Prevention and management of venous thromboembolism
National Meeting draft

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SIGN guidelines are produced using a standard methodology that has been equality impact assessed to ensure that these equality aims are addressed in every guideline. This methodology is set out in the current version of SIGN 50, our guideline manual, which can be found at www.sign.ac.uk/guidelines/fulltext/50/index.html. The EQIA assessment of the manual can be seen at www.sign.ac.uk/pdf/sign50eqia.pdf. The full report in paper form and/or alternative format is available on request from the NHS QIS Equality and Diversity Officer.

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**KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS**

**LEVELS OF EVIDENCE**

<table>
<thead>
<tr>
<th>Level</th>
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<tr>
<td>1++</td>
<td>High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias</td>
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<td>1+</td>
<td>Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias</td>
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<tr>
<td>1−</td>
<td>Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias</td>
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<td>2++</td>
<td>High quality systematic reviews of case control or cohort studies</td>
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<td>High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal</td>
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<td>2+</td>
<td>Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal</td>
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<tr>
<td>2−</td>
<td>Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal</td>
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<td>3</td>
<td>Non-analytic studies, eg case reports, case series</td>
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<td>Expert opinion</td>
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**GRADES OF RECOMMENDATION**

*Note: The grade of recommendation relates to the strength of the supporting evidence on which the evidence is based. It does not reflect the clinical importance of the recommendation.*

**A**

At least one meta-analysis, systematic review, or RCT rated as 1++,
and directly applicable to the target population; or
A body of evidence consisting principally of studies rated as 1+,
directly applicable to the target population, and demonstrating overall consistency of results

**B**

A body of evidence including studies rated as 2++,
directly applicable to the target population, and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 1++ or 1+

**C**

A body of evidence including studies rated as 2+,
directly applicable to the target population and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 2++

**D**

Evidence level 3 or 4; or
Extrapolated evidence from studies rated as 2+

**GOOD PRACTICE POINTS**

☑ Recommended best practice based on the clinical experience of the guideline development group.

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1 Introduction

1.1 THE NEED FOR A GUIDELINE

The need for a national guideline on prophylaxis was highlighted by a study of fatal pulmonary embolism (PE) in surgical patients in Scotland up to 1995, which showed that 56% of patients who died of PE did not receive antithrombotic prophylaxis, despite having major risk factors and no contraindications to standard antithrombotic regimens. Venous thromboembolism (VTE) is probably an escalating public health problem, due to the increasing age of the population.

1.1.1 UPDATING THE GUIDELINE

Prophylaxis and treatment of VTE were considered separately previously, in SIGN guidelines 36 and 62. However, there is considerable overlap in the risk factors relevant to primary and secondary prophylaxis, and in the modalities available for thromboprophylaxis and treatment of established venous thromboembolism. The current guideline provides comprehensive advice on prevention and management of VTE.

The guideline development group based its recommendations on the evidence available to answer a set of key questions, listed in Annex 1.

The revised guideline includes new evidence, systematic reviews, and consensus statements on the prophylaxis and treatment of VTE published from 1998-2009.

1.1.2 EPIDEMIOLOGY OF VENOUS THROMBOEMBOLISM

Deep vein thrombosis (DVT) is a common disease, often asymptomatic, but presenting with clinical symptoms in about 1 per 1,000 people per year in the general population. The deep veins of the lower limbs are affected most commonly, but thrombosis may affect other sites, including the upper limbs, intracranial and splanchnic veins. Complications include pulmonary thromboembolism (PE) and post-thrombotic leg syndrome (PLS). DVT has multiple causes (see Table 1).

Asymptomatic DVT is defined as DVT detected by screening, usually by compression ultrasound, or 125I fibrinogen scanning, or ascending venography.

Symptomatic lower limb DVT (leg pain or swelling) results from occlusion of a major leg vein. It requires specific investigation and treatment, which in hospitalised patients may delay discharge, or require readmission to hospital.

Pulmonary embolism, which in 90% of cases results from an asymptomatic DVT, may present as breathlessness, faintness, collapse, chest pain or sudden death. Non-fatal PE in hospitalised patients may delay discharge, or require readmission to hospital. Fatal PE is under-diagnosed, because of the non-specificity of symptoms and signs prior to death, which may be attributed to myocardial infarction, pneumonia, or other pathology. About 10% of hospital deaths (1% of all admissions) were attributable to PE in the UK in one study from the 1980s. Further studies have continued to highlight the significant contribution of PE to in-hospital mortality, especially after emergency surgery when prophylaxis is often omitted.

Post-thrombotic leg syndrome (chronic leg pain, swelling, dermatitis, ulcers) is a consequence of destruction of leg vein valves by DVT. Leg ulcers are observed in 2-10% of patients approximately 10 years after their first symptomatic DVT. About 0.2% of the general population have venous leg ulcers.

Venous thromboembolism (VTE) is defined as DVT ± PE.
1.1.3 RATIONALE FOR PROPHYLAXIS

The risk of VTE is increased tenfold in patients who are hospitalised after trauma, surgery or immobilising medical illness, and also in pregnant and puerperal women. DVT is common in such individuals. In many, DVT remains asymptomatic but in others it can cause morbidity and mortality. The rationale for prophylaxis is based on its efficacy, the clinically silent nature of VTE, its high prevalence in hospitalised, pregnant or puerperal patients, and its potentially disabling or fatal consequences. There is evidence that routine prophylaxis reduces morbidity, mortality and costs in hospitalised patients at risk of DVT and PE, as highlighted in national and international guidelines. In contrast, screening for asymptomatic DVT, and its treatment, is expensive, insensitive and not cost effective compared to routine prophylaxis in at-risk patients.

1.1.4 RATIONALE FOR TREATMENT

VTE has a high mortality when untreated but treatment also carries risks, principally haemorrhage. Therefore, accurate confirmation of diagnosis is essential in all cases, usually by imaging. In addition, the duration of treatment with antithrombotics requires individual and careful consideration of the balance of benefits (reduced risk of recurrent thrombosis) and risks (principally haemorrhage).

1.2 REMIT OF THE GUIDELINE

1.2.1 OVERALL OBJECTIVES

The guideline identifies patient groups at risk of VTE (see section 3) and describes the available methods of prophylaxis (see section 4), with general recommendations about efficacy, safety, and how they should be used. Appropriate methods of prophylaxis for specific patient groups are considered in subsequent sections.

Important advances in the diagnosis of DVT and PE are described, including the use of diagnostic algorithms incorporating D-dimer assay. Finally, recommendations are made on treatment options for thrombosis in various anatomical regions, including choice of anticoagulant and duration of use, taking account of evidence of risks and benefits of anticoagulant use.

1.2.2 TARGET USERS OF THE GUIDELINE

This guideline will be of particular interest to anaesthetists, cardiologists, dentists, general and specialist physicians, general and specialist surgeons, general practitioners, haematologists, nurses, obstetricians, pharmacists and radiologists.

1.3 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient’s case notes at the time the relevant decision is taken.
1.3.1 PRESCRIBING OF LICENSED MEDICINES OUTWITH THEIR MARKETING AUTHORIZATION

Recommendations within this guideline are based on the best clinical evidence. Some recommendations may be for medicines prescribed outwith the marketing authorisation (product licence). This is known as “off label” use. It is not unusual for medicines to be prescribed outwith their product licence and this can be necessary for a variety of reasons.

Generally the unlicensed use of medicines becomes necessary if the clinical need cannot be met by licensed medicines; such use should be supported by appropriate evidence and experience. 26

Medicines may be prescribed outwith their product licence in the following circumstances:

- for an indication not specified within the marketing authorisation
- for administration via a different route
- for administration of a different dose.

‘Prescribing medicines outside the recommendations of their marketing authorisation alters (and probably increases) the prescribers’ professional responsibility and potential liability. The prescriber should be able to justify and feel competent in using such medicines.’26

Any practitioner following a SIGN recommendation and prescribing a licensed medicine outwith the product licence needs to be aware that they are responsible for this decision, and in the event of adverse outcomes, may be required to justify the actions that they have taken.

Prior to prescribing, the licensing status of a medication should be checked in the current version of the British National Formulary (BNF).26
2 Key recommendations

The following recommendations were highlighted by the guideline development group as the key clinical recommendations that should be prioritised for implementation. The grade of recommendation relates to the strength of the supporting evidence on which the evidence is based. It does not reflect the clinical importance of the recommendation.

Not available in this draft.
3 Risk factors for venous thromboembolism

3.1 INTRODUCTION

VTE is a multicausal disease, the result of the coincidence of several risk factors, which can be grouped as:

- inherent to the individual and may be inherited eg thrombophilia
- inherent to the individual and can be acquired eg obesity, active cancer and certain drug use (eg oral contraceptive pill)
- the result of an enforced period of immobility eg such as major trauma or surgery, serious medical disorder or pregnancy.

In half to three quarters of patients with VTE risk factors are readily identifiable on taking a careful history and clinical examination. There is insufficient evidence to show whether the risk factors are additive or greater, although the interaction between factor V Leiden and use of the combined oral contraceptive has been shown to be multiplicative.

3.2 CLINICAL ASSESSMENT OF VENOUS THROMBOSIS RISK

There is a need for more focus on ensuring that medical patients at risk receive appropriate thromboprophylaxis. Surveys indicate that compliance with VTE prophylaxis guidelines is generally poor on medical wards in particular. A range of interventions designed to improve compliance with thromboprophylaxis among inpatients is under investigation. A review of the literature concluded that passive distribution of guidelines is inadequate and a system involving active reminders is required to improve compliance. Use of electronic alerts resulted in improved compliance and a reduction in the burden of VTE in a randomised study.

An algorithm for assessing the risk of VTE has been designed on behalf of the Department of Health (see Annex 2). Because the relative risks of bleeding and thrombosis may change over time, due to evolution of disease, interventions and treatments, there is a need to review individual circumstances intermittently.

- All patients admitted to hospital for major trauma (eg fracture causing immobilisation), major surgery (eg duration over 30 minutes), or acute medical illness (eg likely to cause limited mobility for three days or more) should be individually assessed for risk of VTE and bleeding.
- The Department of Health checklist is recommended for this purpose.
- The assessment should be repeated regularly and at least every 48 hours.

Assessment of individual risk should include:

- personal risk factors for VTE (see Table 1)
- past history of VTE (hospitalisation increases risk of recurrent VTE)
- type of trauma, surgery (and anaesthesia) or medical illness.

Hospitals should adopt approaches which are likely to increase compliance with thromboprophylaxis.

Use of electronic alerts or other reminders should be considered to improve compliance and outcomes.

Local risk assessment guidelines should be developed and updated for specific patient groups.
### 3.3 Laboratory Tests in Assessment of Thrombosis Risk

Routine screening for thrombophilias prior to risk situations such as prescription of oral contraceptives or hormone replacement therapy, pregnancy, elective major surgery or central venous catheter insertion is not cost effective and is not recommended.¹⁰⁻³⁵

<table>
<thead>
<tr>
<th>Table 1: Risk factors for venous thromboembolism</th>
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<tbody>
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<td><strong>Age</strong>², ³⁶⁻³⁹</td>
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<td><strong>Obesity</strong>², ³⁶, ³⁷, ⁴⁰, ⁴³, ⁴⁴</td>
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<td><strong>Varicose veins</strong>³⁷, ⁴⁵</td>
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<td><strong>Previous VTE</strong>², ²¹</td>
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<td><strong>Family history of VTE</strong></td>
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<td><strong>Thrombophilias</strong>³¹, ⁴⁹, ⁵⁰</td>
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<td><strong>Other thrombotic states</strong></td>
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**Combined oral contraceptives and hormone replacement therapy and anti-oestrogens**

Combined oral contraceptives (COCs): compared with non-users, COC users have 3-6-fold increased risk. Compared with users of COCs containing second generation progestogens, users of COCs containing third generation progestogens have a 1.7-fold further increase in VTE risk.\(^6\) 2.5-fold increased risk of postoperative VTE in COC users.\(^4\) No evidence that progestogen-only oral contraceptives are associated with increased VTE risk but high-dose progestogens used to treat gynaecological problems associated with 6-fold increased VTE risk.

Oral oestrogen hormone replacement therapy (HRT) users have 2.5-fold increased VTE risk but not transdermal oestrogen HRT users.

Heritable thrombophilia further increases VTE risk in COC and oral oestrogen HRT users.\(^3\)\(^4\)\(^5\) Raloxifene and tamoxifen 2-3-fold increased VTE risk.\(^3\)\(^3\)\(^4\)\(^6\)\(^4\)

**Pregnancy, puerperium (see section 7)**

Approximately 10-fold increased risk during pregnancy v non-pregnant and 25-fold increased risk v non-pregnant/non-puerperal during puerperium.\(^1\)\(^1\) Pregnant and puerperal women with thrombophilia have increased risk of VTE compared to pregnant and puerperal women without an identified thrombophilia.\(^3\)\(^2\)\(^3\)\(^5\)\(^6\)

**Immobility**

Bed rest >3 days, plaster cast, paralysis: 10-fold increased VTE risk; increases with duration

**Immobility during travel (see section 8)**

2-3-fold increased risk

**Hospitalisation**

Acute trauma, acute illness, surgery: 10-fold increased VTE risk

**Anaesthesia**

2-3 fold increased risk of postoperative VTE in general v spinal/epidural.\(^4\)\(^5\)\(^6\)

**Central venous catheters**

Compared with subclavian access, femoral route 11.5-fold risk of VTE.\(^6\) Slightly increased risk of central venous catheter (CVC) thrombosis in patients with prothrombin G20210A or factor V Leiden compared to risk in CVC patients with wild type prothrombin and factor V.\(^3\)\(^0\)
4 Methods of prophylaxis

This section discusses the interventions which reduce the incidence of VTE and provides generic recommendations for their use. Recommendations for specific patient groups or circumstances are made in following sections.

4.1 GENERAL MEASURES

4.1.1 MOBILISATION AND LEG EXERCISES

Immobility increases the risk of DVT about tenfold. A meta-analysis of RCTs of bed rest for several medical conditions found no evidence of benefit of bed rest for any condition. In immobilised patients, leg exercises reduce venous stasis and should be encouraged.

Early mobilisation and leg exercises should be encouraged in patients recently immobilised.

4.1.2 HYDRATION, HAEMODILUTION AND VENESECTION

Haemoconcentration increases blood viscosity and reduces blood flow, especially in the deep veins of the leg in immobile patients.

Adequate hydration should be ensured in immobilised patients.

There is insufficient evidence regarding the balance of risks and benefits to support recommendations about the use of either haemodilution, or venesection (apart from in primary proliferative polycythaemia).

4.2 MECHANICAL METHODS

Mechanical methods of antithrombotic prophylaxis work by increasing mean blood flow velocity in leg veins and reducing venous stasis. They include:

- graduated elastic compression stockings (GCS)
- intermittent pneumatic compression (IPC) devices
- mechanical foot pumps.

There are few trials of mechanical methods in medical patients. Unlike pharmacological methods, mechanical methods do not increase the risk of bleeding and may be preferred in patients in whom bleeding risks outweigh the antithrombotic efficacy of pharmacological prophylaxis. Mechanical methods are contraindicated in patients at risk of ischaemic skin necrosis, e.g., those with critical limb ischaemia or severe peripheral neuropathy. Cross-infection is a risk when devices are reused.

Adequate precautions must be taken to prevent cross-infection when mechanical devices are reused by subsequent patients (see manufacturer’s instructions).

4.2.1 GRADUATED ELASTIC COMPRESSION STOCKINGS

A meta-analysis of RCTs of GCS in prevention of asymptomatic DVT in general surgical patients observed that asymptomatic DVT occurred in 8.6% of active patients compared to 27% of controls (odds ratio, OR 0.34, 95% CI 0.25, 0.46). These results are consistent with an earlier meta-analysis, and with historical reports of efficacy of elastic stockings in PE prophylaxis.

In a large multicentre randomised trial of full length GCS in stroke patients no reduction in VTE rates was demonstrated and adverse events (principally skin lesions) were increased.

GCS reduce asymptomatic DVT and symptomatic PE in surgical patients.
A GCS should not be used routinely in stroke patients.

Data are inadequate to make a recommendation on the use of GCS in other medical patients.

GCS are commercially available as both below-knee and above-knee stockings. Most controlled trials have used above-knee stockings. Studies comparing above-knee and below-knee stockings have been too small, although a meta-analysis suggested equivalent efficacy in surgical patients. A large study of above-knee versus below-knee stockings in stroke patients (CLOTS 2) is currently in progress.

Above-knee or below-knee GCS for prophylaxis of DVT may be used for prophylaxis of DVT provided that there are no contraindications, such as peripheral arterial disease or neuropathy, and that attention is paid to correct fitting and application.

Table 2 summarises contraindications and cautions for GCS. It has been suggested that 15-20% of patients cannot effectively wear GCS because of unusual limb size or shape. An educational programme for appropriate use of GCS was found to be useful in one Scottish Board.

Table 2: Contraindications and cautions for use of GCS

<table>
<thead>
<tr>
<th>CONTRAINDICATIONS</th>
<th>CAUTIONS</th>
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<tr>
<td>Massive leg oedema</td>
<td>Select correct size</td>
</tr>
<tr>
<td>Pulmonary oedema (eg heart failure)</td>
<td>Apply carefully, aligning toe hole under toe</td>
</tr>
<tr>
<td>Severe peripheral arterial disease</td>
<td>Check fitting daily for change in leg circumference</td>
</tr>
<tr>
<td>Severe peripheral neuropathy</td>
<td>Do not fold down</td>
</tr>
<tr>
<td>Major leg deformity</td>
<td>Remove daily for no more than 30 minutes</td>
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<tr>
<td>Dermatitis</td>
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4.2.2 GCS PLUS PHARMACOLOGICAL PROPHYLAXIS OR INTERMITTENT PNEUMATIC COMPRESSION

A meta-analysis of RCTs found that GCS combined with pharmacological prophylaxis or IPC increases efficacy of VTE prophylaxis in reducing the incidence of asymptomatic DVT in surgical patients (OR 0.24; CI 95 0.15-0.37).

A multicentre observational study of elective hip replacement patients found that the combination of GCS with pharmacological prophylaxis appeared to be more effective in reduction of asymptomatic DVT than pharmacological prophylaxis alone.

