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Prevention and management of venous thromboembolism

A national clinical guideline

December 2010

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

LEVELS OF EVIDENCE

1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies 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
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

GRADES OF RECOMMENDATION

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation 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

Despite the evidence in support of the efficacy of thromboprophylaxis for venous thromboembolism (VTE) in hospitalised patients there is incomplete implementation of recommendations. This applies particularly to patients with medical illnesses,[1] but also to those admitted to surgical wards.[2] Venous thromboembolism is likely to be an escalating public health problem due to the prominence of age as a risk factor *(see Table 1, section 3.2)* and the increasing age of the population.[3]

1.1.1 UPDATING THE GUIDELINE

Prophylaxis and treatment of VTE were previously considered separately in SIGN guidelines 62 and 36, respectively.[4,5] There is, however, 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 revision is based on new evidence and consensus statements on the prophylaxis and treatment of VTE published from 1998-2010, which includes evidence relating to novel antithrombotic agents, diagnostic methods and complications of treatment.

The current guideline provides comprehensive advice on prevention and management of VTE based on the evidence available to answer a set of key questions, listed in Annex 1.

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 syndrome** (PTS). DVT has multiple contributory risk factors (*see Table 1, section 3.2*).

Asymptomatic DVT is defined as DVT detected by screening, usually by compression ultrasound, ^{125}I fibrinogen scanning, or ascending venography.[6-10]

Symptomatic lower limb DVT (usually leg pain and/or swelling) results from occlusion of a major leg vein and includes both proximal and distal thrombosis. It requires specific investigation and treatment.

Pulmonary embolism, which often results from an asymptomatic DVT,[11] may present as breathlessness, faintness, collapse, chest pain, haemoptysis or sudden death. **Non-fatal PE** in hospitalised patients may delay discharge, or require readmission to hospital. Chronic pulmonary hypertension is an occasional consequence.[12] **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.[11] Further studies have continued to highlight the significant contribution of PE to morbidity and mortality.[13-20]

Post-thrombotic leg syndrome (chronic leg pain, swelling, dermatitis, ulcers) is a consequence of damage to leg vein valves by DVT. Approximately 30% of patients/people develop some symptoms of PTS after lower limb DVT. Leg ulcers are observed in 2-10% of patients approximately 10 years after their first symptomatic DVT.[21-25]

Venous thromboembolism (VTE) is defined as DVT with or without PE.

Incidental VTE is deep vein thrombosis or pulmonary embolism found incidentally on imaging for another purpose such as cancer staging.

1.1.3 RATIONALE FOR PROPHYLAXIS

The risk of VTE is significantly increased in patients who are hospitalised after trauma, surgery or immobilising medical illness, and also in pregnant and puerperal women, and DVT is common in such individuals. In many patients, DVT remains asymptomatic but in others it can cause morbidity and mortality.[3,7,11,26] 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.[3,23,26-29]

There is evidence that routine prophylaxis reduces morbidity, mortality and health service costs in hospitalised patients at risk of DVT and PE, as highlighted in national and international guidelines.[3, 26,29] Recent data indicate, however, that no measurable reduction in DVT, PE or mortality after orthopaedic surgery followed the implementation of the 2007 NICE guidelines *Venous thromboembolism: reducing the risk of venous thromboembolism (deep-vein thrombosis and pulmonary embolism) in patients undergoing surgery*.[30]

In contrast, screening for asymptomatic DVT, and its treatment, is expensive, insensitive and not cost effective compared to routine prophylaxis in at-risk patients.[3,26,29]

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 patients, 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 adult patient groups at risk of VTE *(see section 3)* and describes the available methods of prophylaxis *(see section 4)*. 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 medical practitioners in a wide range of specialties including general practitioners, nurses, pharmacists and dentists.

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 AUTHORISATION

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.[31]

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."[31]

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).[31]

1.3.2 ADDITIONAL ADVICE TO NHSSCOTLAND FROM NHS QUALITY IMPROVEMENT SCOTLAND AND THE SCOTTISH MEDICINES CONSORTIUM

NHS QIS processes multiple technology appraisals (MTAs) for NHSScotland that have been produced by the National Institute for Health and Clinical Excellence (NICE) in England and Wales.

The Scottish Medicines Consortium (SMC) provides advice to NHS Boards and their Area Drug and Therapeutics Committees about the status of all newly licensed medicines and any major new indications for established products.

SMC advice and NHS QIS validated NICE MTAs relevant to this guideline are summarised in section 17.3.

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 recommendation is based. It does not reflect the clinical importance of the recommendation.

2.1 RISK FACTORS FOR VENOUS THROMBOEMBOLISM

2.1.1 CLINICAL ASSESSMENT OF VENOUS THROMBOSIS RISK

D

- **All patients admitted to hospital or presenting acutely to hospital should be individually assessed for risk of venous thromboembolism and bleeding. The risks and benefits of prophylaxis should be discussed with the patient.**
- **The use of a risk assessment method checklist is recommended for this purpose.**
- **The assessment should be repeated regularly and at least every 48 hours.**

2.2 THROMBOPROPHYLAXIS IN SURGICAL PATIENTS

2.2.1 GENERAL SURGERY

A **Patients undergoing abdominal surgery who are at risk due to the procedure or personal risk factors should receive thromboprophylaxis with mechanical methods unless contraindicated and either subcutaneous low molecular weight heparin, unfractionated heparin or fondaparinux.**

2.2.2 ORTHOPAEDIC SURGERY

A **Patients undergoing total hip replacement or total knee replacement surgery should receive pharmacological prophylaxis** *(with low molecular weight heparin, fondaparinux, rivaroxaban or dabigatran)* **combined with mechanical prophylaxis unless contraindicated**.

A **Extended prophylaxis should be given.**

2.3 THROMBOPROPHYLAXIS IN MEDICAL PATIENTS

2.3.1 PHARMACOLOGICAL PROPHYLAXIS TO PREVENT ASYMPTOMATIC AND SYMPTOMATIC VTE

A **When the assessment of risk favours use of thromboprophylaxis, unfractionated heparin, low molecular weight heparin or fondaparinux should be administered.**

2.3.2 OTHER MEDICAL PATIENTS

A **Patients with cancer are generally at high risk of venous thromboembolism and should be considered for prophylaxis with low molecular weight heparin, unfractionated heparin or fondaparinux whilst hospitalised.**

2.4 PREGNANCY AND THE PUERPERIUM

2.4.1 ANTENATAL THROMBOSIS RISK ASSESSMENT

D **All women should be assessed for risk factors for venous thromboembolism when booking for antenatal care and at each subsequent maternity contact.**

2.5 DIAGNOSIS OF VENOUS THROMBOEMBOLISM

2.5.1 DIAGNOSTIC ALGORITHMS

B **A validated clinical decision rule should be used in the initial assessment of outpatients presenting with suspected deep vein thrombosis or pulmonary embolism.**

☑ The results of the initial assessment should be used to determine the diagnostic strategy.

