

Venous thrombosis and thromboembolism

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INTRODUCTION

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major public health problem affecting around 100 per 100,000 population per year and causing thousands of deaths annually. Large population-based studies have shown that factors associated with hospitalisation account for half of the attributable risk of VTE.

The House of Commons Health Committee report, published in 2005, highlighted the urgent need to prevent avoidable deaths from VTE. Two years later, two significant pieces of national guidance were published: the Chief Medical Officer's independent VTE Expert Working Group's Report, which recommended an integrated approach to VTE prevention,¹

and the National Institute for Health and Clinical Excellence (NICE) guidance on VTE risk reduction in surgical patients.² These initiatives provide an impetus for the implementation of thrombosis prevention across the spectrum of healthcare, from acute trusts and out into the community.

This article looks at the diagnosis and management of venous thromboembolic disease from a primary care perspective.

VENOUS THROMBOEMBOLIC DISEASE

Venous thromboembolism is a major cause of morbidity and mortality worldwide, although routine data collection for these conditions is unreliable. It has been estimated that VTE occurs in up to 2% of the UK population annually, while US data suggest that there are around 250,000 hospital admissions, with around 50,000 deaths, due to either DVT or PE per year. The fatality rate from acute PE of approximately 10% appears not to have altered since the 1970s.⁴

DEEP VEIN THROMBOSIS

The classic presentation of DVT is as an acutely painful, red swollen calf. DVT is associated with pregnancy, contraceptive pill use, immobility, surgery, malignancy, advancing age, smoking and certain clotting disorders.⁵ Both proximal and isolated calf vein thromboses can cause post-thrombotic syndrome, recurrent venous thrombosis and pulmonary embolus, with associated morbidity and mortality.

Anticoagulation, in terms of early intervention with heparin and warfarin, followed by prolonged warfarin treatment, has been demonstrated to reduce sequelae associated with DVT, particularly PE.⁶ Anticoagulation therapy carries a risk of haemorrhagic complications so it is important that a diagnosis of DVT is objectively confirmed before starting treatment. The

treatment of below knee DVT remains controversial, but there is evidence to suggest that anticoagulation treatment is of benefit and reduces the risk of extension where calf thrombi are symptomatic.^{7,8}

DIAGNOSIS AND INVESTIGATION

Clinical diagnosis of DVT is made on the basis of pain, swelling and venous distension, but is notoriously unreliable.^{9,10} The clinical sign of pain on forced dorsiflexion of the foot (Homan's sign) has fallen out of favour and is no longer recommended.¹⁰ The differential diagnosis of DVT includes musculoskeletal pain and popliteal inflammatory cysts (Baker's cysts).⁹

The gold standard for diagnosis remains venography, but this is an invasive test that is inconvenient, painful and can be associated with allergic and other side-effects.¹⁰ The most widespread diagnostic procedure in the UK is ultrasound. The reliability of this modality is very user-dependent and, even in the best hands, it is not very useful for diagnosing DVT involving only calf veins.

Other diagnostic techniques include light reflection rheography (LRR), an effective non-invasive technique for screening patients with suspected DVT,¹¹ whilst D-dimer tests can be used as a pre-screening tool before ultrasound.

D-dimer is a fibrin degradation product that can be measured in the blood. It is a marker of activity of clot formation, with higher concentrations being present in venous thromboembolism as well as in cancer, pregnancy, recent surgery, trauma and systemic disease. Recent studies have suggested that D-dimer may be used as a guide for determining who is at risk of recurrence of thrombosis after discontinuing treatment of the initial acute stage.¹² D-dimer tests indicate active fibrinolysis and so provide a screening technique for DVT. While not specific to DVT, D-dimer has a high (> 95%) negative predictive value and is

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a reliable method for the exclusion of DVT in symptomatic patients.¹³

PREVENTION

The evidence that appropriate thromboprophylaxis reduces the burden of VTE is well established and detailed in the American College of Chest Physicians (ACCP) clinical practice guidelines (2008) on prevention of VTE.¹⁴

Overall, VTE deaths in the UK are five times more common than the combined total deaths from breast cancer, AIDS and road traffic accidents. Indeed a revised estimate, based on an epidemiological model using extrapolation from European data, has suggested a figure of approximately 60,000 annual VTE deaths in the UK.¹⁵ Post-mortem data suggest that about 10% of deaths occurring in hospital are due to pulmonary embolism.¹⁶

Surgery

Risks to surgical patients, in particular those undergoing orthopaedic procedures, are well known, but the majority of people who develop VTE while in hospital are medical patients. There is a large body of evidence that shows that pharmacological thromboprophylaxis can reduce the rate of VTE by 60–65%.^{17–19}

In order to prevent VTE, the at-risk patient has to be identified, counselled, and then given appropriate prophylaxis. Risk assessment triggers the thromboprophylaxis pathway, so the recommendation is that every hospitalised patient should be risk-assessed on admission.