Increased efficacy may reflect a combined effect on venous stasis and hypercoagulability. The combined approach is currently commonly employed in Scotland, and the rest of the UK.

GCS may be combined with pharmacological prophylaxis or IPC in surgical patients, to increase efficacy of prophylaxis against DVT.

4.2.3 INTERMITTENT PNEUMATIC COMPRESSION

IPC devices periodically compress the calf and/or thigh muscles of the leg (inflation pressures 35-40 mmHg at about 10 s/min), and stimulate fibrinolysis. Compression devices are usually applied immediately before or during surgery and are often replaced by GCS following surgery as they can cause discomfort in the conscious patient.
Pooled analyses of trials of IPC in prevention of asymptomatic DVT after non-orthopaedic surgery showed a relative risk reduction of around 68%. Similar results have been demonstrated following orthopaedic (mostly elective hip) surgery. An observational study found that IPC reduced the risk of rehospitalisation for symptomatic VTE after elective hip surgery.

**A** IPC devices are effective in prophylaxis of asymptomatic DVT in surgical patients.

### 4.2.4 MECHANICAL FOOT PUMPS AND FOOT IMPULSE TECHNOLOGY

The A-V impulse system foot pump has been developed to provide mechanical prophylaxis in patients who are unable to weight bear and has only been used in orthopaedic surgery. RCT data suggest efficacy in prevention of asymptomatic DVT. There is no evidence that these devices reduce symptomatic DVT or PE. Skin necrosis has been reported and discomfort from the device can lead to poor compliance.

**A** Mechanical foot pumps are effective in prophylaxis of asymptomatic DVT in orthopaedic surgery patients.

### 4.3 ANTIPLATELET AGENTS

#### 4.3.1 EFFICACY AND SAFETY IN SURGICAL PATIENTS

A meta-analysis of 53 RCTs of antplatelet agents (usually aspirin) in prophylaxis of VTE in general or orthopaedic surgery reported significant reductions in risks of asymptomatic DVT (26% vs. 35%), pulmonary embolism (0.6% vs. 1.6%) and fatal PE (0.2% vs. 0.6%); with a non-significant trend to lower mortality and a significant increase in major bleeding. The analysis, however, included many old, and frequently small studies including some with inadequate verification of VTE. A randomised trial, the Pulmonary Embolism Prevention (PEP) Trial supported an effect of aspirin. In this study, 13,356 patients undergoing surgery for hip fracture and 4,088 patients undergoing elective hip arthroplasty were randomised to aspirin (160 mg daily, started preoperatively and continued for 35 days) or placebo; however aspirin was give in addition to ‘any other thromboprophylaxis thought necessary’. Patients were not screened for asymptomatic DVT. Combining the results from all trials revealed no significant reduction in total mortality (3.9% vs. 4.0%), while confirming a significant increase in major bleeding (7.7% v. 6.2%) which was similar to the reduction in symptomatic DVT or PE. There was a significant reduction in fatal PE (0.2% v. 0.6%; number needed to treat (NNT) 250). The overall available data suggest that the efficacy of aspirin is less than that of low dose heparin for VTE thromboprophylaxis. A randomised trial indicated that a heparinoid is more effective than aspirin in hip fracture patients.

**B** Aspirin is not recommended for VTE prophylaxis as other available agents are more effective.

#### 4.3.2 EFFICACY AND SAFETY IN MEDICAL PATIENTS

The efficacy of aspirin in reduction of total cardiovascular events (myocardial infarction (MI) stroke, PE, cardiovascular death) is now clearly established in acute MI and in acute ischaemic stroke and outweighs the increased risk of bleeding (see section 6).

Aspirin is commonly used to prevent MI in the older population. Meta-analyses have shown that patients receiving aspirin combined with low-dose heparins have non-significant trends to increased efficacy in VTE prevention, and to increased risk of bleeding.

In general perioperative low-dose heparin is not contraindicated in patients already taking aspirin.
4.4 UNFRACTIONATED AND LOW MOLECULAR WEIGHT HEPARINS

Unfractionated heparin (UFH) and several low molecular weight heparins (LMWHs; dalteparin, enoxaparin, bemiparin and tinzaparin) are currently licensed in the UK for prophylaxis of VTE. They vary in their manufacture, chemistry and biology, but it is not clear whether or not these characteristics affect clinical efficacy or safety equivalence.

For prophylaxis of VTE, heparins are usually given subcutaneously, in lower doses than are used for the treatment of established thromboembolism. They have little effect on the activated partial thromboplastin time (APTT). LMWHs have a longer half-life than UFH, so can be given as once daily subcutaneous injections for prophylaxis, compared to 8-12 hourly for UFH. Heparin prophylaxis is usually given for at least five days (the minimum duration of prophylaxis in RCTs) or until hospital discharge if earlier. Prolonged prophylaxis may be indicated in patients with continued illness and immobility, and in orthopaedic patients.

Post-discharge prophylaxis should be discussed with the primary care team prior to a patient’s discharge from hospital.

4.4.1 EFFICACY AND SAFETY OF UFH IN SURGICAL PATIENTS

A meta-analysis of RCTs including a large trial found that low-dose subcutaneous UFH significantly reduces the incidence of asymptomatic DVT, symptomatic DVT and PE, fatal PE, and total mortality. A significant increase in major bleeding (from about 4% to 6%) was also observed; however there was no increase in fatal bleeding (n=8 vs. n=6).

4.4.2 EFFICACY AND SAFETY OF LMWHs IN SURGICAL PATIENTS

Meta-analyses of RCTs have shown that subcutaneous LMWHs have similar prophylactic efficacy and risk of bleeding to UFH. Once UFH had been shown to significantly reduce both fatal postoperative PE and mortality, most RCTs of LMWHs have used UFH (or other methods of prophylaxis) in the control group, rather than placebo injections or no specific prophylaxis, for ethical reasons.

4.4.3 EFFICACY AND SAFETY OF UFH AND LMWHs IN MEDICAL PATIENTS

A meta-analysis of RCTs in general medical patients showed similar reductions in asymptomatic DVT and symptomatic PE to those in surgical patients. Subcutaneous low-dose heparin (UFH or LMWH) is effective in prophylaxis of asymptomatic and symptomatic VTE in surgical and medical patients.

Because of their longer half-life, lesser tendency to cause heparin associated thrombocytopenia and once daily dosing schedule, LMWHs are preferred to UFH.

4.4.4 ADMINISTRATION, DOSAGE AND COAGULATION MONITORING

When administered for thromboprophylaxis, both UFH and LMWH are given subcutaneously. The risk of wound haematomas can be reduced by avoiding injection sites close to wounds. The dose of UFH is 5,000 IU 8-12 hourly or 7,500 IU 12-hourly. Consult the appropriate manufacturer’s data sheet for the dose of LMWH. In general, monitoring of the anticoagulant effect of low-dose UFH or LMWH is not required. As LMWHs have little effect on the APTT, plasma anti-Xa activity should be measured if required. Monitoring may be of value:

- in pregnancy (see section 7)
- at extremes of body weight
- if there are complications such as haemorrhage or accidental overdose
- in patients with renal failure given higher (therapeutic) doses of LMWH.

See the SIGN guideline on antithrombotic therapy.
4.4.5 REVERSAL OF HEPARIN ANTICOAGULATION

As the half-life of UFH is short, it is usually sufficient to stop the heparin if mild bleeding occurs. If severe bleeding occurs protamine sulphate should be given. Protamine is less effective in reversal of LMWH anticoagulation (consult manufacturer’s data sheet).

4.5 HEPARINOIDs

The heparinoid, danaparoid, is effective in prophylaxis of DVT in patients undergoing general or orthopaedic surgery. It is also effective in treatment of patients with heparin associated thrombocytopenia, although there is cross-reactivity with heparin in some cases and can be used as short term prophylaxis in patients with a history of this condition.

4.6 HIRUDINS

Hirudins are specific and direct thrombin blockers, which unlike heparins do not require circulating antithrombin.

Lepirudin is effective in treatment of patients with VTE in patients with heparin associated thrombocytopenia.

4.7 PENTASACCHARIDES (FONDAPARINUX)

The synthetic pentasaccharide fondaparinux is a highly selective, indirect inhibitor of activated factor-Xa. In a randomised controlled trial in older acute medical patients fondaparinux was effective in the prevention of asymptomatic and symptomatic DVT.

4.8 ORAL ANTICOAGULANTS

Warfarin is effective in prophylaxis of VTE. However, it is not widely used for this indication in the UK because its use requires daily monitoring by the International Normalised Ratio (INR) of the prothrombin time, and because it increases the risk of bleeding after trauma or surgery, as well as after spinal or epidural anaesthesia.

Contraindications and cautions include:
- bleeding disorders
- bleeding or potentially bleeding lesions
- spinal or epidural anaesthesia
- pregnancy, due to fetal toxicity (see section 7).

In patients on long term oral anticoagulant therapy (eg for atrial fibrillation or heart valve disease/prosthesis) who are immobilised by illness, trauma or surgery, continuation of oral anticoagulants may be appropriate prophylaxis of VTE. However, the INR should be checked and the dose of anticoagulant adjusted according to the perceived balance of risks of thrombosis and bleeding, especially after trauma or surgery.

4.9 DEXTRANS

Intravenous dextrans appear less effective than heparins in prophylaxis of asymptomatic DVT, but may be equally effective in prophylaxis of PE. However, dextrans are not widely used in the UK because of cumbersome administration and adverse effects including allergic reactions (on rare occasions anaphylaxis), bleeding, and fluid overload (especially in patients with renal or cardiac insufficiency).
Dextrans should be avoided in patients with renal or cardiac insufficiency.

Women undergoing Caesarean section have been reported to suffer an anaphylactoid reaction resulting in uterine hypertonus, profound fetal distress and a high incidence of fetal death.\textsuperscript{110}

Dextrans should be avoided peripartum.

4.10 NEW ORAL AGENTS

Dabigatran and rivaroxaban directly inhibit thrombin and factor-Xa respectively. They are active via the oral route and have reproducible pharmacokinetics which allows fixed dosing with no requirement for coagulation monitoring.
5 Thromboprophylaxis in surgical patients

5.1 GENERAL SURGERY
Good quality evidence from a meta-analysis of randomised controlled trials performed on mixed and stratified groups of general surgical patients was identified.\(^{96, 111-114}\) It is reasonable to generalise from these studies to consider all patients having intra-abdominal surgery. Separate analyses have been performed on various aspects of intra-abdominal surgery.\(^{96, 111-114}\) Some patients will have cancer as an added risk factor but each patient should be assessed individually.

5.1.1 RISK OF VTE
Observational studies of patients who did not receive specific thromboprophylaxis prior to abdominal surgery showed a significant incidence of DVT and PE:\(^{2, 6, 7, 9, 22, 102}\)

- asymptomatic DVT at screening: 25%
- asymptomatic proximal DVT at screening: 7%
- symptomatic DVT: 6%
- symptomatic non-fatal PE: 1-2%
- fatal PE: 0.5%

Early mobilisation after open surgery and increased use of laparoscopic procedures with faster recovery may reduce the incidence of DVT but the population undergoing surgery is aging and has increased comorbidity.

A systematic review of RCTs and controlled clinical trials (CCTs) found that for major colorectal surgery thromboprophylaxis significantly reduced VTE. Unfractionated heparin was as effective as low molecular weight heparin and adding stockings produced an additive benefit.\(^{115, 116}\)

5.1.2 UNFRACTIONATED HEPARIN
For patients undergoing abdominal surgery, unfractionated heparin given subcutaneously is effective in reducing the risks of DVT and pulmonary embolism and reducing mortality.

5.1.3 LOW MOLECULAR WEIGHT HEPARIN
Low molecular weight heparin is as effective as unfractionated heparin without increased bleeding compared to unfractionated heparin.\(^{103, 104}\) Low molecular weight heparin can be administered once daily rather than two or three times per day and is less likely to cause heparin induced thrombocytopenia (see section 15.2).

5.1.4 MECHANICAL METHODS
Graduated compression stockings produce a reduction in the rate of DVT when compared to no thromboprophylaxis and their use is additive to that of low-dose and fractionated heparin. Intermittent pneumatic compression may produce similar effects although the evidence is weaker (see section 4.2).
5.1.5 DURATION OF PROPHYLAXIS

There is good evidence that VTE may occur following discharge from hospital. The incidence however is low. One randomised trial of 300 patients receiving either 9 or 28 days of LMWH after abdominal or pelvic surgery showed only two proximal DVTs in the shorter term group and one in the long term group. Studies have compared standard versus extended pharmacological prophylaxis showing a small reduction in the rate of symptomatic VTE but this was not thought to be cost effective.

All surgical patients should be assessed for their individual risk of thrombosis and increased risk of bleeding with thromboprophylaxis.

The preferred methods of prophylaxis in patients undergoing abdominal surgery who are at moderate to high risk of VTE are:

- GCS unless contraindicated
- subcutaneous LMWH
- subcutaneous UFH.

In patients undergoing abdominal surgery GCS can be substituted for UFH or LMWH when these agents are contraindicated for example due to high bleeding risk.

GCS should be combined with UFH or LMWH in patients undergoing abdominal surgery.

Extended prophylaxis should be considered on a case-by-case basis, for example when multiple thrombosis risk factors are present.

5.2 LAPAROSCOPIC SURGERY

The reduced hospitalisation and early ambulation following laparoscopic surgery should decrease the risks of VTE compared to open surgery. The raised intra-abdominal pressure and the head up positioning for much laparoscopic surgery would increase lower limb venous pooling and may increase risks.

There is no evidence that using a laparoscopic technique reduces the risk of VTE. The volume of evidence regarding VTE following laparoscopic surgery is poor. Laparoscopic surgery can include procedures from a very short diagnostic laparoscopic procedure to lengthy major surgery performed using a laparoscopic route, eg laparoscopic colectomy. It is difficult to separate the mode of surgery, ie laparoscopic versus open, from the risks of the procedure and of the underlying condition, when assessing risk of VTE.

There is consistent evidence of very low incidence of VTE following laparoscopic procedures in patients receiving prophylaxis. Rates of VTE appear to be low, however, following laparoscopic surgery even when rates of prophylaxis are also low. Mechanical methods and particularly IPC may reduce lower limb venous pooling. Those studies which have been performed show a low incidence of VTE following the use GCS, IPC or LMWH alone or in combination.

Patients undergoing laparoscopic surgery should be assessed individually and prophylaxis given to patients at moderate or high risk.

The preferred methods of prophylaxis in patients undergoing laparoscopic surgery are GCS, IPC or LMWH alone or in combination.

5.3 BARIATRIC SURGERY

Intra-abdominal bariatric surgery is increasing in volume as evidence of effectiveness becomes established. The increase in morbid obesity in the population also means that increasing numbers of patients who are morbidly obese require other forms of surgery. Obesity appears to be an independent risk factor for VTE (see section 3).
The incidence of VTE following bariatric surgery is low. There is limited evidence from a small number of studies showing an incidence of VTE from 1%-3%, although the data are mostly derived from registries. The evidence for the effectiveness of prophylaxis in these patients is also poor.

- Existing criteria for risk stratification should be applied and patients at moderate to high risk of VTE should be offered prophylaxis.
- Patients undergoing bariatric surgery should receive thromboprophylaxis as recommended for those undergoing general surgery.
- The dosages of heparin may need to be increased in these patients.

5.4 GYNAECOLOGICAL SURGERY

5.4.1 RISK OF VTE

Risk factors for VTE in gynaecological surgical patients include abdominal rather than vaginal approach to surgery, malignancy, age, previous VTE, perioperative blood loss and previous radiotherapy. Cancer is the most significant risk factor. The risk of VTE in gynaecological patients having laparoscopic surgery for non-malignant conditions is low but other comorbid patient factors should be taken into consideration. Patients without other risk factors for VTE undergoing short procedures (<30 minutes) do not require any specific thromboprophylaxis.

5.4.2 HEPARINS

A systematic review found that heparin or LMWH prophylaxis significantly reduced DVT rates in patients undergoing surgery for gynaecological cancer (relative risk reduction, RRR 0.58; 85% CI 0.35-0.95). There is insufficient evidence to say whether unfractionated or LMWH is superior as the studies were not sufficiently powered. The optimal regimen duration of treatment is also uncertain for these patients. An RCT found an RRR of 0.6 for DVT in patients who received LMWH for one month after surgery compared to one week.

5.4.3 MECHANICAL METHODS

There is insufficient evidence to determine whether intermittent pneumatic compression or GCS are effective in their own right or if they increase the efficacy of pharmacological prophylaxis with heparin or LMWH specifically in gynaecological surgery.

- All gynaecological patients should be assessed for their individual risk of VTE and bleeding.
- When the assessment of risk favours use of thromboprophylaxis, heparin should be administered.
- LMWH is preferred to UFH on grounds of convenience also (once rather than twice daily administration)

5.5 ORTHOPAEDIC SURGERY

The evidence of supporting pharmacological prophylaxis (outcome measure reduced incidence of proven DVT) in patients undergoing hip or knee replacement or who have had a hip fracture is strong. There is no evidence that pharmacological prophylaxis reduces risk of fatal pulmonary embolism or total death rate. There is agreement that a combination of mechanical (pneumatic devices) and pharmacological prophylaxis is associated with the lowest DVT risk.
5.5.1 LOW MOLECULAR WEIGHT HEPARIN

Low molecular weight heparin (LMWH) has been extensively studied in this patient population and is effective and safe. LMWH reduces the DVT risk by approximately 60% compared to placebo. LMWH is more effective than unfractionated heparin and also more effective than warfarin at reducing DVT.\(^{96}\)

Large well conducted RCTs have shown that commencing LMWH dosing within eight hours of surgery was as effective as giving the first dose one hour before surgery with a trend to lower bleeding complications compared with preoperative dosing.\(^{96}\)

5.5.2 FONDAPARINUX

In total hip replacement the pentasaccharide factor ii inhibitor (fondaparinux) is slightly more effective at reducing the incidence of asymptomatic DVT, but not symptomatic DVT. Some studies have shown non-significant trends to a higher incidence of bleeding events with fondaparinux compared with LMWH.\(^{96, 113, 121, 122}\)

5.5.3 WARFARIN

Vitamin K antagonists are effective, but not widely used alone in Europe.\(^{96, 113, 120}\) They are less effective than LMWH (risk reduction, RR 1.5), causing an increased risk of bleeding/wound complications.\(^{123}\)

5.5.4 ASPIRIN

Aspirin reduces the DVT risk by approximately 30% compared to placebo. Aspirin is less effective than LMWH/pentasaccharides/warfarin in terms of DVT. If a patient has a high risk of an arterial thrombotic event (coronary stents, unstable angina, stroke) however, aspirin should be continued in the perioperative period.

