement of plasma homocysteine is not currently recommended.

Evolving approaches to predicting the risk of recurrent VTE

Persisting thrombosis on ultrasound following a minimum of three months of anticoagulation therapy has been shown to predict a higher likelihood of recurrence. Prolonging anticoagulation in patients with incomplete clot resolution may reduce the risk of subsequent events.[7] In addition, ultrasonic evidence of venous insufficiency may predict a higher risk of post-phlebitic syndrome. We would therefore suggest repeat venous duplex ultrasound in all patients with proximal lower limb DVT towards the end of their expected anticoagulation period.

D-dimer levels can be used to predict the risk of VTE recurrence. The likelihood of VTE recurrence is higher in patients with a first episode of VTE who have elevated D-dimer levels, when these were performed after the withdrawal of oral anticoagulants, following at least three months of anticoagulation therapy. Although this data is intriguing, further studies are needed to elucidate the natural history of the patient group with persistent elevation of D-dimer.

Conclusion

The clinical utility of identifying thrombophilic states in estimating the risk of recurrent VTE remains controversial as several studies have shown no difference in recurrence rates in patients with or without factor V Leiden, the prothrombin gene mutation, a coagulation protein deficiency or a positive family history for VTE. In addition, there is no evidence demonstrating the efficacy of prolonging anticoagulation or otherwise altering treatment in patients with these single gene defects. It is important to note that inheritance of a recognised thrombophilia gene is not in itself a diagnosis, and only serves to identify a potentially increased risk of venous thrombosis that may be modified by co-inherited or acquired factors.

In order to make rational decisions regarding anticoagulant therapy, a careful evaluation of the entire clinical situation is required including consideration of the patient's age, comorbidities, ability to comply with medications, personal preferences and quality of life issues. Investigation for thrombophilic states may be of value in guiding therapeutic decisions, as outlined above, but given the current state of knowledge, recommendations must to a certain extent be individualised and somewhat qualitative. Advice from a consultant colleague with an expert interest in venous thromboembolic disorders should be sought if in doubt. MT

References

A list of references is available on request to the editorial office.

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