2.5.2 CONFIRMATION OF CLINICALLY SUSPECTED DEEP VEIN THROMBOSIS

C **Patients who have a negative or inadequate initial scan but who have a persisting clinical suspicion of deep vein thrombosis or whose symptoms do not settle should have a repeat ultrasound scan.**

2.6 PRELIMINARY ASSESSMENT

2.6.1 CLINICAL AND LABORATORY INVESTIGATIONS

D **All patients presenting with venous thromboembolism should have a full clinical history and examination undertaken with the aim of detecting underlying conditions contributing to the development of thrombosis and assessing suitability for antithrombotic therapy.**

A **Testing for inherited forms of thrombophilia** *(antithrombin, protein C, protein S deficiency and factor V Leiden and prothrombin G20210A)* **does not influence initial management of venous thromboembolism and should not be performed routinely.**

C **Unselective screening for cancer in patients with deep vein thrombosis or pulmonary embolism is not indicated.**

2.7 INITIAL MANAGEMENT OF VENOUS THROMBOEMBOLISM

2.7.1 SUPERFICIAL THROMBOPHLEBITIS

D **Patients with clinical signs of superficial thrombophlebitis affecting the proximal long saphenous vein should have an ultrasound scan to exclude concurrent deep vein thrombosis.**

B
- **Patients with superficial thrombophlebitis should have anti-embolism stockings and can be considered for treatment with prophylactic doses of low molecular weight heparin for up to 30 days or fondaparinux for 45 days.**
- **If low molecular weight heparin is contraindicated, 8-12 days of oral non-steroidal anti-inflammatory drugs should be offered.**

2.8 FURTHER MANAGEMENT OF VENOUS THROMBOEMBOLISM

2.8.1 CHOICE OF ANTICOAGULANT

A **Low molecular weight heparin rather than warfarin should be considered in venous thromboembolism associated with cancer.**

2.8.2 DURATION OF ANTICOAGULATION IN LOWER LIMB DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM

A **After a first episode of proximal limb deep vein thrombosis or pulmonary embolism, treatment with a vitamin K antagonist should be continued for at least three months.**

☑ Uninterrupted, long term continuation of vitamin K antagonist therapy after a first episode of venous thromboembolism may be appropriate in some patients and can be based on individual assessment, including:

- an unprovoked first event
- the site and severity of the first event
- the presence of persistent comorbidities, eg cancer
- the presence of persistent antiphospholipid antibodies
- male sex *(see Table 2)*
- bleeding risk on anticoagulant treatment
- patient compliance and preference.

2.9 ADVERSE EFFECTS OF VENOUS THROMBOEMBOLISM PROPHYLAXIS AND TREATMENT

2.9.1 HEPARIN INDUCED THROMBOCYTOPENIA

D

- **Monitoring patients for the development of HIT should be by performing serial platelet counts.**
- **Patients who have previously received UFH or LMWH within 100 days or in whom the 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 two to three days from day four to day14 of exposure.**

3 Assessment of risk 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, cancer and certain drug use (eg oral contraceptive pill)
- the result of an intercurrent illness or procedure, or other cause of temporary reduced mobility, eg following major trauma or surgery, serious medical disorder, pregnancy, or long-haul travel.

In half to three quarters of patients with VTE, risk factors are readily identifiable on taking a careful history combined with clinical examination *(see Table 1)*. There is insufficient evidence to show whether the interactions between risk factors are additive or greater, although the interaction between factor V Leiden and use of the combined oral contraceptive, for example, has been shown to be multiplicative.[32]

3.2 CLINICAL ASSESSMENT OF VENOUS THROMBOSIS RISK

Algorithms for assessing the risk of VTE in patients admitted to hospital have been designed and an example is included in Annex 2. The risk factors for VTE and recurrent VTE are listed in Tables 1 and 2. As 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 throughout the period of admission and on discharge.

Table 1: Risk factors for venous thromboembolism

Risk Factor	Comments
Age[7,33-36]	Incidence of first VTE rises exponentially with age. In the general population: < 40 years – annual incidence of 1/10,000 60-69 years – annual incidence of 1/1,000 > 80 years – annual incidence of 1/100 May reflect immobility[37] and coagulation activation[38,39]
Obesity[7,33,34,37,40,41]	2 to 3-fold VTE risk if obese (body mass index > 30 kg/m^2) May reflect immobility and coagulation activation[38,39]
Varicose veins[34,42]	1.5 to 2.5-fold risk after major general/orthopaedic surgery Low risk after varicose vein surgery[22,43]
Family history of VTE	A history of at least one first degree relative having had VTE at age < 50 years or more than one first degree relative with VTE history regardless of age is an indicator of increased risk of first VTE (but not of recurrent VTE).[44]
Thrombophilias[45-47,48]	Low coagulation inhibitors (antithrombin, protein C or S) Activated protein C resistance (eg factor V Leiden) High coagulation factors (I, II, including prothrombin G20210A, VIII, IX, XI) Antiphospholipid antibodies High homocysteine: 1.5 to 2.5-fold VTE risk[49,50] Elevated lipoprotein(a) > 300mg/l: 1.8-fold risk of VTE[51]

Other thrombotic states	Cancer: compared with general population overall 5 to 7-fold risk of first VTE and increased risk of recurrent VTE. Risk varies with type of cancer. Further increased risk associated with surgery, chemotherapy, use of erythropoeisis stimulating agents and central venous catheters[52,53] Heart failure, recent myocardial infarction/stroke Metabolic syndrome: 2-fold increased risk of VTE[54] Severe acute infection Chronic HIV infection[55] Inflammatory bowel disease, nephrotic syndrome Myeloproliferative disease, paraproteinaemia, Bechet's disease, paroxysmal nocturnal haemoglobinuria Sickle cell trait and sickle cell disease[56]
Combined oral contraceptives, hormone relplacement therapy and anti-oestrogens	Combined oral contraceptives (COCs): compared with non-users, COC users have 3 to 6-fold increased risk.[57-60] Compared with users of COCs containing second generation progestogens, users of COCs containing third generation progestogens have a further 1.7-fold increase in VTE risk.[61] 2.5-fold increased risk of postoperative VTE in COC users[42] 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[62] Heritable thrombophilia further increases VTE risk in COC and oral oestrogen HRT users[63,64] Raloxifene and tamoxifen associated with a 2 to 3-fold increased VTE risk[65-68]
Pregnancy, puerperium *(see section 7)*	Approximately 10-fold increased risk during pregnancy compared with non-pregnant and 25-fold increased risk compared with non-pregnant/non-puerperal during puerperium[68] Pregnant and puerperal women with thrombophilia have increased risk of VTE compared to pregnant and puerperal women without an identified thrombophilia[64,68-70]
Immobility	For example, bed rest >3 days, plaster cast, paralysis: 10-fold increased VTE risk; increases with duration
Immobility during travel[33,71] *(see section 8)*	2 to 3-fold increased risk
Hospitalisation[33,71]	Acute trauma, acute illness, surgery: 10-fold increased VTE risk
Anaesthesia	2 to 3-fold increased risk of postoperative VTE in general compared with spinal/epidural[42,72]
Central venous catheters	Compared with subclavian access, femoral route 11.5-fold increased risk of VTE[73] 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[74]

Table 2: Risk factors for recurrent venous thromboembolism (in patients not on long term anticoagulation)

Risk Factor	Comments
Previous unprovoked VTE[75]	Recurrence rate 5% per year after an unprovoked VTE
Male sex[76]	Compared with women, men have an increased relative risk (RR) of recurrent VTE (RR 1.6, 95% confidence interval (CI) 1.2 to 2.0). The higher relative risks reported in some studies[77,78] may be explained by sex-specific factors present at the time of the first VTE events[79]
Obesity[80]	Hazard ratio (HR) 1.6 (95% CI 1.1 to 2.4)
Thrombophilias	Risk of recurrent VTE is not increased in patients with either heterozygous or homozygous factor V Leiden or prothrombin gene G20210A81 but may be increased in patients with antithrombin deficiency[47]

D
- **All patients admitted to hospital or presenting acutely to hospital should be individually assessed for risk of VTE and bleeding. The risks and benefits of prophylaxis should be discussed with the patient.**
- **The use of a risk assessment method checklist is recommended for this purpose.**
- **The assessment should be repeated regularly and at least every 48 hours.**

☑ All patients should be assessed for their individual risk of thrombosis versus increased risk of bleeding with pharmacological prophylaxis.