There is insufficient evidence to support the use of aspirin as sole thromboprophylactic agent.\(^{124, 125}\)

5.5.5 RIVAROXABAN

Rivaroxaban is a new direct oral factor-Xa inhibitor. Four RCTs have shown greater efficacy in preventing DVT compared with enoxaparin (extended prophylaxis of 35 days in total hip replacement (THR), 14 days in total knee replacement (TKR). There was no difference in the incidence of bleeding events.

5.5.6 DABIGATRAN

Dabigatran is a new direct oral thrombin inhibitor. Two RCTs have shown similar rates for DVT/PE for dabigatran compared with LMWH.\(^{126}\)

Rivaroxaban and dabigatran have been accepted by the Scottish Medicines Consortium (SMC) as acceptable agents for thromboprophylaxis in THR and TKR surgery. Both drugs are attractive agents because they are given orally, have predictable pharmacokinetics and dynamics and do not require monitoring.

5.5.7 MECHANICAL PROPHYLAXIS

There is evidence for foot pumps/IPC, but not for GCS in reducing DVT rates. RCTs have shown a beneficial effect of mechanical prophylaxis (foot pumps, IPC) to reduce the risk of DVT/PE and death.\(^{120}\) The main practical difficulty with IPC is patient compliance. The devices have to be used continuously in the postoperative period to be effective.

No good quality studies were identified comparing pharmacological thromboprophylaxis with pharmacological plus mechanical prophylaxis.
5.5.8 DURATION OF PROPHYLAXIS

The evidence supporting more prolonged (post hospital discharge) thromboprophylaxis is strong. An RR of 0.36 and NNT of 36 was found. The benefit of post discharge extended prophylaxis is greater in THR than TKR patients. The incidence of symptomatic DVT was reduced from 2.7% to 1.1% in patients given LMWH extended prophylaxis compared to those who only received it while in hospital after THR. The absolute risk reduction for PE was more modest at 0.4% (95% confidence interval, CI 0.3 to 1.4 NNT 278), and for fatal PE it was 0.1% (95% CI 0.1 to 0.3 NNT 1093).

Prolonged prophylaxis with fondaparinux appears to be even more effective after hip fracture surgery. Pharmacoeconomic studies suggest that extended prophylaxis is cost effective because of the resulting reduced cost of treating VTE.

5.5.9 BLEEDING RISK

All forms of pharmacological prophylaxis are associated with an increased risk of bleeding especially wound haematoma, an important complication of joint replacement surgery. Comparison of published evidence is difficult as no unified definition of bleeding exists. A large meta-analysis has shown that the lowest relative risk of bleeding is for warfarin (0.59) compared with LMWH, which has a lower risk than UFH (1.52) and pentasaccharides (1.52). Introduction postoperatively reduces concerns about vertebral canal haematoma associated with central neuraxial regional anaesthesia techniques which are widely practised in lower limb orthopaedic surgery.

Patients undergoing THR or TKR surgery should receive pharmacological prophylaxis (with LMWH, fondaparinux, rivaroxaban or dabigatran) combined with mechanical prophylaxis unless contraindicated. Dosing should be commenced after surgery within 6-8 hours. Extended prophylaxis with LMWH or fondaparinux in THR and hip fracture and 14 days in TKR can be considered. With dabigatran the recommended duration is nine days for TKR and 27-34 days for THR and with rivaroxaban 14 days and 35 days respectively. Patients with additional risk factors for VTE such as previous VTE should be offered extended prophylaxis.

Patients with increased risk of bleeding should be given mechanical prophylaxis alone (IPC/foot pumps). If the bleeding risk has become acceptable then pharmacological prophylaxis should be added.

5.6 UROLOGICAL SURGERY

There have been very few RCTs of thromboprophylaxis in urological surgery in the past two decades, and only one that was considered to be of good quality evidence. Despite the paucity of evidence in urological patients, the risks of VTE in major urological surgery are similar to those seen in general and gynaecological surgery, so recommendations may be extrapolated from these situations.

The risk of VTE in transurethral surgery is low and use of anticoagulant prophylaxis may increase the risk of bleeding. Unless the patient has other risk factors for VTE, mechanical prophylaxis and early mobilisation will be adequate.

The risk of VTE for laparoscopic urological procedures is also low and pharmacological prophylaxis may increase the risk of bleeding. Mechanical prophylaxis (GCS and/or IPC) and early mobilisation will be adequate unless the patient has additional risk factors for VTE.
In major open urological procedures, such as radical prostatectomy or cystectomy, pharmacological prophylaxis with or without mechanical prophylaxis is recommended. Data on these patients, however, are sparse.

☐ All urological patients should be assessed for their individual risk of VTE and bleeding.

D When the assessment of risk favours use of thromboprophylaxis heparin should be administered.

D ▪ LMWH is preferred to UFH on grounds of convenience also (once rather than twice daily administration).

D ▪ Mechanical prophylaxis (GCS and or IPC) can be used in conjunction with pharmacological prophylaxis.

5.7 NEUROSURGERY AND TRAUMATIC BRAIN INJURY

Patients undergoing major neurosurgery are at high risk of VTE. The risk of total DVT is approximately 20% and 5% for proximal DVT. The risk is similar in patients with a traumatic brain injury. Mechanical thromboprophylaxis is usually recommended because of the increased risk of potentially devastating intracranial bleeding events that are associated with pharmacological prophylaxis.

IPC is very effective in reducing DVT in neurosurgical patients, reducing the absolute DVT rate from 22% to 7%; RRR 68% compared to patients receiving no prophylaxis. Combined IPC and GCS does not increase the efficacy compared to IPC alone.

There have been few large RCTs of pharmacological thromboprophylaxis in neurosurgery. The two largest trials identified compared GCS with GCS and LMWH. Both studies found a significant improvement in DVT rates in the LMWH and GCS groups compared with GCS alone.

There is an increased risk of intracranial bleeding events in patients receiving LMWH compared to mechanical prophylaxis. Reported pooled rates of bleeding are 2.1% for LMWH and 1.1% for mechanical prophylaxis. A meta-analysis found that bleeding at any site was twice as common in patients who had received LMWH (6.1% v 3.0%).

☐ All neurosurgical patients should be assessed for their individual risk of VTE and bleeding.

A Neurosurgical patients should routinely be offered mechanical prophylaxis (with GCS or IPC).

B Combining LMWH with mechanical prophylaxis may be considered in patients with additional risk factors for VTE.

5.8 CARDIOTHORACIC SURGERY

There was little evidence specifically related to cardiac or thoracic surgery. Two guidelines and one review were identified.

There is evidence from a systematic review of two studies that combined modalities are more effective than single modalities for VTE prophylaxis in cardiothoracic surgery.
5.8.1 THORACIC SURGERY

The risk of VTE may be underestimated after thoracic surgery because few prospective studies have recorded this complication. Thoracic surgery appears to be associated with a risk of VTE similar to that seen after major general surgery. The evidence on prevention is limited (two RCTs in the last 30 years). The American College of Chest Physicians evidence based clinical practice guidelines on the prevention of venous thromboembolism recommend routine thromboprophylaxis with LMWH, UFH or fondaparinux during major thoracic surgery and optimal use of mechanical thromboprophylaxis with properly fitted GCS and/or IPC for patients with high risk of bleeding undergoing thoracic surgery.96 Similarly, the NICE guideline on reducing the risk of venous thromboembolism in inpatients undergoing surgery recommends that patients having thoracic surgery should be offered mechanical prophylaxis and those with one or more risk factors for VTE should be offered mechanical prophylaxis and LMWH.113

☑ All patients having thoracic surgery should be assessed for their individual risk of VTE and bleeding.

A Patients having thoracic surgery should be offered mechanical prophylaxis with IPC or GCS.

A Patients having thoracic surgery with any additional risk factors for VTE should be offered mechanical prophylaxis and LMWH.

5.8.2 CARDIAC SURGERY

The incidence of VTE in patients undergoing cardiac surgery is uncertain and the need for thromboprophylaxis is controversial. Coronary artery bypass graft (CABG) is the only procedure considered as other procedures generally require postoperative therapeutic anticoagulation. Due to the limited available evidence, it is unclear whether or not routine thromboprophylaxis should be offered to all patients undergoing CABG.96 Pharmacological agents used during cardiac procedures may alter choice of prophylaxis.113

A Patients having CABG should be offered mechanical prophylaxis.

B Patients having cardiac surgery who are not otherwise receiving anticoagulation therapy and who have any additional risk factors for VTE should be offered mechanical prophylaxis and LMWH.

5.9 VASCULAR SURGERY

Vascular surgery includes aortic surgery, peripheral arterial surgery, the insertion of intravenous lines and venous (varicose vein) surgery. The incidence of VTE in patients with severe peripheral arterial disease is high. The quality of evidence for the benefit of prophylactic measures in these patients, however, is poor. In venous disease the incidence of VTE following uncomplicated venous interventions is low despite the fact that varicose veins are a risk factor for VTE. There is no evidence of the incidence of VTE following non-operative treatment for varicose veins. Evidence is poor so some degree of extrapolation is necessary.

5.9.1 MAJOR VASCULAR SURGERY

Patients undergoing abdominal vascular surgery seem to have a similar incidence of VTE as patients undergoing general abdominal surgery. Most of these patients have systemic anticoagulation during the procedure but should have thromboprophylaxis in the postoperative period.

Patients with critical limb ischaemia or following amputation are at high risk of VTE. Mechanical methods are usually contraindicated in vascular patients but unfractionated or low molecular weight heparin can usually be given. Most of these patients are on aspirin and a statin which should be continued.
In patients with critical limb ischaemia or who are undergoing major peripheral vascular surgery (including amputation), subcutaneous low-dose UFH or LMWH is recommended.

5.9.2 VARICOSE VEIN SURGERY

The risk of VTE following varicose vein surgery appears to be low despite varicose veins being a risk factor for VTE. There is no evidence that the incidence of VTE following “non-operative” varicose vein procedures such as radiofrequency ablation, endovenous laser treatment or foam sclerotherapy is any different from that following open surgery. The consequences of DVT may be higher in these patients.

While the presence of varicose veins increases the risk of DVT after major abdominal, pelvic or orthopaedic surgery (see section 3), the risk of VTE after varicose vein surgery appears low, in the absence of other risk factors (eg previous DVT or PE, prolonged surgery or immobility). GCS are commonly prescribed for such patients; the addition of LMWH or UFH is recommended in those with additional risk factors.

Patients undergoing varicose vein surgery should be assessed individually for thrombosis risk.

In patients undergoing varicose vein surgery who have no additional risk factors for VTE postoperative GCS are recommended (in addition to compression bandaging on the operative leg).

In the presence of additional risk factors the addition of subcutaneous UFH or LMWH is recommended.
6 Thromboprophylaxis in medical patients

6.1 PHARMACOLOGICAL THROMBOPROPHYLAXIS TO PREVENT ASYMPTOMATIC AND SYMPTOMATIC VTE

A systematic review found an incidence of symptomatic VTE among ‘non-specialised’ medical patients (not stroke or acute coronary event patients) of between around 1 and 6%.133

In relation to pharmacological thromboprophylaxis to prevent asymptomatic and symptomatic VTE in medical patients, most studies have employed UFH or LMWH or fondaparinux and have included heterogeneous patient cohorts including some with stroke. There is strong evidence for efficacy from five meta-analyses.134-138 A 48% reduction in symptomatic PE (NNT 241), a 48% reduction in symptomatic DVT (non-significant. NNT 211), and a 51% reduction in asymptomatic DVT (NNT 33) was reported.137 A reduction in all-cause mortality was not found, although one systematic review reported a significant reduction in fatal pulmonary embolism (NNT 400).134 There was overall benefit due to prevention of VTE, despite a significant increased risk of bleeding. When compared directly LMWH is more effective than UFH and less likely to cause injection site haematoma.138

☐ All medical patients should undergo individual assessment for thrombosis risk.

☐ When the assessment of risk favours use of thromboprophylaxis, heparin or fondaparinux should be administered.

☐ LMWH or fondaparinux are preferred to UFH on grounds of convenience (once rather than twice daily administration).

6.2 MECHANICAL PROPHYLAXIS TO PREVENT ASYMPTOMATIC AND SYMPTOMATIC VTE

In relation to physical methods of thromboprophylaxis in medical patients, the data are inadequate. The majority of studies employing graduated compression stockings have been performed on surgical patients, where benefit has been confirmed (see section 4.2.1).

A Health Technology Assessment (HTA) of mechanical methods, oral anticoagulation, dextran and regional anaesthesia as thromboprophylaxis identified a total of only 257 medical patients in two trials.119 In a large multicentre randomised trial of full length GCS in stroke patients no reduction in VTE rates was demonstrated and adverse events (principally skin lesions) were increased.79 The results did not appear to be explained by severity of paralysis. This result sheds doubt on the efficacy of GCS in medical patients in general. There was some limited evidence that below-knee GCS are equivalent to thigh length stockings in surgical patients.1++

☐ GCS should not be used routinely in medical patients.

☐ Their use can be considered in non-stroke patients who are unsuitable for pharmacological prophylaxis, (for example due to risk of bleeding) provided that there is no contraindication.

☐ Below knee stockings may be preferred for reasons of convenience and compliance.

6.3 ACUTE STROKE

Use of pharmacological thromboprophylaxis for VTE with UFH/LMWH/fondaparinux is not recommended routinely in stroke patients as the reduction in VTE is offset by increased bleeding. Where the risk of VTE is deemed to be especially high, LMWH is recommended in preference to UFH.139.
6.4 ACUTE CORONARY SYNDROMES

In acute coronary syndromes, patients in whom there is electrocardiogram (ECG) indication of ischaemia and/or elevation of cardiac markers should receive LMWH or fondaparinux as part of the management of cardiac ischaemia.140

6.5 OTHER MEDICAL PATIENTS

6.5.1 PATIENTS WITH CANCER

A Cochrane review on the use of anticoagulants to prevent in-dwelling venous catheter-related thrombosis in cancer patients reported a trend towards reduced incidence of line related symptomatic deep vein thrombosis with heparin but not with warfarin.141 A recent large randomised trial of warfarin demonstrated no reduction in catheter thrombosis.142

The effect of anticoagulants on survival in patients with cancer was studied in a Cochrane review of five RCTs of warfarin versus placebo.143 There was increased bleeding with no significant reduction in mortality, apart from in a subgroup with small cell lung cancer at six but not at 12 months.143 A systematic review included eight RCTs of LMWH versus vitamin K antagonist (VKA).144 All individual studies were negative and there was no difference detected when the data were combined.

A Neither heparin nor VKA is indicated for prolongation of survival in cancer.

A Neither warfarin nor heparin should be used to prevent catheter-related deep vein thrombosis in cancer patients.

A Patients with active cancer are generally at high risk of VTE and should be considered for prophylaxis with LMWH or fondaparinux whilst hospitalised.
7 Pregnancy and the puerperium

VTE is a major cause of maternal death in the United Kingdom (1.56 per 100,000 maternities). VTE is ten times more common in women during pregnancy and the puerperium, compared to women who are not pregnant. VTE may complicate all stages of pregnancy, including the first trimester.

7.1 RISK FACTORS FOR VTE

Risk factors for the development of VTE in pregnancy and the puerperium are well described in cohort studies, (see Table 3). These have been reviewed in recently updated guidelines in the United Kingdom and in North America ACCP guidelines. Cohort studies have shown that the presence of multiple risk factors increases the risk of VTE. Over 70% of women who suffer a fatal or non-fatal PE in the United Kingdom have identifiable risk factors, hence many PEs are potentially preventable with the appropriate use of thromboprophylaxis.

Table 3: Risk factors for VTE in pregnancy

<table>
<thead>
<tr>
<th>Pre-existing</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Previous VTE (DVT or PE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombophilia (heritable and acquired, including antiphospholipid syndrome, see Table 1)</td>
<td></td>
<td></td>
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<tr>
<td>Age over 35 years</td>
<td></td>
<td></td>
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<tr>
<td>Obesity (BMI &gt; 30 kg/m²) either pre-pregnancy or in early pregnancy</td>
<td></td>
<td></td>
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<tr>
<td>Parity &gt; 4</td>
<td></td>
<td></td>
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<tr>
<td>Gross varicose veins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paraplegia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammatory disorders eg inflammatory bowel disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Some medical disorders, eg nephrotic syndrome, certain cardiac diseases, active cancer, stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myeloproliferative disorders, eg essential thrombocythaemia, polycythaemia vera</td>
<td></td>
<td></td>
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<tr>
<td>Venous hypertension secondary to femoral vein stenosis (intravenous drug abuse)</td>
<td></td>
<td></td>
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<tr>
<td>Multiple pregnancy</td>
<td></td>
<td></td>
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<tr>
<td>Anaemia</td>
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</tr>
</tbody>
</table>

| New onset or transient | | |
| Surgical procedure in pregnancy or puerperium, eg evacuation of retained products of conception, postpartum sterilisation | | |
| Caesarean section | | |
| Hyperemesis | | |
| Dehydration | | |
| Ovarian hyperstimulation syndrome | | |
| Severe infection, eg pyelonephritis | | |
| Immobility (>4 days bed rest) | | |
| Pre-eclampsia | | |
| Excessive blood loss | | |
| Long-haul travel | | |
| Prolonged labour | | |
| Mid-cavity instrumental delivery | | |
| Immobility after delivery | | |
7.2 ANTENATAL THROMBOSIS RISK ASSESSMENT

Women attending for their first antenatal visit should be assessed for risk factors for VTE. Specifically, they should be asked about a personal and family history of VTE and whether an objective diagnosis was made.