There are generally two approaches to risk assessment:

- The first is an individualised or ‘opt-in’ approach, where the risk of VTE is considered in each patient based on his or her predisposing factors and current illness or procedure.
- The second is the exclusion or ‘opt-out’ approach, which delivers group-specific prophylaxis routinely for all patients in the major target groups.

In future, the process of VTE risk assessment might extend into the community. For instance, patients may be risk-assessed in primary care before hospitalisation for high-risk elective procedures. In medical patients, the ongoing VTE risk might need to be considered in nursing home residents and other patients following discharge after treatment for an acute illness.

The patient at risk of VTE should receive appropriate thromboprophylaxis, which might include pharmacological and mechanical measures. Injections of low molecular weight heparin (LMWH) are currently the mainstay of pharmacological prophylaxis in high-risk medical and surgical patients for reasons of efficacy, safety and convenience. Aspirin is unsuitable for

prophylaxis of VTE due to its limited efficacy.

The increased risk of VTE continues beyond the period of hospitalisation for some surgical and medical patients and extended prophylaxis may be warranted. The use of LMWH for extended prophylaxis in the community raises resource issues for primary care around arrangements for administration of injections, blood tests to exclude heparin-induced thrombocytopenia and funding for the drugs. In the future, oral agents such as the direct thrombin inhibitors and anti-factor Xa inhibitors are likely to provide safe and effective thromboprophylaxis and would facilitate delivery of extended prophylaxis regimens.

Female hormones

Female hormones, taken either as hormone replacement therapy (HRT) or as oral contraception, contribute to the development of VTE. The absolute increased risk is very small. However, and particularly in the case of oral contraception, the overall health risk of taking therapy is outweighed by the risk of not taking it.

The absolute risk of venous thrombosis in healthy young women is around one per 10,000 person years, rising to three to four per 10,000 person years during the time that oral contraceptives are being used.²⁰

Pregnancy is itself a risk factor for DVT. Pregnant patients at high risk or with a previous history of thrombosis should be treated with LMWH. Warfarin is generally contraindicated in pregnancy as it is teratogenic.

Conditions that increase clotting

There are various conditions that may predispose to a clotting tendency. These are generally congenital (eg Factor V Leiden, protein C deficiency) but may be acquired (eg lupus anticoagulant). These are generally not problematic and are only investigated if a patient presents with an unusual thrombotic history.

Air travel

An increasing problem encountered in primary care is what to do with patients who have a history of thrombosis and wish to travel by air. The risk of thrombosis appears to be greatest for flights of over six hours where the patient is confined to a particular position (usually sitting).

Traveller’s thrombosis has been reported with air, car and bus travel. Specialist referral is indicated if there is any suggestion of an association between long-distance travel and thrombosis, or there is a strong family history of thrombosis. The risk of prolonged travel, either by air or other means is probably overstated, with patients suffering an event being pre-disposed to thromboembolism anyway.²¹ The principal risk factor for

traveller's thrombosis appears to be previous history of a clot. The main preventive measures are the use of full-length graduated compression stockings²² or prophylactic LMWH.

TREATMENT

Goals of treatment of DVT are prevention of PE with the restoration of venous patency and valvular function.^{23,24} The principles of management for these patients have remained essentially unchanged over several years; however, there has been a shift in terms of admission to hospital. The main initial management is to arrange for diagnostic confirmation, which is usually organised through secondary care.

The ACCP guidelines recommend that initial treatment for patients with VTE should be a once- or twice-daily therapeutic subcutaneous dose of LMWH while also starting an oral vitamin K antagonist, most commonly warfarin.²⁵ However, a recent systematic review has shown improved outcomes in terms of recurrence and/or bleeding when LMWH is used instead of warfarin for at least the first three months of long-term treatment of either DVT or PE in patients with cancer.²⁶

Patients should also be advised to stop smoking, to lose excess weight and to stop taking any combined hormonal contraceptives.

Women who are diagnosed with VTE while pregnant or in the puerperium should be managed according to guidelines published by the Royal College of Obstetrics and Gynaecology.²⁷

Treatment with anticoagulation historically involved a hospital in-patient stay of around seven days for intravenous heparin administration with daily partial thromboplastin time (PTT) estimation, together with warfarin for approximately three months (with monitoring).⁹

Subcutaneous administration of LMWH is now very widely utilised, having been demonstrated to be as safe and effective as traditional intravenous therapy but with fewer complications and the advantage that PTT monitoring is not required.²⁸ Dosing schedules for LMWH are based solely on body weight. Secondary care data suggested that LMWH can be cost-effective due to the reduced cost of monitoring and reduced hospital stay.²⁹ These studies also highlighted the possibility of home treatment, with patients either self-dosing or

receiving injections from a nurse or a relative.³⁰

Whilst oral anticoagulation is well established in the treatment of patients with DVT, the duration of therapy remains debatable. Two prospective randomised studies for treatment of proximal DVT have compared four weeks with three months³¹ and six weeks with six months warfarin therapy,³² and have gone some way to resolving the issue. There are problems in comparing studies due to difficulties in standardising diagnostic criteria, but these studies showed recurrence rates after two years of 8.6% in the four-week treatment group compared with 0.9% in the three-month group (odds ratio 10.1, 95% confidence interval 1.3–81.4), and 18.1% in the six-week group compared to 9.5% in the six-month group (odds ratio 2.1, 95% confidence interval 1.4–3.1).