☑ The risk assessment should be shared with the patient/carer and the outcome of that discussion formally recorded as part of the routine process of informed consent to treatment.

3.2.1 GUIDELINES FOR VTE PROPHYLAXIS

Surveys indicate that compliance with VTE prophylaxis guidelines is generally poor, on medical wards in particular,[1] and there is a need to ensure that medical patients at risk receive appropriate thromboprophylaxis. A range of interventions designed to improve compliance with thromboprophylaxis among inpatients is under investigation and a review of the literature on these concluded that passive distribution of guidelines is inadequate and a system involving active reminders is required to improve compliance.[82] Use of electronic alerts resulted in improved compliance and a reduction in the burden of VTE in a randomised study.[83]

1+
2++

B **Hospitals should adopt approaches which are likely to increase compliance with thromboprophylaxis guidelines and improve patient outcomes.**

D **Local prophylaxis guidelines should be developed and updated for specific patient groups.**

3.3 LABORATORY TESTS IN ASSESSMENT OF THROMBOSIS RISK

Routine laboratory 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.[45,48,63,64,68,69,74]

2++
2+
4

D **Routine laboratory screening for heritable thrombophilias is not recommended.**

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 sections five to eight.

4.1 GENERAL MEASURES

4.1.1 MOBILISATION AND LEG EXERCISES

Immobility increases the risk of DVT about tenfold.[33,71] A meta-analysis of randomised controlled trials (RCTs) of bed rest for several medical conditions found no evidence of benefit of bed rest for any condition.[84] | 2^+ 1^+

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

4.1.2 HYDRATION

Haemoconcentration increases blood viscosity and reduces blood flow, especially in the deep veins of the leg in immobile patients.[85] | 4

☑ Adequate hydration should be ensured in immobilised patients.

4.2 MECHANICAL METHODS

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

- anti-embolism stockings (AES)
- intermittent pneumatic compression (IPC) devices
- pneumatic foot pumps.

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 ANTI-EMBOLISM STOCKINGS

AES are commercially available as both below-knee and above-knee stockings. Most controlled trials have used above-knee stockings.[3,7,26,86-88] Studies comparing above-knee and below-knee stockings have been too small to determine whether or not they are equally effective, although a meta-analysis suggested no major difference in efficacy in surgical patients.[89]

☑ Above-knee or below-knee AES may be used for prophylaxis of DVT in surgical patients provided that there are no contraindications and that attention is paid to correct fitting and application.

Table 3 summarises the contraindications for and application of AES. It has been suggested that 15-20% of patients cannot effectively wear AES because of unusual limb size or shape.[3] An educational programme for appropriate use of AES was found to be useful in one Scottish NHS Board.[90]

Table 3: Contraindications for and application of AES

CONTRAINDICATIONS	
▪ Massive leg oedema	▪ Severe peripheral neuropathy
▪ Pulmonary oedema (eg heart failure)	▪ Major leg deformity
▪ Severe peripheral arterial disease	▪ Dermatitis
APPLICATION	
▪ Select correct size	▪ Do not fold down
▪ Apply carefully, aligning toe hole under toe	▪ Remove daily for no more than 30 minutes
▪ Check fitting daily for change in leg circumference	

4.2.2 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),[3,26] which stimulates fibrinolysis[91] as well as promoting blood flow. Compression devices are usually applied immediately before surgery and are often used along with AES during and after surgery.

4.2.3 PNEUMATIC FOOT PUMPS

The arteriovenous 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.

4.3 ANTIPLATELET AGENTS

4.3.1 ANTIPLATELET AGENTS

A meta-analysis of 53 RCTs of antiplatelet agents (usually aspirin) for prophylaxis of VTE in general or orthopaedic surgery reported significant reductions in risks of asymptomatic DVT (26% *v* 35%), pulmonary embolism (0.6% v 1.6%) and fatal PE (0.2% v 0.6%); with a non-significant trend to lower mortality and a significant increase in major bleeding.[6,8] 1++

There is a paucity of robust direct comparisons between aspirin and other pharmacological methods. In the absence of evidence from such studies, however, and in the face of extensive data from RCTs of heparin and fondaparinux *(see sections 5.1, 5.5 and 6.1)*, use of aspirin as the sole agent for VTE prophylaxis is not appropriate.

4.4 UNFRACTIONATED AND LOW MOLECULAR WEIGHT HEPARINS

Unfractionated heparin (UFH) and several low molecular weight heparins (LMWHs) are currently licensed in the UK for prophylaxis of VTE.[31,92,93] They vary in their manufacture, chemistry and biology, but it is not clear whether these characteristics affect clinical efficacy and safety.[94]

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.

In general, perioperative low-dose heparin is not contraindicated in patients already taking aspirin.

Major side effects of heparin (UFH or LMWH) include bleeding and heparin induced thrombocytopenia. LMWHs are renally excreted and increasing accumulation, and therefore increasing risk of bleeding, is seen with worsening glomerular filtration rate (GFR). Heparin induced thrombocytopenia may occur in any patient who is receiving UFH or LMWH although the incidence is higher in surgical than in medical or obstetric patients *(see section 15.2)*.

The efficacy and safety of UFH and LMWH in surgical and medical patients are addressed in sections 5.1.3, 5.1.4 and 6.1.

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

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

☑ Use of UFH may be preferable if there is a risk of accumulation of LMWH due to renal impairment.

4.4.1 ADMINISTRATION, DOSAGE AND MONITORING

When administered for thromboprophylaxis, both UFH and LMWH are given subcutaneously. The dose of UFH is 5,000 IU 8-12 hourly or 7,500 IU 12-hourly. 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 should be measured if required.[92,95] 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 impairment given higher (therapeutic) doses of LMWH.[95]

The platelet count should be monitored initially *(see section 15.2)*.

4.4.2 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.[31,92] Protamine is less effective in reversal of LMWH anticoagulation (consult the manufacturer's data sheet for further information).

4.5 HEPARINOIDS

The heparinoid, danaparoid, is effective in prophylaxis of DVT in patients undergoing general or orthopaedic surgery but is not widely used for this purpose.[96] It is also effective in treatment of patients with heparin associated thrombocytopenia, although there is cross-reactivity with heparin in some cases,[31,92,97] and can be used as short term prophylaxis in patients with a history of this condition.[31] Like LMWH it should be used with caution in patients with renal impairment.