During pregnancy and the puerperium, the presence of multiple risk factors increases the risk of VTE. Women with a personal history of VTE are at increased risk of recurrence during pregnancy and the puerperium. Recurrence rates of 1.4-11.1% have been reported.148

The risk of recurrent VTE occurring during pregnancy is higher in women who have previously had an unprovoked or oestrogen related episode compared to those whose VTE was provoked by a temporary risk factor that is no longer present.148

The reported risks of VTE in pregnancy associated with thrombophilic defects vary considerably, both between defects and between studies. Women who are heterozygotes for the most common heritable thrombophilias in the United Kingdom (factor V Leiden and prothrombin 20210A) and who have no prior history of VTE, are at low absolute risk of VTE in pregnancy (<1%).

There is a lack of controlled trials of antithrombotic intervention to prevent pregnancy complications. Thus, at present, universal screening for thrombophilia in pregnancy is not justified.32

All women should be assessed for risk factors for VTE when booking for antenatal care and at each subsequent maternity contact.

Routine testing for thrombophilia in pregnancy is not indicated.

- Pregnant women with a family history of VTE in a first degree relative which was unprovoked or pregnancy or COC-related, should be offered testing for heritable thrombophilias.
- The results will be more informative if the first degree relative has a known thrombophilia.

7.3 METHODS OF THROMBOPROPHYLAXIS

7.3.1 ANTICOAGULANTS

In the non-pregnant, LMWH is at least as effective as unfractionated heparin for the prevention of VTE in patients undergoing surgery and in other high risk situations (see section 4.4). Systematic reviews have concluded that LMWH is a safe alternative to unfractionated heparin as an anticoagulant during pregnancy,149 and LMWH has a preferable safety profile.149

The largest of these systematic reviews included 64 studies reporting 2,777 pregnancies in which an LMWH was used for thromboprophylaxis or treatment of VTE (Greer, 2005 #44). There were no studies comparing the safety or efficacy of LMWH with either no anticoagulation or with coumarin anticoagulation. In this systematic review, no comparison with the safety or efficacy of unfractionated heparin was attempted. Compared with unfractionated heparin, the risk of heparin induced thrombocytopenia was substantially lower with LMWH (there were no cases of HIT in the 2,777 pregnancies reported). The incidence of allergic skin reactions was 1.8% (95% CI, 1.34 to 2.37), and of osteoporotic fractures was 0.04% (95% CI, 0.01-0.2). Clinically significant haemorrhage occurred in 1.98% of cases (95% CI, 1.5 to 2.57) and was usually attributable to an obstetric cause.149.
Vitamin K antagonists are known to be teratogenic during pregnancy and may also cause fetal haemorrhage. In a systematic review of anticoagulant therapy in pregnant women with prosthetic heart valves, the use of vitamin K antagonists throughout pregnancy was associated with congenital anomalies in 6.4% of live births (95% CI 4.6 to 8.9%). This compares with a background rate of 3%.

Breast-feeding is not contraindicated with either heparin or vitamin K antagonist therapy.

Women of childbearing potential using vitamin K antagonists should be clearly informed of the risk of teratogenesis associated with these agents and should be advised that they should seek appropriate medical advice if they are planning to become pregnant or as soon as possible (and within two weeks following a first missed period) if they suspect that they may be pregnant.

Low molecular weight heparins are the agents of choice for antenatal thromboprophylaxis.

Where possible, antenatal thromboprophylaxis should be commenced in the first trimester of pregnancy.

Vitamin K antagonists have adverse fetal effects and should be avoided in pregnancy, except perhaps in women with mechanical heart valves.

7.3.2 MECHANICAL PROPHYLAXIS

Guidelines based on expert opinion recommend that all women with previous VTE or a previously identified thrombophilia should wear graduated elastic compression stockings throughout pregnancy and for at least six weeks postnatally.

Women considered to be at high risk of VTE should be fitted with graduated elastic compression stockings, in addition to receiving LMWH.

Women with previous VTE or a previously identified thrombophilia should wear graduated elastic compression stockings throughout pregnancy and for at least six weeks postnatally.

7.4 ANTENATAL THROMBOPROPHYLAXIS

There is no high quality evidence to determine which patients should receive prophylaxis for the prevention of VTE during pregnancy and the puerperium.

A Cochrane systematic review of randomised trials comparing one method of thromboprophylaxis with placebo or no treatment, and randomised trials comparing combined methods of thromboprophylaxis, concluded that there was insufficient evidence on which to base recommendations for thromboprophylaxis during pregnancy and the puerperium. Recommendations for thromboprophylaxis in pregnancy are based on case control studies, and a small number of prospective cohort studies, or are extrapolated from the non-pregnant situation. These studies, including their potential weaknesses, have been thoroughly reviewed in recently revised guideline documents.

Women who have had a previous provoked and non-oestrogen related VTE, do not routinely require antenatal thromboprophylaxis with LMWH.

Women with a previous unprovoked travel or oestrogen related VTE (including pregnancy), or previous recurrent VTE, or other additional risk factors for VTE, should be offered antenatal thromboprophylaxis with LMWH.

Women considered to be at high risk of VTE because of multiple risk factors (more than three) should be considered for thromboprophylaxis with LMWH antenatally.
Women with inherited or acquired thrombophilia, and no previous history of VTE do not require pharmacological thromboprophylaxis antenatally. Exceptions include women with:
- antiphospholipid antibodies who may benefit from low-dose aspirin
- with multiple thrombophilic defects (including homozygosity for factor V Leiden)
- antithrombin deficiency
- heritable thrombophilia and a strong family history of unprovoked VTE, especially if pregnancy-related.

Non-pregnant patients with recurrent VTE are at increased risk of further episodes.\(^\text{96, 151}\) It is expected that these individuals would have a high risk of VTE during pregnancy, though data are lacking to support this.\(^\text{147}\) Those women, who are normally on warfarin therapy should be advised to change to LMWH as soon as pregnancy is confirmed and before the sixth week of pregnancy. Women with a history of recurrent VTE and not normally anticoagulated, should commence LMWH once the pregnancy is confirmed.\(^\text{147}\)

- Women with a history of prior VTE, who are normally anticoagulated with vitamin K antagonists, should switch to intermediate dose LMWH as soon as pregnancy is confirmed.
- A dose between the standard for prophylaxis and the full treatment dose may be appropriate.

### 7.5 DELIVERY AND THE PUERPERIUM

Women should be advised to discontinue LMWH at the onset of labour or prior to a planned delivery to allow them the choice of regional anaesthesia/analgesia. For women receiving intermediate or therapeutic doses of LMWH (for example those normally receiving warfarin outwith pregnancy), the dose of heparin should be reduced to its thromboprophylactic dose on the day prior to induction of labour and if appropriate continued in this dose during labour. Regional anaesthesia/analgesia can be sited only after discussion with a senior anaesthetist, in keeping with local obstetric anaesthetic protocols. It is important to discuss the implications of treatment with LMWH for regional anaesthesia/analgesia with the women prior to labour or Caesarean section.

To minimise or avoid the risk of epidural haematoma:
- Regional techniques should not be used until at least 12 hours after the previous prophylactic dose of LMWH.
- When a woman presents while on a therapeutic regimen of LMWH, regional techniques should not be employed for at least 24 hours after the last dose of LMWH.
- LMWH should not be given for two to four hours after the epidural catheter has been removed and the cannula should not be removed within 10-12 hours of the most recent injection.
- Women who are taking LMWH antenatally and who are for delivery by elective Caesarean section should receive a thromboprophylactic dose of LMWH on the day prior to delivery and, on the day of delivery, any morning dose should be omitted and the operation performed that morning.

There is an increased risk of wound haematoma following Caesarean section with both unfractionated heparin and LMWH of around 2%.\(^\text{149}\) Women at high risk of haemorrhage with risk factors including major antepartum haemorrhage, coagulopathy, progressive wound haematoma, suspected intra-abdominal bleeding and postpartum haemorrhage may be better managed with unfractionated heparin or GCS. If a woman develops a haemorrhagic problem while on LMWH the treatment should be stopped and expert haematological advice sought.

- Women should be advised to discontinue self injections of LMWH as soon as they believe themselves to be in labour.
7.6 POSTNATAL THROMBOPROPHYLAXIS

The highest risk period for VTE, and PE in particular, is during the puerperium. It has therefore been recommended that the threshold for prescribing postpartum thromboprophylaxis should be lower since the risk per day is higher and the duration of risk shorter.\textsuperscript{146}

- All women should be assessed after delivery for risk factors for VTE.
- Women with multiple risk factors for VTE should be considered for postnatal thromboprophylaxis.
  - Women with $\geq 2$ risk factors should receive LMWH for seven days after delivery; women with $\geq 3$ risk factors should be fitted for graduated elastic compression stockings in addition to LMWH.
  - Fondaparinux is an alternative to LMWH.
- All women who have had an emergency Caesarean section and those who have an elective Caesarean section who have $\geq 1$ risk factor for VTE, should receive thromboprophylaxis with LMWH for seven days.
  - Women with a previous VTE should receive LMWH for six weeks following delivery.
  - Women who are known to have an acquired or inherited thrombophilia should be considered for thromboprophylaxis for six weeks following delivery taking account of the family history, any personal risk factors and patient preference.
  - Women receiving prophylaxis antenatally should continue thromboprophylactic doses for six weeks following delivery.
  - Women who are normally anticoagulated with warfarin outwith pregnancy, can recommence warfarin five days after delivery.
8 Travel-related thrombosis

8.1 RISK OF VTE

The absolute risk of VTE associated with long haul-air travel (>4 hours) has been overestimated. Epidemiological data indicate that the risk applies equally to other modes of mechanical transport, including by car and rail.

A reliable estimate of relative risk from epidemiological data is 2 to 3-fold. An estimate of absolute risk based on frequent fliers (likely to be a healthy population) is around one VTE in 4,600 flights over four hours.\textsuperscript{152} The increased risk persists for up to eight weeks after travel.

Risk of flight-related VTE is increased in both shorter and taller subjects, and the overweight and associated with location in a window seat.\textsuperscript{153, 154} Use of the combined oral contraceptive pill and carriage of factor V Leiden also increase risk.\textsuperscript{154} There is no evidence that dehydration plays a role.

There is evidence from a study of pathogenesis of air travel-related VTE that blood coagulation is activated particularly in women with factor V Leiden who use the combined oral contraceptive pill.\textsuperscript{155}

8.2 METHODS OF THROMBOPROPHYLAXIS

8.2.1 EXERCISE

Popliteal venous blood flow appears to be enhanced by seated exercises,\textsuperscript{156, 157} although their efficacy in the prevention of travel-related VTE has been questioned in an epidemiological study.\textsuperscript{153}

8.2.2 MECHANICAL PROPHYLAXIS

There is no high quality, admissible direct evidence for the efficacy of the use of GCS to prevent clinical VTE during longhaul travel, although there are limited data suggesting a reduction in subclinical events, the significance of which is unknown. Their use is based on extrapolation from other situations, especially perioperative. Different pathogenic factors are likely to apply in travel-related VTE, and posture and opportunities to mobilise differ also. Full length GCS are ineffective in VTE prevention after stroke and their apparent efficacy in other hospitalised medical patients is limited. Inappropriately fitted GCS may cause adverse effects.

8.2.3 PHARMACOLOGICAL PROPHYLAXIS

There are no data from randomised trials of the use of pharmacological prophylaxis for the prevention of travel-related VTE.

It is likely that warfarin provides protection in people already using the anticoagulant.

Aspirin has limited efficacy in the prevention of VTE generally and may be offset by an increased incidence of gastric bleeding.

In people deemed to be at especially high risk of travel-related VTE, prophylactic LMWH administered as a single dose subcutaneously on the day of travel could be considered. Although this approach has not been subjected to clinical trial the risk of adverse effects is low. It may be applicable to patients who have suffered VTE provoked by long-haul travel previously who are no longer using warfarin, or when travel is essential during the early postoperative period or when immobilised after lower limb fracture.

**D**

- Travellers should be advised to remain as ambulant as safely possible before, during and after journeys.
- Leg exercise whilst seated may be recommended.
- The use of GCS for prevention of VTE during and after long-haul travel is not routinely recommended.
- When used, care should be taken to ensure an appropriate fit.

Appropriate monitoring of the INR and dosage adjustment is recommended prior to travel for patients taking warfarin.

Aspirin is not recommended for prevention of VTE during and after long-haul travel.

In people deemed to be at especially high risk of travel-related VTE, prophylactic anticoagulant administered as a single dose subcutaneously on the day of travel may be considered.

The risks and possible benefits of any intervention should be discussed with the patient in every case.
9 Diagnosis of venous thromboembolism

9.1 DIAGNOSIS OF ACUTE VENOUS THROMBOEMBOLISM

Acute venous thromboembolism should be suspected in patients with a combination of suggestive symptoms or signs and predisposing factors of either DVT or PE. It should be noted that most patients with proven PE do not have clinically evident DVT.

- Suggestive symptoms or signs:
  - **DVT**: unilateral leg pain, swelling, tenderness, increased temperature, pitting oedema, collateral superficial veins
  - **PE**: tachycardia, breathlessness, faintness, collapse, chest pain, haemoptysis, tachypnoea, raised jugular venous pressure, focal signs in chest or on chest X-ray.

- Predisposing factors (see Table 1)

9.2 DIAGNOSTIC ALGORITHMS

Combinations of clinical decision rules and testing for D-dimer have been evaluated extensively. The performance of any diagnostic test (sensitivity and specificity) compared to a gold standard allows the calculation of the likelihood ratio (LR) for that test. The LR tells us how much more likely it is that a test will be positive in a patient who has a disorder than it will be in a patient who does not have a disorder, or conversely how much more likely it is that a negative test would be found in an individual who does not have a disease. The negative predictive value (NPV) of a test is dependent on the prevalence of a disorder in the population being assessed. Based on the Bayesian method the performance of a test is therefore affected by the pre-test odds that a disorder is present in an individual (post-test odds = pre-test odds x LR of test). It is this observation that underpins the use of clinical decision rules (CDR) to guide the investigation of suspected DVT and PE.

Systematic reviews of cohorts of patients presenting with suspected VTE who were prospectively assessed using a CDR and D-dimer testing and which had a defined end point of the occurrence of objectively proven VTE at three months of follow up show a rate of VTE of 0.45% (95% CI 0.22% to 0.83%) in individuals with a low probability CDR and a negative D-dimer. These results compare favourably with conventional imaging methods used to diagnose suspected VTE.

In individuals in whom suspected DVT was excluded by a combination of a low Wells score and a negative D-dimer the rate of symptomatic and fatal PE was 1 in 2,222 and 1 in 10,000 respectively.158

The three month incidence of VTE in suspected cases where the diagnosis was initially excluded using standard imaging techniques for the diagnosis of DVT and PE are venography 1%, repeat compression ultrasonography (CUS) 0.9%, pulmonary angiography 0.8% and perfusion scanning 1.2%.

A variety of CDR can be used to assess clinical probability of having DVT and PE (see Annexes 3-5). Most commonly used are the Wells score for DVT and PE, the Geneva score and the revised Geneva score for PE. It is important that CDRs are only used in the assessment of appropriate pre-defined groups of patients. For example the Wells score for DVT is not validated for use in patients with previous DVT, hospitalised patients or pregnant women. In assessment of suspected PE the Wells score and the revised Geneva score can be simplified and dichotomised. These changes may facilitate clinical use.
A range of D-dimer tests can be used in the exclusion of suspected VTE in low probability patients. Tests have a range of sensitivities and specificities. Quantitative ELISAs have the highest sensitivities and lower specificities compared to the qualitative assays which use other methodologies. In a systematic review of 11 studies the rate of VTE at three months in patients who had a low CDR score and a negative quantitative or qualitative assay was less than 0.5%. CDR alone and D-dimer alone cannot be used to safely exclude a diagnosis of DVT or PE.

There are inadequate data to confirm whether the use of low probability CDR combined with negative D-dimer testing can be used to safely exclude a diagnosis of PE in patients with a suspected recurrent episode. In a post hoc analysis of patients presenting with suspected recurrence of PE the miss rate at three months for patients who were “PE unlikely” with a negative D-dimer was 0% (95% CI 0-6.9%), while for patients with a normal computed tomography pulmonary angiogram (CTPA) it was 0.8% (95 CI 0.02%-4.3%).

Wells score, Geneva score and revised Geneva score have been prospectively validated in management studies of patients with suspected DVT and PE. These scoring systems can be used in their 3 level (low, intermediate or high risk) or in their 2 level (likely or unlikely) to assess clinical probability of diagnosis of VTE.

In the assessment of patients with suspected PE the revised Geneva score has the advantage of not including a subjective assessment of the patient’s likely diagnosis or the need to interpret a chest X-ray. This may improve the clinical utility of CDR for assessment of PE.

The initial assessment of patients presenting with suspected DVT or PE should include formal clinical probability scoring for the presence of the suspected diagnosis. This information should be used to determine the diagnostic strategy.

Patients with moderate clinical probability based on the Wells score and a negative high sensitivity D-dimer can have a diagnosis of DVT excluded.

In 1 in 200 patients assessed as low clinical probability and with a negative D-dimer, a diagnosis of VTE will become apparent during 3 months of follow up. Patients should be informed of this risk.

Patients who re-present with ongoing symptoms which are not otherwise explained should be re-assessed using the same clinical process as used in the initial assessment.

Patients with high clinical probability of DVT or PE likely should not have D-dimer performed as it is of no value in the diagnostic process for this group. These patients should proceed to imaging to confirm or exclude VTE.

Patients with low or moderate probability CDR or DVT or PE unlikely but a positive D-dimer test should proceed to imaging to confirm or exclude a diagnosis of VTE.

### 9.3 CONFIRMATION OF CLINICALLY SUSPECTED DEEP VENOUS THROMBOSIS

Ultrasound (US) has a high sensitivity (94-99%) and specificity (89-96%) for the diagnosis of symptomatic lower limb proximal DVT when compared to the historical gold standard of contrast venography. Sensitivity and specificity are considerably lower for asymptomatic above-knee DVT and for below-knee (calf) DVT.

The negative predictive value of a single normal ultrasound for exclusion of a proximal DVT in a symptomatic patient is high. There is evidence to support the contention that distal DVT may propagate and subsequently become clinically relevant. The evidence on repeat US at one week is limited. In moderately large population studies the outcome of patients with a negative
initial scan appears to be similar to control populations and the evidence for a general policy of repeat US at one week is weak, but it is prudent to consider repeat examination in those who have a persistent clinical suspicion of DVT.