Whatever the proposed duration of treatment, once a patient with a VTE reaches the end of the planned period of anticoagulant therapy, they need to be reviewed as to whether they are at a high risk of recurrence. Currently, there is little to guide the clinician as to which patients require longer duration of treatment apart from clinical signs that are notoriously inaccurate. Data in this area are conflicting. One cohort study identified thrombophilia, short duration of anticoagulation and ageing as independent risk factors of recurrence with unprovoked DVT, while male gender was not.³³ A similar UK study, however, found that male gender conferred a higher risk, while age did not.³⁴

Medical conditions, such as cancer, inflammatory conditions or nephrotic syndrome, put patients at increased risk of recurrence, as does an initial VTE where no cause was found. A raised D-dimer level at the end of treatment also suggests an increased risk of recurrence, although this is currently largely only used as a research tool.³⁵

The end of treatment is a good opportunity to check that the patient is wearing appropriate graduated compression stockings (if the patient presented initially with a DVT) and to try to reduce their risk of developing post-thrombotic syndrome.

If one or more of the risk factors are present, the risk of recurrence should be discussed with the patient, as well as the possibility of continuing anticoagulant therapy. However, this risk needs to be balanced with the increased risk of bleeding while on

anticoagulant therapy, and how the patient feels about the implications of being on long-term anticoagulant therapy (in terms of regular monitoring and anticoagulant medication interaction with other medications).

Debate continues over the treatment of distal DVT where thrombus is limited to the calf veins. However, evidence for treatment is strong. Untreated symptomatic calf vein thrombosis in non-surgical patients has a recurrence rate of over 25%, with an attendant risk of proximal extension and pulmonary embolisation. This risk is reduced to 7.6% with treatment aiming for an INR of 2.0–3.0 for 3 months, which compares with rates of 12.4% with four weeks, 11.8% with six weeks, and 5.8% with six months oral anticoagulant therapy.³²

RECOMMENDATIONS FOR DEEP VENOUS THROMBOSIS

Treatment of idiopathic proximal DVT should be continued for six months. Six weeks of oral anticoagulation therapy is sufficient for patients with isolated DVT without continuing risk factors. The evidence for patients with idiopathic symptomatic isolated calf vein thrombosis supports treatment aimed at a target INR of 2.5 for three months. For post-operative calf-vein thrombosis, however, six weeks' therapy is as effective as treatment for three months. The guidelines recommend lifelong therapy for recurrent thrombosis while off treatment, and lifelong therapy at a higher therapeutic intensity for recurrence while on treatment.

PULMONARY EMBOLISM

Pulmonary emboli usually arise from veins in the pelvis and leg. The risk factors are the same as for DVT. Up to 50% of those with fatal PE have no warning signs. The clinical presentation depends on the size of the emboli, with small emboli remaining asymptomatic.

Large non-fatal emboli cause acute pleuritic chest pain associated with shortness of breath, tachycardia and pyrexia. Associated features include haemoptysis, pleural effusion, hypotension, cyanosis and shock. All cases of suspected PE need to be treated as acute medical emergencies with admission to hospital arranged if possible. The mainstay of diagnosis remains the ventilation/perfusion scan although a spiral CT scan is now regarded as the gold standard for diagnosis.

TREATMENT

The traditional management of PE has been to stabilise the patient medically and then anticoagulate in exactly the same manner as for DVT. This remains essentially the same today; however, advances in the use of LMWH for DVT have seen investigation into the use of LMWH for the home management of PE.³⁶ This may be suitable for a small number of stable patients, but the main priority from a primary care perspective is to arrange for hospital admission for assessment, stabilisation and confirmation of diagnosis.

No studies have looked specifically at the intensity of oral anticoagulation therapy for the treatment of PE. The current UK recommendation for patients diagnosed with a first PE is to aim for an INR of 2.5. This is based on results of studies primarily investigating the treatment of proximal DVT where the occurrence of a PE was taken as an endpoint in interventional studies.

Data are available which show that fatal recurrence of PE following DVT is extremely rare when treated initially with heparin, followed by a longer period of warfarin therapy.³⁷ The range of INR between 2.0 and 3.0 was chosen as it gives the lowest recurrence and bleeding rates in treatment of proximal DVT.³⁸

RECOMMENDATIONS FOR PULMONARY EMBOLUS

The clinical decision as to whether or not to anticoagulate patients with suspected PE will depend on the strength of the clinical suspicion (pre-test probability) combined with the results of ventilation/perfusion scanning.³⁹ Patients with a normal or low probability scan should not be treated.⁴⁰

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