4.6 FONDAPARINUX

The synthetic pentasaccharide fondaparinux is a highly selective, indirect inhibitor of factor Xa. It is licensed for use in thromboprophylaxis in medical patients, and in patients undergoing major lower limb orthopaedic surgery or abdominal surgery. It should be used with caution in patients with renal impairment.[98] For recommendations on the use of fondaparinux see sections 5.1.5, 5.5.2 and 6.1.

4.7 HIRUDINS

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

Lepirudin is a recombinant hirudin and is effective in the management of VTE in patients with thrombosis and heparin associated thrombocytopenia.[92] It should be used with caution in patients with renal impairment.

4.8 DEXTRANS

Intravenous dextrans appear less effective than heparins in prophylaxis of asymptomatic DVT, but may be equally effective in prophylaxis of PE.[3] However, dextrans are not widely used in the UK[99,100] 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).[101]

☑ 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.[102]

☑ Dextrans should be avoided peripartum.

4.9 VITAMIN K ANTAGONISTS

Warfarin is the principal vitamin K antagonist used in the UK. Warfarin is effective in the prophylaxis of VTE in lower limb major orthopaedic surgery and possibly general surgery.[3] However, it is not widely used for this indication in the UK[99,100] because its use requires daily monitoring by the International Normalised Ratio (INR), and because it increases the risk of bleeding after trauma or surgery,[3,26] 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*).
- severe renal impairment.[31]

In patients on long term oral anticoagulant therapy, such as warfarin, (eg for atrial fibrillation or heart valve disease/prosthesis) who are immobilised by illness, trauma or surgery, continuation of oral anticoagulants may be appropriate and sufficient prophylaxis of VTE following appropriate risk assessment. 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.

☑ In patients receiving long term oral anticoagulant therapy who are immobilised by illness, trauma or surgery, continuation of oral anticoagulants at the usual target INR may be appropriate prophylaxis.

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. At present they are licensed for use in hip and knee replacement surgery *(see sections 5.5.5 and 5.5.6)*.

4.11 COMBINED MECHANICAL AND PHARMACOLOGICAL PROPHYLAXIS

A Cochrane systematic review concluded that, compared with compression alone, combining IPC with pharmacological thromboprophylaxis resulted in a significant reduction in both symptomatic DVT (from about 4% to 1%; OR 0.43, 95% CI 0.24 to 0.76) and PE (from about 3% to 1%; OR 0.39, 95% CI 0.25 to 0.63).[103] 1^{++}

Increased efficacy may reflect a combined effect on venous stasis and hypercoagulability. The combined approach is currently commonly employed in Scotland,[104] and the rest of the UK.[99]

5 Thromboprophylaxis in surgical patients

All surgical interventions carry a risk of VTE and attention should be paid to modifiable risk factors. For example, although there are few data on the risk of VTE in women on combined oral contraceptives or hormone replacement therapy, one large epidemiological study suggested around a 2-fold increased risk in women using a combined pill.[105] It is likely that interruption of these hormone treatments prior to planned surgery reduces the risk of VTE but consideration should be given to the risk of unplanned pregnancy and debilitating menopausal symptoms.

5.1 GENERAL SURGERY

Individual assessment of the risks of bleeding and thrombosis should be performed *(see section 3.2)*. The nature of the surgical procedure should be taken into consideration.

Good quality evidence was identified from a meta-analysis and systematic reviews performed on mixed and stratified groups of general surgical patients.[106-110] It is reasonable to generalise from these studies to all patients having intra-abdominal surgery. Separate analyses have been performed on various surgical procedures.[106-110] 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 for abdominal surgery showed a significant incidence of DVT and PE:[3, 6, 9,26,29,104]

- asymptomatic DVT at post operative screening 25%
- asymptomatic proximal DVT at post operative 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 ageing and has increased comorbidity.

A large prospective cohort study in the United Kingdom (The Million Women Study) indicated that the risk of VTE after surgery is substantially increased in the first 12 weeks after an operation. Although the risk varies with type of surgery, the risk is increased even after day-case surgery. The highest levels of risk were associated with hip and knee replacement surgery and surgery for cancer. Overall, compared with women not having surgery, there was a 70-fold increased risk of admission with VTE within six weeks of general surgery (relative risk 69.1, 95% CI 63.1 to 75.6) and a 10-fold risk after day-case surgery (relative risk 9.6, 95% CI 8.0 to 11.5).[18] Standardised incidence rates in the 12 weeks after inpatient surgery were 2.6 per 1,000 patient months. This varied markedly with type of surgery, the highest rates being 7.7 for hip or knee replacement, and 4.3 for patients with cancer.

5.1.2 ANTIPLATELET AGENTS

Combining the results from a meta-analysis of 53 RCTs of antiplatelet agents[6, 8] and the Pulmonary Embolism Prevention (PEP) Trial[111] revealed no significant reduction in total mortality (3.9% *v* 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). 1^{++} 1^{-}

5.1.3 UFH

A meta-analysis of RCTs,[9] including a large trial,[112] found that low-dose subcutaneous UFH significantly reduces the incidence of asymptomatic DVT, symptomatic DVT and PE, fatal PE, and total mortality in surgical patients. A significant increase in major bleeding (from about 4% to 6%) was also observed; however there was no increase in fatal bleeding. 1++

For patients undergoing abdominal surgery, UFH given subcutaneously is effective in reducing the risks of DVT and pulmonary embolism and in reducing mortality.[9,113]

A systematic review of RCTs and controlled clinical trials found that for major colorectal surgery thromboprophylaxis significantly reduced VTE. Unfractionated heparin was as effective as low molecular weight heparin and adding AES produced an additive benefit.[114,115] 1+

5.1.4 LMWH

Meta-analyses of RCTs have shown that subcutaneous LMWHs have similar prophylactic efficacy and risk of bleeding to UFH in patients undergoing surgery,[116,117] including in cancer patients undergoing surgery.[118] Once UFH had been shown to significantly reduce both fatal postoperative PE and mortality,[9,112] 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. 1++

LMWH is as effective as UFH in reducing the risk of DVT and PE and bleeding risks are comparable.[116,117] LMWH 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*).[119] 1++ 1+

5.1.5 FONDAPARINUX

In an RCT, fondaparinux administered postoperatively was at least as effective as a LMWH at reducing the risk of VTE in patients undergoing high-risk abdominal surgery, with comparable rates of major bleeding.[120] 1+

5.1.6 MECHANICAL METHODS

Patients who are positioned in the lithotomy position during surgical procedures which last more than four hours are at risk of lower leg compartment syndrome.[121-123] Concomitant use of AES or intermittent pneumatic compression devices may increase this risk and one study suggests that it is safer to avoid both methods of mechanical thromboprophylaxis in patients who will have their legs elevated for prolonged periods of time.[124,125]

A meta-analysis of RCTs of AES 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 to 0.46).[88] These results are consistent with an earlier meta-analysis,[86] and with historical reports of efficacy of elastic stockings in PE prophylaxis.[87,126] 1++ 1+

The use of AES reduces the rate of DVT, when compared to no thromboprophylaxis, and increases the efficacy of LMWH and UFH. Intermittent pneumatic compression is an alternative.[86-88, 126] (*see sections 4.11 and 5.1.7.*) 1+