The preferred initial imaging test for patients with suspected upper extremity DVT (UEDVT) is duplex ultrasound because of its non-invasive nature and high sensitivity and specificity for UEDVT. However, false-negative studies do occur and if clinical suspicion remains high, contrast venography may be required to confirm a diagnosis of UEDVT.

- Ultrasound is the imaging investigation of choice for patients with suspected DVT.
- Patients who have a negative initial scan but who have a high clinical suspicion of DVT or whose symptoms do not settle should have a repeat US scan at five to seven days.
- With its absence of ionising radiation, US is the recommended imaging test for diagnosing DVT in pregnant patients.

### 9.4 CONFIRMATION OF CLINICALLY SUSPECTED PULMONARY EMBOLISM

CTPA is now the gold standard for detection of acute pulmonary embolus with a high sensitivity (83-100%) and specificity (89-97%) for detection of acute PE. Assessment of right ventricular/left ventricular (RV/LV) ratio as seen at CTPA is a useful indicator of severity of PE in the acute situation.

Isotope lung scintigraphy (ILS) scanning, once the principal imaging investigation for suspected acute pulmonary embolism, has been largely superseded by CTPA. ILS still has a place in the investigation of suspected PE, particularly in patients with contraindications to CTPA, and is particularly useful in patients with a normal CXR without underlying lung disease.

The optimal imaging of suspected PE in pregnancy is still a matter of debate. There are no good trials and policy depends on a balance between limiting the radiation dose to mother and fetus and optimal accuracy. ILS results in a substantially lower radiation dose to the mother than CTPA and should be considered when a chest X-ray is normal. If the perfusion scan is normal, the ventilation scan need not be performed.

- Under most circumstances CT pulmonary angiography using multislice CT should be the firstline investigation of suspected severe or non-severe PTE.
- When interpreting the CTPA the right ventricular/left ventricular ratio should be assessed as an indicator of severity.
- Radiologists should comment on right ventricular/left ventricular ratio when moderate or large pulmonary emboli are identified at CTPA.
- Perfusion scintigraphy is an acceptable option if CTPA is unavailable and the patient is stable and at low risk, and is of most use in:
  - patients with a normal chest X-ray and no underlying chronic lung disease
  - patients with a contraindication for CTPA.
- Pregnant patients who have a normal chest X-ray to avoid the high radiation burden of CTPA to the mother’s breast tissue.

### 9.4.1 BIOCHEMICAL MARKERS

Cardiovascularly stable patients at intermediate risk of PE should be assessed for markers of right ventricular dysfunction and/or myocardial injury, and if present should continue to be monitored for evidence of deterioration. 

- Non-high-risk PE patients (cardiovascularly stable) should be assessed for markers of myocardial injury and right ventricular dysfunction.
10 Initial management of venous thromboembolism

10.1 PULMONARY EMBOLISM

Initial clinical assessment of a patient with suspected PE is essential to estimate the severity of PE, as this may dictate treatment options. Patients presenting with cardiogenic shock or sustained systolic hypotension (systolic blood pressure, SBP < 90 mmHg for > 15 minutes) should be regarded as high risk with a 15% early (<30 days) mortality rate. Non-high-risk patients who are initially cardiovascularly stable, can be subclassified into low risk (30 day mortality < 1%) or intermediate risk (30 day mortality 3-15%) if there is evidence of myocardial injury and/or right ventricular dysfunction. SIGN 36 recommended that pulmonary embolism should be managed with early initiation of treatment doses of heparin (UFH or LMWH) continued until therapeutic levels of vitamin K antagonist had been established.

Despite evidence from RCTs demonstrating a superiority of LMWH over UFH for treatment of DVT, this has not been shown for treatment of PE where an OR of 0.88 (95% CI 0.48 to 1.63) was found for risk of recurrent VTE in a Cochrane review (fixed dose LMWH v adjusted dose UFH for venous thromboembolism). A systematic review of pentasaccharide for treatment of VTE identified one RCT of around 3,000 patients which found fondaparinux to have equivalent efficacy (recurrent VTE and mortality at three months, 3.8% v 5.0% and 5.2% v 4.4% respectively) and safety (major haemorrhage during initial therapy, 1.3% v 1.1%) as UFH in the treatment of PE. LMWH, UFH and fondaparinux can all be regarded as suitable agents for initial anticoagulation in patients presenting with PE.

10.1.1 HIGH-RISK PE

Initial management of the shocked patient with PE will include haemodynamic (dobutamine, epinephrine) and respiratory (oxygen) support. Intravenous UFH is preferred to subcutaneous LMWH in this situation as it is likely to achieve therapeutic levels more rapidly and can be adjusted more readily should thrombolytic therapy be necessary. There are very few RCTs addressing management of this high-risk group of PE patients. A Cochrane review identified only one small RCT in unstable PE. This appeared to demonstrate a survival advantage in patients treated with thrombolysis. However the majority of RCTs of thrombolytic therapy excluded unstable patients and failed to show significant clinical benefit in terms of mortality or recurrent VTE. In a review of eight studies randomising 679 patients to either thrombolysis and heparin or heparin alone, there was no benefit in terms of early all-cause mortality (OR = 0.89, 95% CI 0.45 to 1.78) or recurrent PE (pooled analysis from five of the studies, OR = 0.63, 95% CI 0.33 to 1.20), but nor was major haemorrhage more frequent (10.4% v 6.4%, OR = 1.61, 95% CI 0.91 to 2.86). Thrombolysis, however, did result in early improved haemodynamic outcomes (pulmonary artery pressures) and perfusion lung scanning, pulmonary angiography and echocardiographic assessments compared to heparin alone. None of the studies reported on potential late benefits of thrombolytic therapy (eg reduced risk of developing chronic thromboembolic pulmonary hypertension).

High risk PE (shocked patient with an early mortality rate of >15%) should be managed with UFH and considered for thrombolytic therapy.

Such patients should be managed in a coronary care unit or high dependency unit.
10.1.2 INTERMEDIATE RISK PE

Since thrombolysis carries a significant risk of major haemorrhage and there is no clear evidence of improved survival benefit or reduced PE recurrence, it should not routinely be used in patients at intermediate risk of PE. However given the potential for early improvement in haemodynamic function, such treatment could be considered within a trial setting or possibly in young patients deemed to be in the upper region of intermediate risk and at low risk for haemorrhagic complications.151

A  Non-high-risk PE patients (cardiovascually stable) should be anticoagulated with LMWH, UFH or fondaparinux.

B  These patients should not routinely receive thrombolytic therapy.

☑  Intermediate risk PE patients should be monitored in hospital and be considered for thrombolysis should they deteriorate.

10.1.3 LOW-RISK PE

PE patients deemed to be at low risk should be managed with standard LMWH therapy followed by oral anticoagulation. Such patients would be most suitable for outpatient management or early discharge (see section 14.2).

B  Low-risk PE patients should be anticoagulated with LMWH or fondaparinux and considered for outpatient management or early discharge.

10.1.4 VENA-CAVAL FILTERS

No evidence was identified to support the routine placement of a vena-caval filter when a patient is able to be anticoagulated. If anticoagulation therapy is not possible for patients with acute deep venous thrombosis then placement of an inferior vena cava (IVC) filter will lead to reduction in radiologically diagnosed pulmonary embolus but no difference in symptomatic pulmonary embolus. There was no overall mortality benefit or evidence of an increase in recurrent deep venous thrombosis in the longer term. Once any contraindication to anticoagulation has passed, it should be reinstituted. Whenever possible the filter should be removed.

There is no evidence to support long term anticoagulation merely to prevent IVC filter thrombosis.

IVC filters significantly reduce the number of consequent PEs suffered by patients who present with proximal DVT (1.1% v 4.8% OR 0.22) but they are associated with an increase in the development of recurrent DVT (20.8% v 11.6% OR 1.87) at two years follow up. This is the major complication of IVC filter insertion in patients with proximal DVT. Other complications include:

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<thead>
<tr>
<th>Immediate</th>
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<tr>
<td>Misplacement</td>
<td>1.3%</td>
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<tr>
<td>Haematoma</td>
<td>0.6%</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>0.02%</td>
</tr>
<tr>
<td>Air embolus</td>
<td>0.2%</td>
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<tr>
<td>Carotid artery puncture</td>
<td>0.04%</td>
</tr>
<tr>
<td>Atrioventricular fistula</td>
<td>0.02%</td>
</tr>
</tbody>
</table>
Early

<table>
<thead>
<tr>
<th>Condition</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insertion site thrombosis</td>
<td>8.5%</td>
</tr>
<tr>
<td>Infection</td>
<td></td>
</tr>
</tbody>
</table>

Late

<table>
<thead>
<tr>
<th>Condition</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT</td>
<td>21%</td>
</tr>
<tr>
<td>IVC thrombosis</td>
<td>2-10%</td>
</tr>
<tr>
<td>Post-thrombotic syndrome</td>
<td>15-40%</td>
</tr>
<tr>
<td>IVC penetration</td>
<td>0.3%</td>
</tr>
<tr>
<td>Filter migration</td>
<td>0.3%</td>
</tr>
<tr>
<td>Entrapment of guidewires</td>
<td></td>
</tr>
<tr>
<td>Filter tilting</td>
<td></td>
</tr>
<tr>
<td>Fracture</td>
<td></td>
</tr>
</tbody>
</table>

☐ Retrievable IVC filters should be used.

- Where IVC filters have been fitted because of an existing contraindication to anticoagulants at the time of presentation, anticoagulation may be introduced when the contraindication is resolved.
- Long term anticoagulation merely to prevent IVC filter thrombosis is not recommended.

10.2 LOWER LIMB DVT

10.2.1 ANTICOAGULATION

Meta-analyses have demonstrated superiority of LMWH over UFH in the initial treatment of DVT. A Cochrane review included 22 studies of over 8000 patients of which 75% had DVT and 25% lone PE.163 LMWH treatment was associated with lower rates of VTE recurrence or extension (3.6% v 5.4%; OR 0.68, 95% CI 0.55 to 0.84), lower mortality (4.5% v 6.0%; OR 0.76, 95% CI 0.63 to 0.92) and less major bleeding during the initial treatment period (1.2% v 2.0%; OR 0.57, 95% CI 0.39 to 0.83).163. When analyses were confined to nine studies treating proximal DVT the same superiority of LMWH was seen. The survival advantage with LMWH appeared to be confined to VTE patients with cancer (OR 0.53, 95% CI 0.33 to 0.85) rather than non-cancer patients (OR 0.97, 95% CI 0.61 to 1.56).

A further Cochrane review identified four studies comparing once daily with twice daily LMWH.165 There were no significant differences in terms of recurrent VTE or major haemorrhage, although there was a trend to lower event rates with once daily LMWH (OR for recurrent VTE 0.82, 95% CI 0.49 to 1.39; OR for major haemorrhage 0.77, 95% CI 0.40 to 1.45).

Few studies have directly compared different LMWH preparations, however a review of the limited data available suggests they have similar efficacy as does outpatient compared to inpatient administration.151

A review of studies assessing the efficacy of pentasaccharides in the treatment of VTE, identified a single RCT demonstrating non-inferiority in terms of recurrent VTE at three months, death at three months and major haemorrhage during initial therapy when compared to twice daily LMWH.122

For the majority of patients, LMWH therapy can be discontinued once therapeutic anticoagulation with a vitamin K antagonist has been established (usually 6-10 days).151 There is some evidence, however, that cancer patients with VTE benefit from continued LMWH therapy rather than vitamin K antagonist. This option is also a suitable alternative for patients intolerant of, or unsuitable for, vitamin K antagonist therapy.
A Patients with suspected DVT should be treated with therapeutic doses of LMWH until the diagnosis has been deemed very unlikely or alternative oral anticoagulant therapy has been established.

B Intravenous UFH is an inferior, albeit effective, alternative and may be appropriate in certain circumstance eg if thrombolysis is being considered, in the immediate postoperative period or where there is particular risk of bleeding.

B Subcutaneous fondaparinux may be a suitable alternative to LMWH.

10.2.2 THROMBOLYSIS

Few studies were identified which specifically addressed management of massive limb threatening DVT.

Studies assessing thrombolytic therapy for DVT included a spectrum of patients and were often small and poorly controlled. Several reviews and meta-analyses have demonstrated thrombolysis to produce superior early clot lysis, improved patency rates and reduced incidence of post-thrombotic syndrome. There is no evidence, however, of reduced early PE, recurrent VTE or mortality. In contrast, such therapy is associated with a higher major haemorrhage rate in the region of 8-10%. Despite this relatively weak evidence some authors have concluded that carefully selected patients with low bleeding risk (often younger patients) and extensive proximal iliofemoral DVT may benefit from thrombolysis, particularly catheter-directed thrombolysis, when the systemic thrombolytic effect and bleeding rates are less.166-169

D Thrombolysis is not routinely recommended.

Thrombolysis, preferably catheter-directed thrombolysis, can be considered on an individual basis, particularly in patients at low bleeding risk with limb threatening or massive iliofemoral DVT.

11.2.4 DISTAL (CALF) DVT

A small study of 51 patients with symptomatic distal leg DVT randomised patients to receive three months of VKA or nothing after five days of UFH. The VTE recurrence rates at three months and one year were 0% and 4.3% versus 29% and 32% respectively (p<0.1 and p <0.2). This finding is consistent with another study suggesting that six weeks anticoagulant therapy for calf vein DVT prevented recurrences. Follow up, however, in this study was shorter and some patients had initial asymptomatic DVT.

B All patients with symptomatic distal DVT should receive therapeutic anticoagulation for 6-12 weeks.

10.3 SUPERFICIAL THROMBOPHLEBITIS

Superficial vein thrombosis or thrombophlebitis (STP) in the lower limb is a relatively common, painful, and in many cases self limiting condition. Around 10% of patients with STP will already have DVT at presentation and a further 3-4% will progress to it if untreated.

A Cochrane review and a guideline have reviewed the evidence base for a variety of treatment options.151, 170 While topical gels and sprays containing heparin, heparinoids or oral non-steroidal anti-inflammatory drugs (NSAID) can reduce local symptoms there is no evidence that they reduce the risk of STP extension, recurrence or progression to DVT. NSAIDs, however, significantly reduce STP extension and/or recurrence by 67% compared to placebo (OR 0.33; 95% CI 0.16 to 0.68). Several placebo-controlled RCTs have also addressed the efficacy of UFH or LMWH in prophylactic and therapeutic doses compared to placebo (both groups wore compression stockings).
In all cases extension and/or recurrence of STP was significantly reduced by 67-84%, even with short term treatment for 8-12 days. This benefit remained significant at three month follow up. This study was probably underpowered to detect differences in DVT rate and differences between LMWH and NSAIDs. There was a non-significant trend to fewer early DVT events in the heparin arms, but this trend was lost by three months suggesting that therapy for longer than 12 days may be required. There was no clear difference in outcome between prophylactic and therapeutic doses of LMWH, also seen in another study comparing low-dose LMWH versus therapeutic dose for 30 days. Five out of 21 patients with STP extension in the long saphenous vein towards the sphenofemoral junction subsequently developed DVT. Early surgical treatment of STP can reduce STP extension and/or recurrence, but this approach is no better than LMWH and indeed appears to have a higher complication rate.170

Patients with clinical signs of STP should have an ultrasound scan.

Patients with STP should have compression stockings and be considered for treatment for up to 30 days with prophylactic doses of LMWH.

If LMWH is contraindicated, 8-12 days of oral NSAIDs should be offered.

Patients with STP at, or extending towards, the sapheno-femoral junction should be considered for therapeutic anticoagulation for 6-12 weeks.

10.4 UPPER LIMB VENOUS THROMBOEMBOLIC DISEASE

Upper extremity DVT (UEDVT) is relatively unusual and most is secondary to an underlying cause of mechanical intervention due to central venous pressure (CVP) lines, malignancy or compression of the vein by extrinsic structures.

The studies identified were heterogeneous case series rather than randomised controlled trials. Many series follow a mixed population without separating those with an underlying mechanical cause. There were no trials evaluating methods of initial anticoagulation separately for upper limb thrombosis. The role of thrombolysis was also described in case series.171

In those patients with UEDVT without underlying risk factors there is evidence that risk of recurrence is significantly less than following leg DVT (over five years, recurrence rates of 2% (95% CI 0 to 6) in patients with UEDVT compared to 19% (95% CI 16 to 22) in leg DVT). Prolonged anticoagulation for these patients is generally not indicated.171 There was no good quality evidence to support the initial treatment of upper limb thrombosis any differently from lower limb thrombosis.

Management of UEDVT needs to be on an individual patient basis and should include treatment of any underlying condition.

Patients with UEDVT without underlying risk factors such as antiphospholipid antibodies do not require prolonged (more than 3-6 months) anticoagulant treatment.

10.5 CEREBRAL VEIN THROMBOSIS

10.5.1 ANTICOAGULATION

Thrombosis of the cerebral veins and sinuses is uncommon with an estimated annual incidence of 3-4 per million. The majority of patients make a full recovery however there is an early, in-hospital fatality rate of around 5%, and overall mortality rate of approximately 10%.172 Cerebral haemorrhage, secondary to the cerebral vein thrombosis (CVT), has been noted in 39% of cases at presentation and has raised concerns about the safety of anticoagulant therapy.
However a Cochrane review identified two small RCTs including 79 patients randomised to anticoagulation or not.\textsuperscript{173} Although the results were not statistically significant there was an overall trend to lower mortality and dependency in the anticoagulated patients (RR 0.46; 95% CI 0.16 to 1.31) with an absolute reduction in risk of death of 13% (95% CI -30 to 3%). In addition they showed no new or enlarging cerebral haemorrhage with anticoagulation.

Long term cohort follow-up studies indicate that recurrent CVT is uncommon (2-3%) as is VTE elsewhere (4-5%), perhaps because many initial CVT events occur in young patients with temporary precipitating factors.\textsuperscript{174} In excess of 80% patients show recanalisation of the thrombosed cerebral vein after six months. Furthermore the presence of heritable thrombophilia does not appear to influence recurrence risk, suggesting that long term anticoagulation should be unnecessary in most patients. The use of steroid therapy for CVT has also been examined in a Cochrane review which demonstrated no outcome benefits in a modest sized case control study.\textsuperscript{175}

**C** Patients with acute CVT should be considered for therapeutic anticoagulation with heparin and then warfarin for up to six months.

