Prevention and treatment of venous thromboembolic disease

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Awareness of the risk factors for venous thromboembolic (VTE) disease and timely administration of thromboprophylaxis can prevent many VTE events. This article examines these risk factors and the recommended strategies to prevent VTE, as well as discussing the diagnosis and treatment of an event that has already occurred.

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are both manifestations of venous thromboembolic (VTE) disease and together have an annual incidence of 1–2 per 1000 population. Both can cause significant morbidity, and in the case of PE an early fatality rate of approximately 5%. While up to half of VTE events appear unprovoked, many are associated with known risk factors including surgery or acute medical admission to hospital. Thus, careful application of thromboprophylaxis strategies for those at high risk, and early diagnosis and treatment for those with acute VTE, are the cornerstones of reducing the burden of these largely preventable conditions.

This article will focus on DVT (see Figure 1); however, it should be noted that prevention, diagnosis and treatment strategies are broadly similar for PE.

Risk factors for VTE

There are numerous risk factors for VTE, both congenital and acquired (see Table 1), with the presence of multiple factors often having a greater than additive effect.

Increasing age is an inherent VTE risk, in particular when over the age of 60 years. Women who use combined oral contraception or hormone-replacement therapy (HRT) have a two- to three-fold increased VTE risk secondary to exposure to exogenous estrogen. The level of risk is increased by a higher estrogen dose, the use of third-generation progestogens and with concurrent smoking or obesity. Non-oral administration of HRT is associated with the least risk. Women should be discouraged from using such hormonal preparations if they have a family history of VTE, and they are contraindicated in women with a previous VTE. In women at high risk of VTE, progestogens can be used for contraception but there is a small increased VTE risk in women requiring higher doses for menstrual irregularities.

Figure 1. Acute deep vein thrombosis of left leg
Pregnancy is associated with a 10-fold increased risk of VTE. The risk is similar throughout all trimesters and is at its greatest during the six weeks postpartum. All pregnant women with a personal history of VTE or multiple risk factors for VTE should be referred to an obstetrician-led antenatal clinic at an early stage of pregnancy for specialist assessment and advice.

Admission to hospital is also a significant risk factor for VTE. Surgical procedures increase the risk, which persists for up to three months following discharge, with a similar but lesser effect following day surgery (see Figure 2). This prolonged risk is particularly prevalent in patients who have undergone lower-limb arthroplasty. Patients hospitalised with an acute medical illness are also at significantly increased risk of VTE, although it is unknown how long this risk persists post-discharge.

Malignancy imparts a very high risk of VTE, with the level of risk dependent on the type of malignancy, its stage and concurrent use of chemotherapy. However, there is no evidence that these patients should routinely receive formal thromboprophylaxis unless hospitalised. One exception to this is in ambulatory patients with myeloma receiving chemotherapy.

Air travel is considered by the general public to present a significant risk for the development of VTE. However, the risk is very low and only applies to journeys over four hours, albeit using any mode of transport.

Smoking and obesity also carry a small risk of VTE but this risk is multiplied when they occur concurrently or in association with other VTE risk factors.

Inherited thrombophilias are congenital coagulation factor abnormalities that increase VTE risk. These vary in frequency and in the level of associated risk, eg anti-thrombin deficiency carries the greatest VTE risk and is uncommon, factor V Leiden is present in 3–5% of the general population and is associated with the least risk. Antiphospholipid syndrome is an acquired thrombophilia that is associated with a very high risk of VTE recurrence.

**Prevention of VTE**

**Mechanical methods**

Above-knee anti-embolism stockings (AES) have a role in VTE prevention in many circumstances. Patients should always be measured accurately prior to use and Sigel-compliant stock-

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**Table 1. Congenital and acquired risk factors for venous thromboembolism (VTE) – deep vein thrombosis (DVT) or pulmonary embolism (PE)**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Approximate increased risk of first event (compared with general population)</th>
<th>Risk Factor</th>
<th>Approximate increased risk of first event (compared with general population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombin deficiency</td>
<td>40x</td>
<td>Hospitalisation with an acute medical illness</td>
<td>8x</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>10x</td>
<td>Surgery</td>
<td>70x</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>10x</td>
<td>Malignancy</td>
<td>50x</td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>2–3x</td>
<td>Age &gt;60 years</td>
<td>10x</td>
</tr>
<tr>
<td>Prothrombin gene mutation G20210A</td>
<td>2–3x</td>
<td>Combined oral contraceptive pill/HRT</td>
<td>2-3x</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pregnancy/postpartum</td>
<td>10x</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Smoking</td>
<td>1.5x</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Obesity</td>
<td>1.5x</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Long-haul travel &gt;4 hours</td>
<td>1.5x</td>
</tr>
</tbody>
</table>

**Figure 2. Relative risk of venous thromboembolism by time since inpatient surgery or since day case surgery (from Sweetland S, et al., BMJ 2009;339:b4583)**

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ings prescribed. There is good evidence that these have a role alongside low-molecular-weight heparin (LMWH) in preventing VTE following all forms of surgery, particularly orthopaedic procedures.