Pooled analyses of trials of IPC in prevention of asymptomatic DVT after non-orthopaedic surgery showed a relative risk reduction of around 68%.[26] Similar results have been demonstrated following orthopaedic (mostly elective hip) surgery.[26] An observational study found that IPC reduced the risk of rehospitalisation for symptomatic VTE after elective hip surgery.[127] 2+ 4

5.1.7 COMBINED MECHANICAL AND PHARMACOLOGICAL PROPHYLAXIS

A meta-analysis of RCTs found that AES combined with pharmacological prophylaxis or IPC increased efficacy of VTE prophylaxis by reducing the incidence of asymptomatic DVT in surgical patients (OR 0.24, 95% CI 0.15 to 0.37).[88] 1+

5.1.8 DURATION OF PROPHYLAXIS

There is good evidence that VTE occurs following discharge from hospital with a peak at three weeks.[18] One randomised trial of 300 patients receiving either nine or 28 days of LMWH after abdominal or pelvic surgery showed only two proximal DVTs in the shorter term group and one in the longer term group.[128] Studies comparing standard versus extended pharmacological prophylaxis have shown a small reduction in the rate of symptomatic VTE following extended prophylaxis but extended prophylaxis was not thought to be cost effective.[129] 1+ 4

In a systematic review of extended perioperative thromboprophylaxis in patients with cancer, only low quality evidence was identified, with no data on symptomatic DVT. An extended regimen was associated with a significantly lower rate of asymptomatic DVT (relative risk 0.21, 95% CI 0.05 to 0.94) and no significant difference in deaths at three months.[130] 1++

5.1.9 RECOMMENDATIONS

A **Patients undergoing abdominal surgery who are at risk due to the procedure or personal risk factors should receive thromboprophylaxis with mechanical methods unless contraindicated and either subcutaneous LMWH, UFH or fondaparinux.**

A **AES are recommended for prophylaxis in surgical patients, in the absence of contraindications.**

D **IPC devices are recommended for prophylaxis of DVT in surgical patients.**

A **In patients undergoing abdominal surgery AES can be used alone when pharmacological agents are contraindicated, for example due to high bleeding risk.**

C **Aspirin is not recommended as the sole pharmacological agent for VTE prophylaxis in surgical patients, as other available agents are more effective.**

☑ Pharmacological thromboprophylaxis is typically continued until discharge. Extended prophylaxis should be considered on a case-by-case basis, for example when multiple thrombosis risk factors are present.

☑ The use of AES should continue until there is a return to the pre-morbid level of mobility.

5.2 LAPAROSCOPIC SURGERY

In theory, the reduced length of hospital stay and early ambulation of patients 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, however, increases lower limb venous pooling and may increase risks. Laparoscopic surgery can include procedures ranging from a very short diagnostic laparoscopic procedure to lengthy major surgery, 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 that the incidence of VTE following laparoscopic procedures in patients receiving prophylaxis is low.[131,132] However, rates of VTE appear to be low following laparoscopic surgery even when rates of prophylaxis are also low. Mechanical methods and particularly IPC may reduce lower limb venous pooling. Studies show a low incidence of VTE following the use of AES, IPC or LMWH alone or in combination.[133,134] 2+

☑ Thromboprophylaxis should be considered in patients undergoing laparoscopic surgery. Mechanical methods either alone or in combination with UFH, LMWH or fondaparinux should be considered.

5.3 BARIATRIC SURGERY

Obesity is an independent risk factor for VTE *(see section 3)*.

According to the limited evidence available from a small number of studies, the incidence of VTE following bariatric surgery is low, ranging from 1-3%, although the data are mostly derived from registries.[113,135] The evidence for the effectiveness of prophylaxis in these patients is poor.

☑
- Patients undergoing bariatric surgery should receive thromboprophylaxis as recommended for those undergoing general surgery.
- The dosages of heparin may need to be increased in patients who are obese.

5.4 GYNAECOLOGICAL SURGERY

5.4.1 RISK OF VTE

Cancer is the most significant risk factor for patients having gynaecological surgery.[136,137] In gynaecological surgical patients an abdominal rather than a vaginal approach carries a greater risk of VTE. — 2+

The risk of VTE in gynaecological patients having laparoscopic surgery for non-malignant conditions is low but the possible presence of additional risk factors should be taken into consideration.[107] — 4

5.4.2 HEPARINS

A systematic review found that compared to patients who received neither UFH nor LMWH, UFH or LMWH prophylaxis significantly reduced DVT rates in patients undergoing surgery for gynaecological cancer (relative risk reduction, RRR 0.58, 95% CI 0.35 to 0.95).[138] There is insufficient evidence to say whether UFH or LMWH is superior as the studies were not sufficiently powered to address this.[138] The optimal regimen and duration of treatment is also uncertain for these patients. An RCT of 332 patients undergoing abdominal or pelvic surgery for malignancy found an RRR of 0.6 (95% CI 0.1 to 0.82) for DVT in patients who received LMWH for one month after surgery compared to one week.[139] — 1+

5.4.3 MECHANICAL METHODS

There is insufficient evidence to determine whether IPC or AES are effective in their own right or if they increase the efficacy of pharmacological prophylaxis with UFH or LMWH specifically in gynaecological surgery.

B **In patients undergoing gynaecological surgery, when assessment of risk favours pharmacological thromboprophylaxis, UFH or LMWH may be used.**

☑ Mechanical methods can be considered in addition to pharmacological methods.

5.5 ORTHOPAEDIC SURGERY

There is strong evidence that pharmacological prophylaxis reduces the risk of VTE in patients undergoing hip or knee replacement or who have had a hip fracture.[107,110,140] In addition, there is evidence that pharmacological prophylaxis reduces the risk of fatal pulmonary embolism (RR 0.27, 95% CI 0.10 to 0.74 for any heparin and 0.44, 95% CI 0.28 to 0.68 for antiplatelet agents), but not the all-cause mortality.[6,8,9,111,116,117] Heparins and antiplatelet drugs increase the rate of major bleeding (RR 1.42, 95% CI 0.84 to 2.42 for any heparin versus control, and RR 1.24, 95% CI 1.12 to 1.37 for any antiplatelet agent, mainly aspirin versus control).[6,8,9,111,116,117] — 1++ 1+ 2++ 4

An observational study concluded that all-cause mortality in patients undergoing total hip or knee arthroplasty on any of LMWH, fondaparinux, rivaroxaban or dabigatran is higher than in patients undergoing similar surgery under regional analgesia with or without heparin during surgery or pneumatic compression and aspirin after surgery.[141] However, caution is needed in the interpretation of these results due to concerns regarding the comparability of groups in this study. Nevertheless, the rate of VTE after major lower limb orthopaedic surgery remains higher than that after other forms of surgery,[18] reinforcing the need to seek effective but safe thromboprophylactic measures.[141] — 3