### 10.5.2 THROMBOLYSIS

A Cochrane review of thrombolysis for cerebral venous thrombosis identified no RCTs.\textsuperscript{176}

A retrospective non-randomised study of local urokinase suggested that thrombolysis in cerebral venous thrombosis appears safe but its routine clinical use cannot be supported.\textsuperscript{177} It may be indicated in selected cases where there is ongoing clinical deterioration despite other therapy.\textsuperscript{178, 179}

There is insufficient evidence to support thrombolysis for cerebral venous thrombosis.

### 10.6 SPLANCHNIC VEIN THROMBOSIS

Thrombosis of hepatic, portal and mesenteric veins is rare and most often associated with an underlying myeloproliferative disorder (especially true for hepatic and portal vein thromboses) or local or systemic inflammatory process. A review identified no randomised trials,\textsuperscript{172} but found case series and observational cohort studies which implied a mortality rate of around 10% and a recurrence rate of 18.5% at 41 months in non-anticoagulated patients.\textsuperscript{180} Thirty nine per cent of patients with underlying myeloproliferative disorder suffered a recurrent venous thrombosis. Anticoagulation appeared to reduce recurrence and led to recanalisation in 45% of cases. These clinical benefits could be anticipated to reduce the risk of the problematic sequelae to splanchnic vein thrombosis (portal hypertension with oesophageal varices and hypersplenism with thrombocytopaenia). The presence of such sequelae will of course increase the risk of bleeding should anticoagulation be prescribed.

**D** Patients with acute splanchnic vein thrombosis should have treatment for any underlying disease and be considered on an individual basis for anticoagulation after careful assessment of individual risks and benefits.

### 10.7 PREGNANCY

The management of pregnancy-related venous thromboembolism has been fully discussed in a recent national guideline.\textsuperscript{70}
11 Preliminary Assessment

11.1 CLINICAL AND LABORATORY INVESTIGATIONS

There are several issues that need to be considered before embarking upon anticoagulant therapy following a diagnosis of VTE. These relate to:

- investigation into disorders underlying the development of DVT or PE
- investigations to reassure that anticoagulation is safe
- investigations to ensure that monitoring of anticoagulation can be safely and accurately performed
- investigations to allow monitoring for side effects of anticoagulant drugs
- clinical assessment of the risks of anticoagulation.

Good clinical history taking and examination is essential in the assessment of factors contributing to the development of VTE and to the fitness of the patient for anticoagulation or other interventions required in the treatment of an episode of VTE.

The presence of inherited thrombophilia does not influence the choice of initial anticoagulant therapy, the intensity of treatment (INR target) or the duration of anticoagulation. 1++

The pharmacology of the anticoagulants which are currently most often used in the management of VTE indicates that assessment of baseline coagulation and renal function is required prior to embarking on therapy. Most LMWHs are almost entirely metabolised by the kidney and standard manufacturers advice is that dose reduction should be considered in patients with glomerular filtration rate (GFR) <30 mls/min. Cases of fatal bleeding have been described in patients with impaired renal function.

Poor renal function is also a risk factor for bleeding in patients on warfarin. 2++

The prothrombin time is used to monitor the anticoagulant effect of coumarins and the APTT is used to monitor the anticoagulant effect of unfractionated heparin. A baseline assessment of PT and APTT is required to identify underlying coagulopathy that might contraindicate anticoagulation or affect monitoring of treatment.

Treatment with all forms of heparin is associated with a risk of developing heparin induced thrombocytopenia (see section 15.2). All patients embarking on anticoagulation with heparin or LMWH should have baseline platelet count performed before starting treatment with heparin.

The outpatient bleeding risk score indicates the annual risk of major bleeding in patients being treated with coumarins. This can be performed by simple clinical assessment combined with a full blood count and assessment serum creatinine. Assessment of age, history of gastrointestinal (GI) bleeding, history of stroke (haemorrhagic or ischaemic) and a history of concomitant medical illness (recent MI, renal impairment, anaemia or diabetes mellitus can be used to assess bleeding risk.

There is a well documented association between cancer and VTE. Many episodes of VTE occur in patients with active cancer and in patients undergoing treatment for cancer.

The question of whether or not patients presenting with apparently unprovoked VTE should be screened for various types of cancer using a combination of laboratory based tests and imaging has been the subject of many studies and these have been subject to systematic review. It is presently felt that unselective screening for all malignancies in patients with unprovoked VTE is not of clinical value.

A full clinical history and examination should be undertaken in all patients presenting with VTE with the aim of detecting possible underlying conditions contributing to the development of VTE and assessing the suitability of a patient for thrombolytic therapy, anticoagulant therapy, or other interventions deemed appropriate in the management of the event.
Testing for inherited forms of thrombophilia (AT, PC, PS deficiency and factor V Leiden and prothrombin 20210) does not influence initial management of VTE and should not be performed for this purpose.

Patients commencing treatment with heparin, LMWH and warfarin should have a baseline assessment of renal function, PT, APTT.

Patients commencing treatment with heparin, LMWH and warfarin should have a full blood count to:

- monitor for the development of HIT
- exclude overt myeloproliferative disease as a contributing factor in the development of VTE.

Patients for whom anticoagulation is planned should be assessed for their risk of anticoagulant induced bleeding using the outpatient bleeding score.

Unselective screening for cancer in patients with DVT or PE is not indicated.
12 Further Management of venous thromboembolism

12.1 CHOICE OF ANTICOAGULANT

The risk of recurrent VTE is reduced for the duration of vitamin K antagonist (VKA) therapy but the risk of bleeding is increased (see section 15.1). The annual risk of bleeding during VKA therapy is around 1% for organ or life threatening bleeds.

Use of LMWH for the prevention of recurrent VTE was addressed in three systematic reviews.\textsuperscript{181-183} LMWH is at least as effective as warfarin for prevention of recurrent VTE and appears to be more effective in patients with cancer. A Cochrane review and meta-analysis of six randomised controlled trials comparing low molecular weight heparin with an oral anticoagulation and two studies comparing other treatment modalities found no statistically significant difference in mortality but identified a significant reduction in recurrent symptomatic venous thromboembolic disease in favour of treatment with low molecular weight heparin.\textsuperscript{144}

The efficacy of aspirin against VTE is inferior to that of VKA and LMWH in all situations studied.\textsuperscript{184} Evidence is lacking for the efficacy of aspirin for the prevention of recurrent VTE after discontinuation of VKA therapy.

Some observational and case control studies have suggested that statin use is associated with a reduced incidence of VTE. Furthermore a large randomised controlled study demonstrated a reduction in first episodes of VTE among older patients treated with rosuvastatin. However there are no data to date to support use of statin to reduce the risk of recurrence after discontinuation of VKA therapy for VTE.

A After a first episode of limb deep vein thrombosis or pulmonary embolism, treatment with a VKA should be initiated.

A Use of LMWH is an alternative and can be considered if VKA therapy is problematic, for example due to poor compliance/erratic intensity of anticoagulation.

A LMWH rather than warfarin should be considered in VTE associated with cancer.

C Neither aspirin nor statin is recommended for the prevention of recurrent VTE after discontinuation of VKA therapy.

12.1.1 INTENSITY OF ANTICOAGULATION

Intensity of anticoagulation with warfarin for the management of VTE has been addressed in randomised clinical trials,\textsuperscript{58,60,62-64} which indicate the use of a target INR of 2.5, range 2.0-3.0. This is supported by retrospective descriptive studies which have shown a higher risk of recurrence when INR values are below 1.9,\textsuperscript{16} or lower risk of bleeding at INR 2.0-3.0.

Reduced intensity treatment (INR 1.5-2.0) is associated with a higher rate of recurrent VTE than standard intensity treatment.

A After a first episode of limb deep vein thrombosis or pulmonary embolism the target INR should be 2.5.

A A higher target INR (3.5) may be considered if there is recurrent VTE whilst in the target range.

Although a higher than usual target INR has been recommended for prevention of recurrent VTE in antiphospholipid syndrome, two randomised controlled trials have refuted this. In antiphospholipid syndrome a target INR of 2.5 is at least as effective as a higher target INR in prevention of recurrence.
In antiphospholipid syndrome and VTE, anticoagulation with a VKA, target INR 2.5, should be implemented.

12.1.2 DURATION OF ANTICOAGULATION IN LOWER LIMB DVT

Four systematic reviews have addressed the duration of anticoagulation with a vitamin K antagonist, principally warfarin, after an episode of lower limb deep vein thrombosis or pulmonary embolism. Treatment for a shorter term with VKA (median 1.75 months, interquartile range, IQR 1-3 months) results in more recurrences than treatment for a longer term (median 6 months, IQR 3-10.5 months). After stopping VKA a similar risk of recurrence occurs after discontinuation at six or 12 months as that after discontinuation at three months.

The risk of recurrent VTE after discontinuation of VKA therapy may be higher in patients with antiphospholipid antibodies.

A After a first episode of limb deep vein thrombosis or pulmonary embolism, treatment with a VKA should be continued for 3-6 months.
B Treatment for three months is generally adequate after VTE provoked by surgery.
D The duration of anticoagulation (3-6 months or long term) should be determined on an individual basis, taking account:
  • the presence or absence of avoidable risk factors and comorbidities, including active cancer
  • bleeding risk on anticoagulant treatment
  • the site and severity of the first event
  • patient compliance and preference.

12.2 GRADUATED COMPRESSION STOCKINGS

Two systematic reviews have examined the limited number of studies of the effect of use of GCS for the prevention and severity of post-phlebitic syndrome. The use of GCS (eg providing 40 mm Hg at the ankle) on the affected leg for two years after lower limb VTE reduces the risk of post-thrombotic syndrome. Below-knee GCS appear to be effective.

A After deep vein thrombosis affecting a lower limb, the use of well fitted GCS for two years should be encouraged in order to reduce the risk of post-phlebitic syndrome.

12.3 RECURRENT VENOUS THROMBOEMBOLISM

The risk of recurrent VTE after discontinuation of treatment following a first episode of lower limb DVT or pulmonary embolism with a VKA is around 11% in two years after a first unprovoked event but considerably lower after VTE clearly associated with a temporary risk factor, such as surgery. The markedly lower risk of recurrent lower limb VTE after a first lower limb DVT or pulmonary embolism provoked by surgery has been demonstrated in case series. There are limited data that the thrombosis recurrence rate and incidence of pulmonary embolism are lower in association with upper limb DVT than lower limb DVT.

D • After recurrent VTE, long term treatment with a VKA is recommended but the nature of the recurrence (provoked or unprovoked), the elapsed time between episodes and risk of bleeding should be considered in reaching this decision.
• The use of long term VKA should be subjected to periodic review, to include anticoagulant control, bleeding episodes and altered risk of bleeding.
13 Monitoring the anticoagulant effect

SIGN 36 identified evidence that when treating acute VTE, failure to achieve early therapeutic anticoagulation is associated with higher rates of early extension and late recurrence of VTE. This is a less pressing problem since the widespread introduction of LMWHs.

13.1 UNFRACTIONATED HEPARIN

If using UFH, monitoring of treatment with appropriate dose adjustment is important. This is best achieved using an APTT assay, initially four hours after starting infusion and after any dose change. Once stabilised it should be assessed at least daily. Different APTT reagents may have clinically important differences in heparin sensitivity. Therefore the British Committee for Standards in Haematology (BCSH) recommends assays should be calibrated locally to establish an appropriate target APTT ratio.191

13.2 LOW MOLECULAR WEIGHT HEPARIN

Therapy with low molecular weight heparin (LMWH) does not require routine monitoring since weight-adjusted dosing, or a fixed dose for thromboprophylaxis, has been shown in clinical trials to provide a predictable clinical response. Such dosing may be unreliable, however in patients at extremes of weight, with severe renal impairment or during pregnancy when the pharmacokinetics of LMWH may be altered. In such circumstances, or if there is unexpected bleeding, there may be some merit in assessing LMWH activity. Peak levels can be measured 4-6 hours after a subcutaneous dose of LMWH. The APTT assay is unsuitable for this purpose, and therefore a chromogenic anti-Xa assay using an LMWH standard is recommended, although such assays also have their limitations. 191

13.3 WARFARIN

Warfarin has a narrow therapeutic window and there is considerable inter-individual, as well as temporal intra-individual, variability which demands regular monitoring. The prothrombin time assay, with the result expressed as an INR, remains the best measure of vitamin K antagonist (eg warfarin) therapy. A moderately sensitive INR reagent (with an ISI <1.7) is recommended, as is establishing the local reagent plus machine ISI.192

13.3.1 INR CONTROL

Cohort studies have established that high quality INR control, as assessed by high percentage of time spent in target INR range, is associated with better clinical outcomes. During anticoagulant therapy, particularly the first 90 days, periods of INR >4.5 are associated with increased bleeding risk (RR 5.96; 95% CI 3.68 to 9.67; p<0.0001) while INR <2 are associated with increased thrombotic events (RR 1.88; 95% CI 1.16 to 3.07, p<0.05).193, 194 Poor quality INR control, as assessed by percentage time with INR <1.5, is associated with a long term higher risk of recurrent VTE after eventual anticoagulant cessation (RR 2.7; 95% CI 1.39-5.25; p=0.003).195

The optimal model for oral anticoagulant monitoring has been assessed in many studies, which generally show superior quality of INR control by specialised anticoagulant services, or patient self management, compared to personal physician management.192 Within specialized anticoagulant services computer assisted dosing is at least as effective as manual dosing, although one randomized study has demonstrated fewer adverse clinical events, primarily bleeding events, in VTE patients in the computer assisted dosing arm.196

More frequent INR monitoring, once a patient is stabilised on warfarin, has been shown to improve quality of INR control. The optimal recommended frequency is four weeks, however some studies (particularly those involving patient self testing) have suggested that even more frequent monitoring may yield improved time in target range.
Patient self management using a point of care testing device is a choice made by patients and their healthcare provider that depends on many factors. In suitably selected and trained patients anticoagulation self management is an effective alternative treatment model.

C Therapeutic dosing of UFH should be monitored by use of a locally calibrated APTT assay.

C In general, therapeutic dosing of LMWH does not require monitoring.

C In order to attain optimal efficacy and safety of VKA (warfarin) treatment, it is recommended that INR monitoring is undertaken optimally every 4 weeks by a dedicated anticoagulant service, if possible using computer assisted dosing software.

D Patient self testing and self management, supported by a dedicated anticoagulant service is an equally effective option for selected patients.
14 Outpatient management

The widespread use of LMWH (administered subcutaneously once daily and without requiring laboratory monitoring) in the initial treatment of VTE has led to the increasing practice of treating patients with acute DVT, or even PE, as outpatients. Such strategies can yield significant resource benefits to the NHS, but have to be balanced against the risks of patients with VTE managed in the community suffering early recurrent VTE (especially fatal PE) or major haemorrhage. While patients who are clinically unstable, have significant comorbid disease or have severe mobility problems should continue to be managed as inpatients, advice and evidence is required to assist in selection of the remainder who can be most safely managed in the community.

14.1 DEEP VEIN THROMBOSIS

A Cochrane review identified six RCTs, including 1,708 patients, with acute DVT randomised to outpatient treatment with LMWH or inpatient treatment with UFH (five studies) or LMWH (one study).197 All six trials had fundamental flaws including high exclusion rates and partial hospital treatment prior to outpatient management. Outpatient treatment was associated with significantly lower recurrent VTE rate (RR 0.61, 95% CI 0.42 to 0.90) and a trend to lower major bleeding (RR 0.67, 95% CI 0.33 to 1.36) and mortality (RR 0.72, 0.45-1.15) rates, but higher minor bleeding rate (RR 1.29, 95% CI 0.94 to 1.78). While some of the apparent benefit from outpatient treatment could actually have reflected the comparison of LMWH to UFH, the single study comparing LMWH in the two settings showed a similar pattern of results to the meta-analysis. The authors concluded that outpatient therapy is as safe and effective as inpatient treatment for DVT in appropriately chosen patients if support services are in place. This approach is supported by the 2008 ACCP Clinical Practice Guideline on treatment of VTE.151

Characteristics which identify DVT patients less suitable for outpatient management have been identified from the prospective Italian register, Registro Informatizado de la Enfermedad Tromboembólica (RIETE).198 Body weight <70 kg, cancer, prior immobility, chronic heart failure, renal insufficiency and bilateral DVT were independently associated with an increased risk for adverse events (symptomatic PE, recurrent DVT, major bleeding and death). Patients at low risk, constituting approximately two thirds of DVT patients, had a 1.2% incidence of adverse events (23/1,935) compared with 6.8% in high risk patients (69/1,012). The BCSH guideline suggested that DVT patients unlikely to be suitable for outpatient treatment would include those with coexistent serious medical pathology, severe acute venous obstruction (phlegmasia cerulean dolens), significant pain or renal impairment, significant communication or mobility problems, poor social circumstances, known heparin allergy or those with active bleeding or at high risk of bleeding.199

14.2 PULMONARY EMBOLISM

Patients presenting with high risk PE who are shocked or hypotensive are unsuitable for outpatient management or even early discharge. Which cardiovascularly stable PE patients can be safely managed in the community remains the subject of retrospective and prospective trials. It is acknowledged, however, that 35% with DVT managed as outpatients will have sub-clinical PE. To date there is little evidence from management studies regarding outpatient treatment of PE.168
Jimenez and Yusen (2008) reviewed five prognostic prediction models for patients with acute PE (Geneva score, Pulmonary Embolism Severity Index (PESI), the Spanish score, the Davies criteria and the Home management exclusion criteria). The PESI model, derived from the largest study (n=10,354) takes account of 11 routinely available clinical parameters and categorised risk of 30 day mortality into five groups. Low risk patients (groups I and II constituting 43-47% of PE patients) had a 30 day mortality rate of 0.9-2.6%. Sensitivity was 91 (95% CI 81 to 97%) and the negative predictive value was 99% (95% CI: 97 to 100%) for overall mortality.

A systematic review identified six prospective and one retrospective study assessing whether selected low-risk patients with acute PE can be safely treated as outpatients or after early hospital discharge. At three months follow up there were no deaths from PE and <0.5% deaths from haemorrhage in both treatment categories. The authors concluded there is a lack of evidence comparing inpatient with outpatient management of low-risk patients with acute PE. Outpatient treatment appears safe provided the patient is at low risk of an adverse outcome.