AES are also an effective alternative method of VTE prevention in those patients at increased bleeding risk who cannot safely receive heparin. There is less evidence for their use in hospitalised medical patients and AES are ineffective in VTE prevention for patients with recent stroke. AES are sometimes used in obstetric patients but the evidence for effectiveness is limited. AES are usually recommended during hospital admission but may be continued post-discharge if immobility persists.7

Pharmacological methods
LMWH has been demonstrated in both medical and surgical inpatients to be effective in the prevention of VTE, reducing the risk by approximately 60% compared with placebo.8 LMWH also has a role in obstetric patients assessed to be at high VTE risk. This therapy is as effective as unfractionated heparin but with fewer side-effects. However, it must be avoided in patients at increased risk of bleeding, including those with severe renal impairment.

Post-operative patients remain at risk of VTE following discharge, and in some patients there is a benefit in continuing LMWH for up to six weeks. This particularly applies to those patients who have undergone lower-limb arthroplasty and those deemed to be at very high VTE risk, eg those undergoing major surgery for cancer.9

For air travel, very few people require preventive LMWH and consideration should be given to discussing such cases with a haematologist if there is any doubt, as there is no reliable evidence base for LMWH in this setting.9

Direct oral anticoagulants (DOACs) licensed for orthopaedic thromboprophylaxis include dabigatran etexilate (a direct thrombin inhibitor), rivaroxaban (a direct Factor Xa inhibitor) and apixaban (also a direct Factor Xa inhibitor). Such agents require no monitoring to assess therapeutic levels and have minimal side-effects, although they still impart a bleeding risk similar to that of LMWH. These drugs are easier to administer for extended thromboprophylaxis as their oral formulation avoids a prolonged period of daily injections as an outpatient. These medications continue to undergo research for thromboprophylaxis in other clinical situations.10

Finally, aspirin is known to provide a modest reduction in VTE rate in at-risk patients but there is far stronger evidence for the effectiveness of LMWH. For this reason, aspirin is no longer recommended as a sole pharmacological agent in the prevention of VTE by reputable guidelines, including NICE.6

Signs and symptoms
Signs and symptoms can be relatively non-specific. Therefore, DVT can often be included in the differential diagnosis of patients with otherwise unexplained leg symptoms.11 Symptomatic DVT and PE are not commonly seen simultaneously – most patients with acute PE will have no leg symptoms, presumably because the precipitating DVT has been non-occlusive or already embolised. Acute DVT is associated with asymptomatic PE in 30–50% of cases.12

The presence of key signs or symptoms (see Table 2), either in the absence of an obvious cause or in the presence of known risk factors for VTE, should prompt systematic assessment for DVT and/or referral to secondary care.

**Diagnosis of DVT**
It is long accepted that a ‘clinical diagnosis’ of DVT, or indeed PE, even as assessed by an ‘expert’, is an unreliable basis for committing a patient to a protracted period of anticoagulation. Thus, an objective diagnosis is required – historically by leg vein venography but now more conveniently for patient and operator

![Figure 3. Diagnostic algorithm for deep vein thrombosis (DVT)](image_url)

Table 2. Signs and symptoms of deep vein thrombosis (DVT) and pulmonary embolism (PE)

<table>
<thead>
<tr>
<th>DVT (usually unilateral)</th>
<th>PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Chest pain</td>
</tr>
<tr>
<td>Swelling</td>
<td>Collapse</td>
</tr>
<tr>
<td>Pitting oedema</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Tenderness</td>
<td>Cyanosis/hypoxia</td>
</tr>
<tr>
<td>Increased temperature</td>
<td>Breathlessness/tachypnoea</td>
</tr>
<tr>
<td>Prominent superficial veins</td>
<td>Tachycardia</td>
</tr>
<tr>
<td></td>
<td>Focal chest signs (of infarction)</td>
</tr>
<tr>
<td></td>
<td>Haemoptysis</td>
</tr>
</tbody>
</table>