A systematic review in high-risk patients indicated that compared with compression alone, adding pharmacological prophylaxis to compression decreased the incidence of symptomatic PE (from 2.7% to 1.1%) and DVT (from 4.0% to 1.6%). Adding compression to pharmacological prophylaxis compared to pharmacological prophylaxis alone also reduced the incidence of DVT (from 4.21% to 0.65%) although there were insufficient events to determine if there was a benefit on incidence of PE.[103] In a randomised trial in hip surgery, however, the use of graduated compression stockings in patients given fondaparinux offered no additional benefit.[142] — 1++

In the Pulmonary Embolism Prevention (PEP) Trial, 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 given in addition to 'any other thromboprophylaxis thought necessary'.[111] Patients were not screened for asymptomatic DVT. Any benefit was confined to hip fracture patients.[111] — 1-

5.5.1 LMWH

LMWH has been extensively studied in major lower limb orthopaedic surgery and is effective. LMWH reduces the DVT risk (asymptomatic and symptomatic) by approximately 60% compared to placebo. LMWH is more effective than UFH and also more effective than warfarin at reducing DVT.[111,143-148] — 1++

A large well conducted RCT showed that commencing LMWH dosing within eight hours (mean 6.6 ± 2.4 hours) after surgery was as effective as giving the first dose one hour before surgery with a trend to lower bleeding complications compared with preoperative dosing.[149,150] — 1-

5.5.2 FONDAPARINUX

In total hip replacement fondaparinux is slightly more effective than enoxaparin at reducing the incidence of asymptomatic DVT, but not symptomatic DVT.[151] Some studies have shown non-significant trends to a higher incidence of bleeding events with fondaparinux compared with LMWH.[110,151,152] — 1+ 4

5.5.3 VITAMIN K ANTAGONISTS

Vitamin K antagonists (VKA) are effective, but not widely used in Europe as the sole method of prophylaxis.[107,110,153] They are less effective than LMWH (RR 1.5), with an increased risk of bleeding/wound complications.[152,154] — 1+ 1- 2++ 4

5.5.4 ASPIRIN

Aspirin reduces the DVT risk by approximately 25-30% compared to placebo but may be less effective than LMWH/fondaparinux/warfarin, although few direct comparisons have been performed.[155] If a patient has a high risk of arterial thrombotic events (coronary stents, unstable angina, stroke), however, aspirin should be continued in the perioperative period to reduce the risk.[156] A randomised trial indicated that a heparinoid is more effective than aspirin in hip fracture patients.[157] There is insufficient evidence to support the use of aspirin as the sole thromboprophylactic agent, however in patients who require aspirin for other reasons, the additional small reduction in VTE risk is an added benefit.[155,158] — 1+ 2+ 4

5.5.5 RIVAROXABAN

Rivaroxaban is a direct oral Xa inhibitor. Three RCTs, the RECORD studies, found that rivaroxaban had greater efficacy in preventing DVT compared with enoxaparin in total hip replacement (THR) and total knee replacement (TKR) (extended prophylaxis of 35 days in THR, 14 days in TKR).[159-161] In RECORD 1, rivaroxaban 10 mg once daily beginning after surgery was significantly more effective than enoxaparin 40 mg subcutaneously once daily beginning the evening before surgery in THR with similar safety (absolute risk reduction (ARR) for the primary end point of any DVT, non-fatal PE or death within 36 days 2.6%, 95% CI 1.3 to 3.7).[159] In RECORD 3, rivaroxaban 10 mg once daily was more effective than enoxaparin 40 mg subcutaneously once daily in TKR, with similar rates of bleeding (ARR for the primary end point of any DVT, non-fatal PE or death from any cause within 13 to 17 days after surgery 9.2%, 95% CI 5.9 to 12.4).[160] 1+

5.5.6 DABIGATRAN

Dabigatran is a direct oral thrombin inhibitor. A non-inferiority RCT, the RE-NOVATE study, found that dabigatran etexilate in a dose of either 220 mg or 150 mg once daily (starting with a half dose 1-4 hours after surgery) had a similar safety profile to enoxaparin 40 mg subcutaneously once daily (started on the evening before surgery) in THR and was as effective in relation to the primary end point of any VTE or death.[162] Using the same daily doses, similar results in TKR were reported in the RE-MODEL study.[163] A meta-analysis which included these two studies and a third study comparing dabigatran etexilate with enoxaparin 30 mg twice daily confirmed that there were no significant differences in any of the outcomes analysed.[164] 1+

Rivaroxaban and dabigatran are attractive agents because they are given orally, extended prophylaxis can be administered conveniently and they have predictable pharmacokinetics and dynamics and do not require monitoring. However, the lack of easy reversibility should be taken into consideration.

5.5.7 MECHANICAL PROPHYLAXIS

A recent Cochrane review found that AES are effective alone or in combination with another method of prophylaxis in diminishing the risk of DVT in hospitalised patients.[88] The main practical difficulty with IPC is patient compliance. The devices have to be used continuously while on bed rest in the postoperative period to be effective. 1++

A multicentre observational study of elective hip replacement patients found that the combination of AES and pharmacological prophylaxis appeared to be more effective in reducing asymptomatic DVT than pharmacological prophylaxis alone.[34] 2+

The arteriovenous 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.[165-174] 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.[165] 1+

5.5.8 DURATION OF PROPHYLAXIS

The majority of episodes of post operative VTE occur after discharge from hospital, even when prophylaxis has been employed during the admission.[18]

The evidence supporting more prolonged (post hospital discharge) thromboprophylaxis is strong. A systematic review found an RR of 0.36 and NNT of 36 for symptomatic VTE with LMWH.[175] The benefit of post discharge extended prophylaxis with LMWH is greater in THR than TKR patients.[176] 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.[177] 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 1,093).[177] The optimal duration of extended prophylaxis is unclear. 1++

Prolonged prophylaxis with fondaparinux is effective after hip fracture surgery.[107,178] SIGN 111 recommends that when fondaparinux is used in hip fracture it should be continued for 28 days in patients with no contraindication.[179] 1+ 4

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 severity exists.[180] A meta-analysis including 21 studies and 20,523 patients found that compared with LMWH the combined relative risk of 'major bleeding' was 0.59 for warfarin (95% CI 0.44 to 0.80), 1.52 for UFH (95% CI 1.04 to 2.23) and 1.52 for pentasaccharide (95% CI 1.11 to 2.09).[181] An RCT found that the overall risk of 'major' or 'clinically significant' bleeding was 5% with LMWH.[182] Another study showed that the risk of 'major bleeding' (stroke or life threatening GI haemorrhage) was lowest for aspirin.[183] The introduction of pharmacological thromboprophylaxis postoperatively reduces concerns about vertebral canal haematoma associated with central neuraxial regional anaesthesia techniques which are widely practised in lower limb orthopaedic surgery.[184] 1+ 1- 4

5.5.10 OTHER ORTHOPAEDIC SURGERY

The evidence for, and efficacy of, pharmacological thromboprophylaxis for more minor orthopaedic procedures is weak. A small, placebo-controlled, randomised trial revealed a high incidence of, mainly distal, DVT detected by screening after surgery and immobilisation for Achilles tendon rupture, with no reduction in DVT events with prophylactic LMWH for six weeks.[185] A similar result was found in a study of surgery for ankle fracture.[186] In relation to lower limb immobilisation after fracture, a Cochrane review concluded that LMWH significantly reduces the incidence of DVT but the study data were heterogeneous.[187] 2-

5.5.11 RECOMMENDATIONS

A **Patients undergoing THR or TKR surgery should receive pharmacological prophylaxis** *(with LMWH, fondaparinux, rivaroxaban or dabigatran)* **combined with mechanical prophylaxis unless contraindicated**.*

A **Extended prophylaxis should be given.**

C **As other agents are more effective for prevention of DVT, aspirin is not recommended as the sole pharmacological agent for VTE prophylaxis in orthopaedic patients.**

C
- **Patients with increased risk of bleeding should be given mechanical prophylaxis alone.**
- **If the bleeding risk has become acceptable then pharmacological prophylaxis should be added.**

A **Pneumatic foot pumps can be considered for prophylaxis as an alternative to IPC in orthopaedic surgery patients.**

☑ Patients undergoing less invasive orthopaedic procedures and plaster of Paris immobilisation should be assessed for their thrombosis and bleeding risks and pharmacological thromboprophylaxis with heparin or fondaparinux considered, particularly in those patients who will be subject to prolonged immobility.