Cardiovascularly stable low-risk PE patients may be identified by virtue of a low clinical prognostic score (eg PESI) and normal right ventricular dimensions and normal biochemical markers which have individual negative predictive values for early mortality of 60-73% (see section 9.4.1).

It is likely that a combination of biochemical markers and RV functional assessment will assist in categorising patients with acute PE as suggested in recent ESC guideline.

| A | Outpatient therapy of DVT is safe and effective in selected patients with appropriate support services in place. |
| B | Validated prognostic models to identify patients at low risk of adverse outcomes may be incorporated into treatment algorithms for the management of patients with PE, to identify those suitable for outpatient management or early discharge. |
15 Adverse effects of VTE prophylaxis and treatment

15.1 BLEEDING

A good quality systematic review of 33 RCTs included 3,3813 patients in studies of pharmacological prophylaxis for major general surgery. Different doses and preparations of heparins (and LMWH) were used but justifiably the patients were divided into five groups for analysis; high dose LMWH >3,400 u/day, low dose LMWH <3,400 u/day, high-dose UFH 5000 u three times a day, low-dose UFH < 5000 u three times a day and placebo. Some patients also received mechanical thromboprophylaxis but these were deemed to be unlikely to contribute to bleeding risk. Eight outcomes were analysed; injection site bruising, wound haematoma, drain site bleeding, haematuria, GI bleeding, retroperitoneal bleeding, discontinuation of thromboprophylaxis, subsequent operation required as result of bleeding. In patients undergoing general surgery there was a higher rate of wound haematoma and drain site bleeding in patients who received thromboprophylaxis with UFH or LMWH than controls. The rate of re-operation to control bleeding was, however, very low (and the same) in recipients of heparins and controls (0.7%). Given the benefit in terms of reduction of VTE and the low rate of serious bleeding complications associated with use of UFH and LMWH it is appropriate to consider these drugs for thromboprophylaxis in general surgery.

A systematic review and meta-analysis of major bleeding after pharmaceutical prophylaxis for major orthopaedic surgery in 21 studies including 20,523 patients showed that different drugs were associated with a different risk of major bleeding. The analysis found that the relative risk of bleeding was lowest for warfarin, followed by LMWH followed by UFH and fondaparinux. As well as being apparent on the pooled analysis these findings were consistent across the studies considered. One weakness of this study was that the doses of the drugs used were not considered and nor were the regimens used (preoperative versus postoperative initiation and duration of treatment) Data on the comparative effectiveness of the drugs were not included.

Several observational studies reported on the rate of major bleeding in patients on warfarin. The outcomes are likely to be affected by the characteristics of the population of patients and the definition of “major bleeding”. The reported rate of major haemorrhage per 100 patient years in patients receiving long-term warfarin ranges from 1.1 to 13.4. There is a general consensus that the rate is around 2%. Major bleeding on warfarin is more common in the early phase of therapy. Several studies have reported that an excess of the cases of bleeding observed in the first year of treatment occur in the first month. This is probably related to overanticoagulation upon induction of therapy and the fact that predisposed individuals succumb soon after the onset of initiation of treatment. The annual rate of major haemorrhage in patients receiving long term warfarin is around 1%.

Case series consistently report that reversal of coumarin induced anticoagulation can be achieved using small doses (1-2.5 mg) of vitamin K given orally or intravenously. This was confirmed in a systematic review which showed that reversal of anticoagulation into the therapeutic range was achieved in around 80% of cases. In an RCT of overanticoagulated patients (INR 4.5-10) who were not bleeding, low-dose vitamin K (1.25 mg) did not reduce bleeding or result in an increased thrombosis risk over the subsequent 30 days. In the event of major or life threatening bleeding more rapid reversal of anticoagulation is required. This can be achieved by replacing the vitamin K dependent coagulation proteins which are depleted by the action of warfarin. This is best achieved using prothrombin complex concentrate in a dose that is adjusted depending on the presenting INR. Intravenous vitamin K reverses anticoagulation with a more rapid onset than oral vitamin K and so in such cases larger doses of vitamin K (5-10 mg) should be given intravenously. Reversal of heparin anticoagulation is covered in section 4.4.5.
It is appropriate to consider UFH and LMWH for thromboprophylaxis in general surgery.

In choosing pharmacological thromboprophylaxis the risks of bleeding and other complications need to be considered alongside the likely benefits.

- Major bleeding in patients who are receiving warfarin and other coumarins should be treated by immediate reversal of anticoagulation.
- This is best achieved by early administration of intravenous vitamin K and prothrombin complex concentrate.

Minor bleeding in patients who are anticoagulated with warfarin should be reversed using low doses of vitamin K (1-2.5 mg) given either intravenously or orally depending on the clinical circumstances and assessment of the bleeding.

In patients who are overanticoagulated warfarin therapy should be temporarily discontinued or continued at a decreased dose.

- Episodes of bleeding on warfarin therapy are most frequently observed in the first months of treatment.
- Monitoring of patients should be more intensive during this period.

15.2 HEPARIN INDUCED THROMBOCYTOPENIA

Heparin induced thrombocytopenia (HIT) is a recognised complication of the use of heparins. It presents with thrombocytopenia which develops in association with the use of heparin. It constitutes a prothrombotic state which presents with either asymptomatic thrombocytopenia or with venous or arterial thrombosis, skin lesions or rarely with a generalised systemic reaction which can be severe or even fatal. HIT may occur in any patient who is receiving a heparin (UFH and LMWH). The incidence of HIT is higher in surgical patients than it is in medical patients and obstetric patients. The highest incidence is in patients who have undergone major lower limb orthopaedic surgery and cardiac surgery. The incidence of HIT in obstetric patients receiving heparin for thromboprophylaxis or as part of the management of recurrent pregnancy failure is very low. The highest risk of HIT is in day 5-10 of exposure although recently exposed patients (within previous 100 days) may develop HIT within the first 24 hours of re-exposure.

Porcine heparins are associated with a lower incidence of HIT than bovine heparins and should be used in preference to them. Low molecular weight heparins are associated with a lower incidence of HIT than UFH.

The diagnosis of HIT is based on the presence of a combination of clinical and laboratory features. Assessment of cases using a clinical scoring system allows identification of low-, intermediate- and high-risk patients. The diagnosis can be confirmed in intermediate- and high-risk cases using laboratory tests to detect the anti-heparin/ anti-platelet factor 4 (PF4) antibodies which result in the disorder. In patients with HIT alternative anticoagulation should be provided irrespective of whether or not there is evidence of a new thrombotic event unless the risk of haemorrhage is deemed excessive. In the immediate management there is evidence for two drugs which are licensed for this indication in the UK at present; lepirudin and danaparoid. Documentation of HIT and heparin exposure in clinical notes is important.

To minimise the incidence of HIT:

- porcine heparins should be used in preference to bovine heparins
- low molecular weight heparins should be used in preference to unfractionated heparins.

All groups of patients who are receiving treatment doses of heparin or LMWH and all surgical and medical patients who are receiving a heparin for thromboprophylaxis should be monitored for the development of HIT.
All patients who are to receive UFH or LMWH for prophylaxis or treatment of VTE should have a platelet count performed in the 24 hours beforehand.

- Monitoring patients for the development of HIT should be by performing serial platelet counts.
- Patients who have received UFH or LMWH in the past 100 days or in whom history of recent exposure to heparins is not clear should have a platelet count performed within 24 hours of receiving the first dose of treatment.
- All other patients for whom monitoring is indicated should have platelet counts performed every 2 to 3 days from day 4 to day 14 of exposure or until treatment stops.
- Patients who are at highest risk such as those receiving UFH in treatment doses or after cardiac or orthopaedic surgery should be considered for more frequent monitoring.

- HIT should be suspected in patients who drop their platelet counts by 30% or more or who develop thrombocytopenia (<140 x 10^9/l) whilst receiving UFH or LMWH.
- It should be considered in patients who develop a new thrombosis or in whom thrombosis extends or in patients, who develop typical skin lesions or features of a systemic response such as fever, chills shivering or unusual neurological symptoms whilst receiving any form of heparin.
- In cases where HIT is suspected the patient should be evaluated using a clinical scoring system to assess the pre-test probability of having the condition.
- This should be followed where appropriate by laboratory testing for anti-HIT antibodies. The combined information should be used to assess the probability of having HIT.

Whether or not there is evidence of a new thrombotic episode related to HIT, patients should receive therapeutic doses of lepirudin (designed to cause prolongation of the APTT test) or danaparoid at treatment, as opposed to prophylactic doses.

Where warfarin therapy is proposed it should not be introduced until the platelet count has risen to greater than 100 x 10^9/l.

When it is introduced it should be at low dose (5 mg daily) as opposed to a loading dose and in overlap with danaparoid or lepirudin which should be withdrawn only after the INR has been >2 on two consecutive days.

A history of HIT should be carefully documented in the patient’s discharge letter and notes.

15.3 BONE MINERAL DENSITY

It was previously suggested that prolonged exposure to unfractionated heparin (UFH) resulted in an excess of osteoporosis in pregnant women. Recent evidence from a well performed RCT indicates that women with prolonged exposure to dalteparin in pregnancy did not have significantly lower bone densities than controls suggesting that this is not an issue for low molecular weight heparin. In a systematic review of 2,777 pregnant women exposed to low molecular weight heparin only one osteoporotic fracture was observed.

A Prolonged exposure to LMWH is not associated with a significant increased risk of osteoporotic fracture in pregnancy.
16 Provision of information

This section reflects the issues likely to be of most concern to patients and their carers. These points are provided for use by health professionals when discussing deep vein thrombosis with patients and carers and in guiding the production of locally produced information materials.

16.1 CHECKLIST FOR PROVISION OF INFORMATION

This section gives examples of the information patients/carers may find helpful at the key stages of the patient journey. The checklist was designed by members of the guideline development group based on their experience and their understanding of the evidence base. The checklist is neither exhaustive nor exclusive.

<table>
<thead>
<tr>
<th>Initial presentation/assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Explain to patients what a DVT is and the causes. Discuss risk factors including family history of DVT.</td>
</tr>
<tr>
<td>▪ Explain symptoms and warning signs.</td>
</tr>
<tr>
<td>▪ Explain that patients will be assessed using clinical examination and blood tests.</td>
</tr>
<tr>
<td>▪ Explain to patients who have tested negative for DVT using clinical examination and blood tests why further tests are unnecessary. Explain to them that they should return to their emergency department for further assessment if they have particular symptoms (see section 9.1).</td>
</tr>
<tr>
<td>▪ Explain to patients who had a suspected DVT but negative ultrasound to return to emergency if they have the following symptoms:</td>
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<tr>
<td>▪ Explain to patients who have tested positive for a DVT that family members may be at risk and that they should be encouraged to be screened. Advise patients to make family members aware of symptoms and encourage them to seek medical help immediately should they experience symptoms.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Explain treatment options to patients and discuss the benefits, risks and side effects of treatments.</td>
</tr>
<tr>
<td>▪ Explain the importance of early mobilisation and encourage patients confined to a chair or bed to perform regular leg exercises.</td>
</tr>
<tr>
<td>▪ Advise patients to drink plenty of fluids.</td>
</tr>
<tr>
<td>▪ Encourage patients to wear good fit compression stockings and advise them of the discomfort that may be associated with them.</td>
</tr>
<tr>
<td>▪ Advise patients of the need to arrange alternative contraception if COC is to be discontinued.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Discuss lifestyle issues with patients.</td>
</tr>
<tr>
<td>▪ Explain the risks of DVT to patients starting COC and HRT and advise them to seek medical help immediately if they experience symptoms.</td>
</tr>
<tr>
<td>▪ Advise patients who have experienced a DVT of the warning signs and advise them that medical treatment must be sought immediately.</td>
</tr>
<tr>
<td>▪ Encourage patients to avoid long periods of inactivity.</td>
</tr>
</tbody>
</table>
16.2 SOURCES OF FURTHER INFORMATION

Lifeblood – the thrombosis charity
c/o the Thrombosis and Haemostasis Centre
Level 1, North Wing
St Thomas’ Hospital
London
SE1 7EH
Tel: 0207 633 9937

www.thrombosis-charity.org.uk
Lifeblood’s website includes a range of information on various conditions linked with thrombosis.

NHS24
Tel: 08454 24 24 24
NHS24 can answer questions on any health matter and offer advice.

16.3 PATIENT INFORMATION LEAFLETS

See Annexes 6 and 7
17 Implementing the guideline

This section provides advice on the resource implications associated with implementing the key clinical recommendations, and advice on audit as a tool to aid implementation.

Implementation of national clinical guidelines is the responsibility of each NHS Board and is an essential part of clinical governance. Mechanisms should be in place to review care provided against the guideline recommendations. The reasons for any differences should be assessed and addressed where appropriate. Local arrangements should then be made to implement the national guideline in individual hospitals, units and practices.

17.1 RESOURCE IMPLICATIONS OF KEY RECOMMENDATIONS

Not available in this draft

17.2 AUDITING CURRENT PRACTICE

A first step in implementing a clinical practice guideline is to gain an understanding of current clinical practice. Audit tools designed around guideline recommendations can assist in this process. Audit tools should be comprehensive but not time consuming to use. Successful implementation and audit of guideline recommendations requires good communication between staff and multidisciplinary team working.

Not available in this draft
18 The evidence base

18.1 SYSTEMATIC LITERATURE REVIEW

The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using an explicit search strategy devised by a SIGN Information Officer. Databases searched include Medline, Embase, Cinahl, PsycINFO and the Cochrane Library. The year range covered was 1998-2009. Internet searches were carried out on various websites including the US National Guidelines Clearinghouse. The main searches were supplemented by material identified by individual members of the development group. Each of the selected papers was evaluated by two members of the group using standard SIGN methodological checklists before conclusions were considered as evidence.

18.1.1 LITERATURE SEARCH FOR PATIENT ISSUES

At the start of the guideline development process, a SIGN Information Officer conducted a literature search for qualitative and quantitative studies that addressed patient issues of relevance to early management of patients with a head injury. Databases searched include Medline, Embase, Cinahl and PsycINFO, and the results were summarised and presented to the guideline development group.

18.2 RECOMMENDATIONS FOR RESEARCH

Not available in this draft
19 Development of the guideline

19.1 INTRODUCTION

SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of NHS Quality Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practising clinicians using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in “SIGN 50: A Guideline Developer’s Handbook”, available at www.sign.ac.uk.

19.2 THE GUIDELINE DEVELOPMENT GROUP

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Dr Henry Watson  Consultant Haematologist, Aberdeen Royal Infirmary

The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest and further details of these are available on request from the SIGN Executive.

Guideline development and literature review expertise, support and facilitation were provided by the SIGN Executive.
# Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCP</td>
<td>American College of Chest Physicians</td>
</tr>
<tr>
<td>APTT</td>
<td>activated partial thromboplastin time</td>
</tr>
<tr>
<td>AT</td>
<td>antithrombin</td>
</tr>
<tr>
<td>BCSH</td>
<td>British Committee for Standards in Haematology</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>BNF</td>
<td>British National Formulary</td>
</tr>
<tr>
<td>BNP</td>
<td>B-type natriuretic peptide</td>
</tr>
<tr>
<td>CABG</td>
<td>coronary artery bypass graft</td>
</tr>
<tr>
<td>CCT</td>
<td>controlled clinical trials</td>
</tr>
<tr>
<td>CDR</td>
<td>clinical decision rules</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CLOTS 2</td>
<td>Clots in Legs Or sStockings after Stroke</td>
</tr>
<tr>
<td>COC</td>
<td>combined oral contraceptives</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>CTPA</td>
<td>computed tomography pulmonary angiogram</td>
</tr>
<tr>
<td>CUS</td>
<td>compression ultrasonography</td>
</tr>
<tr>
<td>CVC</td>
<td>central venous catheter</td>
</tr>
<tr>
<td>CVP</td>
<td>central venous pressure</td>
</tr>
<tr>
<td>CVT</td>
<td>cerebral vein thrombosis</td>
</tr>
<tr>
<td>CXR</td>
<td>chest X-ray</td>
</tr>
<tr>
<td>ELISA</td>
<td>enzyme linked immunosorbent assay</td>
</tr>
<tr>
<td>DVT</td>
<td>deep vein thrombosis</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>ESC</td>
<td>European Society of Cardiology</td>
</tr>
<tr>
<td>GCS</td>
<td>graduated elastic compression stockings</td>
</tr>
<tr>
<td>GFR</td>
<td>glomerular filtration rate</td>
</tr>
<tr>
<td>GI</td>
<td>gastrointestinal</td>
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<tr>
<td>HAT</td>
<td>heparin induced thrombocytopenia</td>
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<tr>
<td>HRT</td>
<td>hormone replacement therapy</td>
</tr>
<tr>
<td>HTA</td>
<td>Health Technology Assessment</td>
</tr>
<tr>
<td>ILS</td>
<td>isotope lung scintigraphy</td>
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<tr>
<td>INR</td>
<td>International Normalized Ratio</td>
</tr>
<tr>
<td>IPC</td>
<td>intermittent pneumatic compression</td>
</tr>
<tr>
<td>IQR</td>
<td>interquartile range</td>
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<tr>
<td>IU</td>
<td>international unit</td>
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</tbody>
</table>
IVC  inferior vena cava
LEDVT  lower extremity DVT
LMWH  low molecular weight heparin
LR  likelihood ratio
MI  myocardial infarction
NHSQIS  NHS Quality Improvement Scotland
NICE  National Institute for Health and Clinical Excellence
NNT  number needed to treat
NPV  negative predictive value
NSAID  non-steroidal anti-inflammatory drug
OR  odds ratio
PC  protein C
PE  pulmonary embolism
PEP  Pulmonary Embolism Prevention trial
PESI  Pulmonary Embolism Severity Index
PF4  anti-platelet factor 4
PLS  post-thrombotic leg syndrome
PS  protein S
RCT  randomised controlled trial
RIETE  Registro Informatizado de la Enfermedad Tromboembólica
RR  risk reduction
RRR  relative risk reduction
RV  right ventricular
RV/LV  right ventricular/left ventricular
SBP  systolic blood pressure
SIGN  Scottish Intercollegiate Guidelines Network
SMC  Scottish Medicines Consortium
STP  superficial vein thrombosis or thrombophlebitis
THR  total hip replacement
TKR  total knee replacement
UEDVT  upper extremity DVT
UFH  unfractionated heparin
UK  United Kingdom
US  ultrasound
VKA  vitamin K antagonist
VTE  venous thromboembolism
Annex 1