**Table 2. Signs and symptoms of deep vein thrombosis (DVT) and pulmonary embolism (PE)**

**Figure 3. Diagnostic algorithm for deep vein thrombosis (DVT)**
by Doppler ultrasound scan of leg veins. However only 10–15% of patients presenting to an Accident and Emergency department with possible DVT will have this diagnosis.\(^3\)

Therefore, in order to preserve resources, initial systematic assessment for DVT will normally include application of a clinical scoring system combined with a blood test to quantify fibrin D-dimer levels (see Figure 3). Such algorithms, when applied to the appropriate population, have been shown to effectively categorise patients into two groups:

- Those in whom acute DVT is very unlikely (\(\leq 0.5\%\) risk of presenting with acute VTE during the following three months) and therefore no anticoagulation or radiographic imaging is required
- Those in whom DVT cannot be excluded and who therefore require anticoagulation while awaiting Doppler ultrasound to confirm or exclude DVT.

Similar diagnostic algorithms also exist for PE, while variations of the DVT algorithm have been tested in the community setting.\(^3\)

**Treatment**

Once a diagnosis of DVT has been established, the patient will most often be commenced on a DOAC, unless there is a contraindication to its use, eg renal impairment with estimated glomerular filtration rate (eGFR) <30ml/min, or severe liver disease.\(^3,8\) Apixaban is a commonly used DOAC because of the low incidence of bleeding episodes in both clinical trial and real-world data. Apixaban is commenced at a dosage of 10mg twice daily for seven days then reduced to 5mg twice daily thereafter with no requirement for monitoring (see Table 3).

For those patients in whom a DOAC is felt to be unsuit-
able, the oral anticoagulant warfarin may be used with LMWH treatment initially given concurrently for five to seven days until the warfarin effect is fully established with an International Normalised Ratio (INR) between 2.0 and 3.0. INR levels below 2.0 are suboptimal and those above 3.0 are associated with a higher bleeding risk, and are unnecessary unless a patient has suffered a VTE event despite an INR in the 2–3 range.3,8

Patients with underlying cancer should be offered treatment with LMWH throughout, rather than introducing warfarin, as this strategy has been shown to be superior in this patient category in terms of both lower recurrent VTE and bleeding rates. The use of DOACs in cancer-associated DVT is currently under investigation in clinical trials.12,14

Outpatient diagnosis and treatment of patients with DVT has been shown to be safe and easily managed within rapid medical assessment units or dedicated VTE services.

Duration of anticoagulation will be determined by the presence of risk factors at the time of the event, and whether these persist. Typically, patients with proximal DVT will require three months of anticoagulation. Patients with persisting major risk factors and those with unprovoked VTE events, particularly males for whom the recurrence risk is higher, may be considered for indefinite anticoagulation. Such patients should be assessed individually and the potential benefits of long-term anticoagulation weighed against the bleeding risk.3

Use of risk scoring systems can provide an assessment of risk of recurrent DVT.15,16 The DASH score is one such scoring system, in which a patient receives one point for each of the following: age <50 years and male sex; and two points for a positive D-dimer off-anticoagulation (three to five weeks after cessation of therapy). The system deducts two points for hormone-associated thrombosis. A score ≥2 suggests an above-average risk of VTE recurrence and a likely overall benefit from long-term anticoagulation.15 The HERDOO2 clinical decision rule can be applied without stopping anticoagulation before measurement of D-dimer. The HERDOO2 rule identifies women with one or fewer of the following four criteria as being at low risk of recurrence: hyperpigmentation, oedema or redness in either leg; D-dimer level ≥250µg/L during treatment with anticoagulants; obesity with body mass index ≥30; and age >65 years.16

Following DVT, there is a long-term risk of post-thrombotic syndrome, including pain, swelling, skin discoloration and itch, venous insufficiency, varicosities and, in extreme cases, ulceration. The use of graduated elastic compression stockings can alleviate symptoms for many patients and should be used for as long as they are felt to be effective.7

**Conclusion**

VTE is a common event that can lead to significant morbidity and mortality. There are well-recognised risk factors for VTE and an awareness of these risk factors can lead to the timely administration of thromboprophylaxis and prevention of many VTE events. When a patient does present with symptoms or signs suggestive of VTE, they should be promptly assessed using a clinical decision algorithm leading to an objectively confirmed diagnosis and treatment in an effort to prevent serious long-term sequelae.

**References**


**Declaration of interests**

None to declare.

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