☑ Patients with additional risk factors for VTE, such as previous VTE, should be considered for additional extended prophylaxis.

**See section 19.3*

5.6 UROLOGICAL SURGERY

There have been very few RCTs of thromboprophylaxis in urological surgery. 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 *(see section 5.1)*.[107]

The risk of VTE in transurethral surgery is low and use of anticoagulant prophylaxis may increase the risk of bleeding.[188] Unless the patient has other risk factors for VTE, mechanical prophylaxis and early mobilisation is adequate.[107,189-191] 1+

The risk of VTE in laparoscopic urological procedures is also low and pharmacological prophylaxis may increase the risk of bleeding. Mechanical prophylaxis (AES and/or IPC) and early mobilisation will be adequate unless the patient has additional risk factors for VTE.[107] 1-

In major open urological procedures, such as radical prostatectomy or cystectomy, mechanical prophylaxis with or without pharmacological prophylaxis is recommended.[9, 192] However, data on these patients are sparse.[107] 2+ 3 4

D **Patients having urological surgery should be offered mechanical prophylaxis with IPC or AES.**

D **Patients having urological surgery who have any additional risk factors for VTE should be offered mechanical prophylaxis and LMWH.**

5.7 NEUROSURGERY AND TRAUMATIC BRAIN INJURY

Patients undergoing major neurosurgery are at high risk of VTE. The risk of DVT is approximately 20% and the risk of proximal DVT approximately 5%.[3] The risk is similar in patients with traumatic brain injury.[193] Mechanical thromboprophylaxis is usually recommended because of concern about the risk of potentially devastating intracranial bleeding events that may be associated with pharmacological prophylaxis.

In a small RCT, AES, both alone and in combination with IPC, were more effective than no intervention.[194] 1+

A meta-analysis of thromboprophylaxis in neurosurgical patients concluded that both mechanical and pharmacological methods were safe and effective. There was no statistically significant difference in the rates of intracranial bleeding events in head-to-head trials with patients treated with LMWH compared with those receiving mechanical prophylaxis.[195] 1+

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

B **Combining LMWH with mechanical prophylaxis may be considered in patients with additional risk factors for VTE, such as patients with intracranial neoplasm.**

5.7.1 SPINAL CORD INJURY

Spinal cord injury is associated with a high risk of VTE.[196] Small randomised trials and non-randomised studies suggest that heparin thromboprophylaxis may be of benefit and LMWH may be preferable to UFH due to the lower risk of bleeding. Limited data support the use of physical methods combined with heparin. The appropriate duration of thromboprophylaxis is uncertain.[196] 2-

5.8 CARDIOTHORACIC SURGERY

There is little evidence specifically related to cardiac or thoracic surgery. Two guidelines and one review were identified.[107,129,197]

In a systematic review of the effectiveness of combined modalities in the prevention of VTE, two of the 17 studies included in the review related specifically to cardiothoracic surgery, and these showed that combined modalities are more effective than single modalities for VTE prophylaxis in cardiothoracic surgery.[197]

5.8.1 THORACIC SURGERY

Many patients undergoing thoracic surgery have cancer and mobilisation may be slow postoperatively. The evidence on prevention of VTE is extremely limited. The American College of Chest Physicians' guideline on prevention of venous thromboembolism recommends routine thromboprophylaxis with LMWH, UFH or fondaparinux for major thoracic surgery. Optimal use of mechanical thromboprophylaxis with properly fitted AES and/or IPC is recommended for patients with a high risk of bleeding.[107] The NICE guideline on reducing the risk of venous thromboembolism in patients admitted to hospital recommends that patients having thoracic surgery should be offered mechanical prophylaxis, with pharmacological thromboprophylaxis with LMWH added for those patients without increased risk of bleeding.[110] 4

D **Patients undergoing thoracic surgery should be offered mechanical prophylaxis with IPC or AES.**

D **Patients undergoing thoracic surgery who are not at high risk of bleeding should be offered pharmacological thromboprophylaxis with UFH or LMWH in addition to mechanical thromboprophylaxis.**

5.8.2 CARDIAC SURGERY

The incidence of VTE in patients undergoing cardiac surgery with modern techniques is uncertain and the need for thromboprophylaxis is disputed. With the exception of coronary artery bypass graft (CABG) surgery, most procedures generally require postoperative therapeutic anticoagulation.[107] It is unclear whether postoperative thromboprophylaxis should be offered to patients undergoing CABG surgery, especially as most will receive heparin during the procedure and antiplatelet drugs are usually administered postoperatively, possibly providing some protection against VTE. Also, bilateral lower limb mechanical prophylaxis may not be practicable in patients who have undergone vein harvesting.[107] For patients at increased risk and not receiving parenteral anticoagulants, NICE recommends mechanical methods and consideration of UFH or LMWH depending upon individual patient features in terms of bleeding and thrombosis risk.[110] 4

Pharmacological agents used during cardiac procedures may alter choice of prophylaxis.[110]

D **Patients undergoing CABG surgery should be offered mechanical thromboprophylaxis where feasible.**

D **Patients undergoing CABG surgery who are not at high risk of bleeding can be offered pharmacological thromboprophylaxis with UFH or LMWH in addition to mechanical thromboprophylaxis.**

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.

5.9.1 MAJOR VASCULAR SURGERY

The incidence of VTE in patients undergoing abdominal vascular surgery is reported to be similar to the incidence in patients undergoing general abdominal surgery.[26,198] Most of these patients have systemic anticoagulation during the procedure.[199] A meta-analysis of thromboprophylaxis in aortic surgery concluded that there was no evidence to support its routine use.[199] Prophylaxis should be considered on a case-by-case basis for those at high risk. 1++ 3 4

Patients with critical limb ischaemia or patients who have had an amputation are at high risk of VTE.[198,200] Mechanical methods of thromboprophylaxis may be contraindicated in vascular patients but UFH or LMWH can usually be given. Most of these patients are on aspirin and a statin and these should be continued.[201]

D **Patients with critical limb ischaemia or who are undergoing major abdominal or peripheral vascular surgery** *(including amputation),* **should be considered for thromboprophylaxis.**

5.9.2 VARICOSE VEIN SURGERY

While the presence of varicose veins increases the risk of DVT after major abdominal, pelvic or orthopaedic surgery (*see Table 1*), 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).[43] AES are commonly prescribed for such patients; the addition of LMWH or UFH is recommended in those with additional risk factors. 3

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.