Key questions used to develop the guideline

THE KEY QUESTIONS USED TO DEVELOP THE GUIDELINE

RISK FACTORS

<table>
<thead>
<tr>
<th>Key question</th>
<th>Inclusion/exclusion criteria</th>
<th>See guideline section</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. What are the risk factors for venous thromboembolism (VTE) (first and recurrent)?</td>
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<tr>
<td>Consider: age, gender, ethnicity, obesity, varicose veins, previous VTE, thrombophilias, other thrombotic states, hormone therapy, contraceptives, other drugs (antipsychotics, thalidomide, EPO, COX-2, SERMs) pregnancy, puerperium, immobility, hospitalisation, anaesthesia, assisted reproduction, transgender, family history, smoking, intravenous drug abuse, venous canula, folic acid deficiency, active and past history of cancer.</td>
<td>See guideline section</td>
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</tr>
</tbody>
</table>

PREVENTION

<table>
<thead>
<tr>
<th>Key question</th>
<th>Inclusion/exclusion criteria</th>
<th>See guideline section</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. In patients undergoing invasive procedures, who should receive prophylaxis for the prevention of VTE and what VTE prophylaxis treatment (including duration of treatment) is most effective in reducing the incidence of VTE (asymptomatic, symptomatic and fatal)?</td>
<td></td>
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</tr>
<tr>
<td>Invasive procedures to include: general and gynaecological surgery, orthopaedic surgery, urological surgery, neurosurgery, cardiothoracic surgery, peripheral vascular surgery, minimal access surgery, central venous catheters. Consider mechanical and pharmaceutical treatments; alternative/homeopathic treatments. Mechanical: graduated elastic compression stockings, intermittent pneumatic compression devices, mechanical foot pumps, venal cava filters. Pharmaceutical: antiplatelet agents (aspirin), heparins (unfractionated heparin and low molecular weight heparins), heparinoids, hirudins, pentasaccharides (fondaparinux), oral anticoagulants (warfarin), dextran, direct thrombin inhibitors, factor-Xa inhibitors.</td>
<td>See guideline section</td>
<td></td>
</tr>
<tr>
<td>3. In medical patients, who should receive prophylaxis for the prevention of VTE and what VTE prophylaxis treatment (including duration of treatment) is most effective in reducing the incidence of VTE (asymptomatic, symptomatic and fatal)? Medical patients to include: those who have suffered myocardial infarction or stroke, cancer patients, spinal injuries, paraplegic, cardiac failure, nephrotic syndrome. Consider same treatments as listed in question 2.</td>
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</tbody>
</table>
4. During pregnancy and the puerperium which patients should receive prophylaxis for the prevention of VTE and what VTE prophylaxis treatment is most effective in reducing the incidence of VTE? Consider same treatments as listed in question 2.

5. What are the risks of VTE associated with long-distance travel and what VTE prophylaxis treatment is most effective in reducing the incidence of VTE when travelling? Consider same treatments as listed in question 2.

6. What investigations predict risk of VTE, and in whom should they be performed? First VTE and recurrent VTE. Consider: thrombophilia testing, factor V Leiden, prothrombin G20210A, Protein C antithrombin deficiency, Factor VIII, homocysteine, MTHFR, antiprophospholipid, CD14, CD 16, CD55, CD59, lipoprotein A, Protein S, JAK-2, D-dimer, ultrasound? Consider the following populations: pregnancy, contraception users, HRT users, pre-op patients, long-haul travel, family history.

ADVERSE EFFECTS

<table>
<thead>
<tr>
<th>Key question</th>
<th>Inclusion/exclusion criteria</th>
<th>See guideline section</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. What are the adverse effects associated with VTE prophylaxis/treatment, both pharmacological and mechanical, and how should they be managed? Pharmacological: spinal bleeding, bleeding, regional anaesthesia, HIT (heparin induced thrombocytopenia), bone density, teratogenicity, allergy, rebound phenomena Mechanical: pressure effects of mechanical devices, phlebitis.</td>
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INVESTIGATION

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<tr>
<th>Key question</th>
<th>Inclusion/exclusion criteria</th>
<th>See guideline section</th>
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<tbody>
<tr>
<td>8. What evidence is there for the use of diagnostic algorithms (decision rules, flowcharts, D-dimer tests) in diagnosing VTE (DVT/PTE) first episode and recurrence? Consider: Wells score, Geneva score, D-dimer tests.</td>
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<tr>
<td>9. What diagnostic techniques should be used to diagnose clinically suspected DVT? Consider: duplex scan, venography, ultrasound (compression or duplex), MRI, plethysmography.</td>
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<td></td>
</tr>
<tr>
<td>10. Which diagnostic techniques should be used to diagnose clinically suspected severe and non-severe PTE? Consider: ventilation perfusion lung scan, VQ scan, Computed Tomography angiogram, Magnetic Resonance Angiography (MRA), pulmonary angiogram, Chest X-ray (CXR), ECHO, blood gas analysis, pulse oximetry, ECG, troponin, clinical features (hypotension).</td>
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</tbody>
</table>
MANAGEMENT OF VTE

<table>
<thead>
<tr>
<th>Key question</th>
<th>Inclusion/exclusion criteria</th>
<th>See guideline section</th>
</tr>
</thead>
<tbody>
<tr>
<td>11. In patients with acute limb threatening and non-limb threatening DVT what is the optimal initial management? Consider: all sites of VTE (leg, upper limb, lung, cerebral, portal; exclude retinal vein thrombosis) Consider: thrombolysis, anticoagulants, IVC filter; hydration, elevation, mobilisation.</td>
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<tr>
<td>12. In patients with acute severe and non-severe PTE what is the optimal initial management? Consider: thrombolysis, anticoagulants, IVC filter.</td>
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<td></td>
</tr>
<tr>
<td>13. In patients presenting with VTE/DVT/PTE are there any clinical or laboratory investigations which need to be carried out a) before starting anticoagulation therapy or b) at a later stage?</td>
<td>a) Renal function, clotting screen, assessment of bleeding risks, full blood count b) Cancer screening.</td>
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</tr>
<tr>
<td>14. Which patients with VTE can be managed successfully in an outpatient setting?</td>
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<tr>
<td>15. What is the appropriate duration, intensity and choice of anticoagulant, and value of compression hosiery in patients with VTE? Consider: populations – cancer, pregnancy, prior VTE, intravenous drug users Consider: anticoagulants, GCS.</td>
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</table>
Annex 2

Algorithm for assessing the risk of venous thromboembolism (VTE)²⁹

RISK ASSESSMENT FOR VENOUS THROMBOEMBOLISM (VTE)

Risk assessment is recommended for all patients on admission to hospital. It is recommended that all patients are periodically reassessed during inpatient stay as risk may change. Reassessment after at least 48 to 72 hours is recommended.

STEP ONE
Review the patient-related factors shown on the assessment sheet against thrombosis risk, ticking each box that applies (more than one box can be ticked). Use the highest category of risk if more than one box is ticked (e.g. if both moderate and high risk are ticked, use guidance for high-risk patients).

Any tick for thrombosis risk should prompt thromboprophylaxis according to local policy.

The risk factors identified are not exhaustive. Clinicians may consider additional risks in individual patients and offer thromboprophylaxis as appropriate.

STEP TWO
Review the patient-related factors shown against bleeding risk and tick each box that applies (more than one box can be ticked).

Any tick for bleeding risk should prompt clinical staff to consider if bleeding risk is sufficient to preclude pharmacological intervention.

STEP THREE
If the form has been filled out correctly and no boxes are ticked, then the patient is at low risk of venous thromboembolism and no intervention is indicated.

Guidance on thromboprophylaxis is available at:


This document has been authorised by the Department of Health
Gateway reference no 10278

DH Department of Health
### Annex 2
*(continued)*

#### Risk Assessment for Venous Thromboembolism (VTE)

<table>
<thead>
<tr>
<th>Thrombosis risk</th>
<th>Patient related</th>
<th>Procedure related</th>
<th>Tick</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt;60 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous pulmonary embolism or deep vein thrombosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute or chronic lung disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute or chronic inflammatory disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower limb paralysis (excluding acute stroke)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute infectious disease, e.g. pneumonia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI &gt;30kg/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hip or knee replacement</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hip fracture</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other major orthopaedic surgery</td>
<td></td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Surgical procedure lasting &gt;30 minutes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plaster cast immobilisation of lower limb</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bleeding risk</th>
<th>Patient related</th>
<th>Procedure related</th>
<th>Tick</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemophilia or other known bleeding disorder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Known platelet count &lt;100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute stroke in previous month (haemorrhagic or ischaemic)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure &gt;200 systolic or 120 diastolic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe liver disease (prothrombin time above normal or known varices)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe renal disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding risk, existing anticoagulant therapy or antiplatelet therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neurosurgery, spinal surgery or eye surgery</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other procedure with high bleeding risk</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lumbar puncture/spinal/epidural in previous 4 hours</td>
<td></td>
</tr>
</tbody>
</table>

---
Annex 3
The Geneva score for assessment of probability of PE

The original Geneva score is calculated using seven risk factors and clinical variables:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score (points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age:</td>
<td></td>
</tr>
<tr>
<td>60-79 years</td>
<td>1</td>
</tr>
<tr>
<td>over 80 years</td>
<td>2</td>
</tr>
<tr>
<td>Previous DVT or PE</td>
<td>2</td>
</tr>
<tr>
<td>Recent surgery within four weeks</td>
<td>3</td>
</tr>
<tr>
<td>Heart rate &gt;100 beats per minute</td>
<td>1</td>
</tr>
<tr>
<td>PaCO₂ (partial pressure of CO₂ in arterial blood):</td>
<td></td>
</tr>
<tr>
<td>&lt;35 mmHg</td>
<td>2</td>
</tr>
<tr>
<td>35-39 mmHg</td>
<td>1</td>
</tr>
<tr>
<td>PaO₂ (partial pressure of O₂ in arterial blood):</td>
<td></td>
</tr>
<tr>
<td>&lt;49 mmHg</td>
<td>4</td>
</tr>
<tr>
<td>49-59 mmHg</td>
<td>3</td>
</tr>
<tr>
<td>60-71 mmHg</td>
<td>2</td>
</tr>
<tr>
<td>72-82 mmHg</td>
<td>1</td>
</tr>
<tr>
<td>Chest X-ray findings:</td>
<td></td>
</tr>
<tr>
<td>Band atelectasis</td>
<td>1</td>
</tr>
<tr>
<td>Elevation of hemidiaphragm</td>
<td>1</td>
</tr>
</tbody>
</table>

The score obtained relates to the probability of the patient having had a pulmonary embolism (the lower the score, the lower the probability):

- <5 points indicates a low probability of PE
- 5-8 points indicates a moderate probability of PE
- >8 points indicates a high probability of PE
Annex 4

The revised Geneva score for assessment of probability of PE

The revised Geneva score uses eight parameters, but does not include figures which require an arterial blood gas sample to be performed:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score (points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 65 years or over</td>
<td>1</td>
</tr>
<tr>
<td>Previous DVT or PE</td>
<td>3</td>
</tr>
<tr>
<td>Surgery or fracture within one month</td>
<td>2</td>
</tr>
<tr>
<td>Active malignant condition</td>
<td>2</td>
</tr>
<tr>
<td>Unilateral lower limb pain</td>
<td>3</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>2</td>
</tr>
<tr>
<td>Heart rate:</td>
<td></td>
</tr>
<tr>
<td>75 to 94 beats per minute</td>
<td>3</td>
</tr>
<tr>
<td>95 or more beats per minute</td>
<td>5</td>
</tr>
<tr>
<td>Pain on deep palpation of lower limb and unilateral oedema</td>
<td>4</td>
</tr>
</tbody>
</table>

The score obtained relates to probability of PE:

- 0-3 points indicates low probability (8%)
- 4-10 points indicates intermediate probability (28%)
- 11 points or more indicates high probability (74%)
Annex 5
The Wells score or criteria for assessment of suspected DVT

Wells score or criteria: (possible score -2 to 9)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score (points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active cancer (treatment within last six months or palliative)</td>
<td>1</td>
</tr>
<tr>
<td>2. Calf swelling &gt;3 cm compared to other calf (measured 10 cm below tibial tuberosity)</td>
<td>1</td>
</tr>
<tr>
<td>3. Collateral superficial veins (non-varicose)</td>
<td>1</td>
</tr>
<tr>
<td>4. Pitting oedema (confined to symptomatic leg)</td>
<td>1</td>
</tr>
<tr>
<td>5. Swelling of entire leg</td>
<td>1</td>
</tr>
<tr>
<td>6. Localized pain along distribution of deep venous system</td>
<td>1</td>
</tr>
<tr>
<td>7. Paralysis, paresis, or recent cast immobilization of lower extremities</td>
<td>1</td>
</tr>
<tr>
<td>8. Recently bedridden &gt;3 days, or major surgery requiring regional or general anesthetic in past four weeks</td>
<td>1</td>
</tr>
<tr>
<td>9. Alternative diagnosis at least as likely subtract 2</td>
<td></td>
</tr>
</tbody>
</table>

**Interpretation:** For dichotomised evaluation (likely v unlikely)

<table>
<thead>
<tr>
<th>Score of 2 or higher</th>
<th>deep vein thrombosis is likely. Consider imaging the leg veins.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score of less than 2</td>
<td>deep vein thrombosis is unlikely. Consider blood test such as D-dimer test to further rule out deep vein thrombosis</td>
</tr>
</tbody>
</table>

**For low, intermediate and high scoring**

<table>
<thead>
<tr>
<th>Probability</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>&gt;3 points</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1 or 2 points</td>
</tr>
<tr>
<td>Low</td>
<td>&lt;0 points</td>
</tr>
</tbody>
</table>
Annex 6

Example advice leaflet for patients discharged from the ED

Issued by the Chief Medical Officer (cmo@scotland.gsi.gov.uk) 26 January 2008

**Emergency Department Leaflet**

*Discharge advice for patients following attendance with a possible clot in the leg (Deep Venous Thrombosis ~ DVT)*

You have been assessed today (date: ___ / ___ / ___) for a possible blood clot in your leg(s) using a clinical examination and blood test. The results suggest that you are very unlikely to have such a clot.

**Why is my leg sore or swollen then?**

You may have been given a specific explanation for this. However, if there is no other obvious cause, the most common explanation is a muscle injury which should go away over the next week.

**Can I still have a clot?**

The blood test and clinical examination system we use can never completely exclude a clot. The chance of us failing to detect a clot has however been estimated to be very low, (typically less than 1 in 200 for people like yourself who have a sore leg).

**Why didn’t I get blood thinning drugs?**

This treatment is not without risks, such as bleeding. Although these risks are uncommon, they mean we should use the drugs only when there is a clear benefit to outweigh these risks.

**Why did I not get any other tests (e.g. an ultrasound scan)?**

We feel this is unnecessary because your chance of having a clot is so low. However, since we can never fully exclude the possibility of a clot (DVT), and in the interests of your own health, you are advised to return to the Emergency Department circumstances – see below.

**What should I look out for?**

- Increased pain or swelling in the leg
- Sudden onset of breathlessness that is unusual for you
- Chest and/or back pains that are unusual for you
- Coughing or spitting up blood
- Any episode of collapse
- Fast heart rate, racing pulse or palpitations
- If there is absolutely no improvement in your symptoms, with the treatment given, within the next few days

If you have unusual chest or back pain, coughing or spitting up blood, or an episode of recent collapse, call 999 immediately and advise the operator that you have recently been tested for DVT.
Annex 7
Example advice leaflet for patients discharged from the outpatient DVT Service

Issued by the Chief Medical Officer (cmo@scotland.gsi.gov.uk) 26 January 2008

Outpatient DVT Service

Discharge advice for patients attending hospital with suspected Deep Vein Thrombosis (DVT)

Discharge advice for patients attending with suspected Deep Vein Thrombosis (DVT) but negative ultrasound.

The scan (ultrasound) investigation carried out on __ / __ / __ has not shown any evidence of a clot (also known as a Deep Vein Thrombosis or DVT) in the blood vessels in your leg. However, this test is unable to exclude a clot completely. Although the probability of a clot is very low, you should be aware that it is important to check that your symptoms are not getting any worse.

What should I do if I have these symptoms?

- Seek urgent medical advice, either from your GP, or from NHS24 or your nearest Accident & Emergency department.

What should I look out for?

- Increased pain or swelling in the leg
- Sudden onset of breathlessness that is unusual for you
- Chest or back pain that is unusual for you
- Coughing or spitting up blood
- Any episode of collapse

In the case of unusual chest or back pain, coughing or spitting up blood, or episode of recent collapse, call 999 immediately and advise the operator that you have recently been tested for DVT.

Is there anything else I should do?

- If any further tests have been organised for you it is important that you attend for them.
- If you have been prescribed any medicine you should take it regularly and finish the course.
- If you have been given a diagnosis of muscle injury and your symptoms have shown no improvement within a few days, seek further medical advice, either from your GP or Accident and Emergency.

If you are unclear about any of the above instructions, please contact the DVT service:
[Include contact details here]
References


67. Hamilton HC, Foxcroft DR. Central venous access sites for the prevention of venous thrombosis, stenosis and infection in patients requiring long-term intravenous therapy. Cochrane Database of Systematic Reviews 2007;3.


158. Wells PS, Owen C, Doucette S, Fergusson D, Tran H. Does this patient have deep vein thrombosis?[see comment]. Jama 2006;295(2):199-207.


165. van Dongen CJ, Vink R, Hutten BA, Buller HR, Prins MH. The incidence of recurrent venous thromboembolism after treatment with vitamin K antagonists in relation to time since first event: a meta-analysis.[see comment]. Archives of Internal Medicine 2003;163(11):1285-93.


204. Janjua M, Badshah A, Matta F, Danescu LG, Yaekoub AY, Stein PD. Treatment of acute pulmonary embolism as outpatients or following early discharge - A systematic review. Thrombosis and Haemostasis 2008;100(5):756-61.