D **In patients undergoing varicose vein surgery who have no additional risk factors for VTE postoperative AES are recommended.**

D **In the presence of additional risk factors the addition of UFH or LMWH is recommended.**

5.10 PLASTIC AND RECONSTRUCTIVE SURGERY

Observational studies indicate that VTE is a frequent complication of plastic and reconstructive procedures, including abdominoplasty and breast reconstructive surgery.[202] Being overweight and using hormone therapies are contributory factors.[203] Thermally injured patients appear to be at particularly high risk of VTE.[202]

There is a lack of evidence of thromboprophylaxis in this area.

☑ Patients scheduled for plastic and reconstructive surgery should be considered for mechanical prophylaxis and pharmacological thromboprophylaxis with LMWH.

5.11 ENT SURGERY

Many patients undergoing ENT surgery are at relatively low risk of VTE due to young age, brevity of procedure and no requirement for immobility after procedure. More invasive procedures, eg laryngectomy, may confer a higher risk. There is a lack of evidence of thromboprophylaxis in this area.[204]

☑ Mechanical methods and pharmacological prophylaxis with LMWH may be considered for patients undergoing high-risk ENT surgery.

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%.[205]

Aspirin is commonly used to prevent MI in the older population. Aspirin reduces the incidence of VTE in high-risk medical patients by around 25%, but with increased bleeding.[155] 1+

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.[6,8,111] 1++

Most studies of pharmacological thromboprophylaxis to prevent asymptomatic and symptomatic VTE in medical patients have used UFH, LMWH or fondaparinux and have included heterogeneous cohorts including patients with congestive cardiac failure, respiratory disease, non-pulmonary sepsis, cancer and stroke. There is strong evidence for efficacy from five meta-analyses,[206-210] with one reporting a risk ratio of 0.52 (95% CI 0.29 to 0.91, NNT 241) in symptomatic PE, a risk ratio of 0.53 (95% CI 0.25 to 1.08, NNT 271, non-significant) in symptomatic DVT, and a risk ratio of 0.49 (95% CI 0.38 to 0.64, NNT 33) in asymptomatic DVT.[209] A reduction in all-cause mortality was not found, although one systematic review reported a significant reduction in fatal pulmonary embolism (NNT 400).[206] There was overall benefit due to prevention of VTE, despite a significant increased risk of bleeding. A recent Cochrane review gave comparable results.[211] One meta-analysis reported that LMWH is more effective than UFH,[210] but others did not find a significant difference in efficacy.[211,212] LMWH is, however, less likely to cause injection site haematoma,[210] and possibly major bleeding.[211] LMWH is associated with a lower incidence of HIT than UFH *(see section 15.2)*. In a randomised controlled trial in older acute medical patients fondaparinux was effective in the prevention of asymptomatic and symptomatic DVT.[213] 1+

Prolonged prophylaxis (after discharge) can be considered when there is ongoing risk from immobility and disease, but the optimal duration is unknown.

A **When the assessment of risk favours use of thromboprophylaxis, UFH, LMWH or fondaparinux should be administered.**

C **Aspirin is not recommended as the sole pharmacological agent for VTE prophylaxis in medical patients.**

6.2 MECHANICAL PROPHYLAXIS TO PREVENT ASYMPTOMATIC AND SYMPTOMATIC VTE

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, eg those with critical limb ischaemia or severe peripheral neuropathy.[88,214]

The data relating to the efficacy of mechanical methods of thromboprophylaxis in medical patients are inadequate. The majority of studies of anti-embolism stockings (AES) were in surgical patients, where benefit has been confirmed (*see section 5.1.6)*.

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.[140] 1++

6.3 ACUTE STROKE

Management of acute stroke is described in SIGN 108.[215] Patients with ischaemic stroke will generally be taking aspirin.

Pharmacological thromboprophylaxis for VTE with UFH/LMWH/fondaparinux is not recommended routinely in acute stroke patients as the reduction in VTE is offset by increased bleeding.[216] Where the risk of VTE is deemed to be especially high, LMWH is recommended in preference to UFH.[217] 1+

In a large multicentre randomised trial of full length AES in stroke patients no reduction in VTE rates was demonstrated and adverse events (principally skin lesions) were increased.[218] The results were not explained by severity of paralysis.

A large study (n = 3,114) of above-knee versus below-knee stockings in stroke patients (CLOTS 2) concluded that although above-knee stockings are more effective than below-knee stockings in preventing DVT (6.3% versus 8.8% for above-knee versus below-knee, respectively) they are unlikely to have clinically important benefits for patients with stroke.[219] 1++

A **AES should not be used routinely in stroke patients.**

A **In patients with non-haemorrhagic stroke at high risk of VTE, LMWH can be considered.**

6.4 ACUTE CORONARY SYNDROMES

Management of actue coronary syndromes (ACS) is covered in SIGN 93.[220]

In acute coronary syndromes, patients in whom there is electrocardiogram (ECG) indication of ischaemia and/or elevation of cardiac markers should receive therapeutic doses of LMWH or fondaparinux as part of the management of cardiac ischaemia.[220]

6.5 OTHER MEDICAL PATIENTS

6.5.1 PATIENTS WITH CANCER

Cancer patients are at particularly high risk of VTE *(see Table 1)*. Risk relates to malignancy, cancer therapy, immobility, hospitalisation and indwelling lines.

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.[221] A recent large randomised trial with fixed dose warfarin 1 mg/day or adjusted dose warfarin (INR 1.5-2.0) demonstrated no reduction in catheter thrombosis.[222] 1+

The effect of anticoagulants on survival in patients with cancer was studied in a Cochrane review of five RCTs of warfarin versus placebo.[223] 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.[223] In a systematic review including eight RCTs of LMWH versus vitamin K antagonists (VKA),[224] all individual studies were negative and no difference was detected when the data were combined.

A **Patients with cancer are generally at high risk of VTE and should be considered for prophylaxis with LMWH, UFH or fondaparinux whilst hospitalised.**

A **Neither heparin nor vitamin K antagonists are 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.**

6.6 PATIENTS IN THE INTENSIVE CARE UNIT SETTING

Medical and surgical patients in intensive care units frequently have multiple risk factors for both thrombosis and bleeding. A systematic review concluded that there are insufficient data to support the recommendation of routine use of heparin thromboprophylaxis in such patients.[225] 1-

Other forms of thromboprophylaxis, including mechanical measures, have not been adequately studied in the ICU setting,[226] although a small randomised study of 120 ICU patients with head/spinal trauma [227] and an RCT of patients admitted to a trauma unit[228] found no significant difference between LMWH and IPC in incidence of DVT detected by screening ultrasound after prophylaxis with either LMWH or IPC. 1++

7 Pregnancy and the puerperium

VTE is a major cause of maternal death in the United Kingdom (1.56 per 100,000 maternities).[19] VTE is at least ten times more common in women during pregnancy and the puerperium, compared to women who are not pregnant *(see Table 1)*.[229] VTE may complicate all stages of pregnancy, including the first trimester.

☑ A multidisciplinary team approach should be encouraged for prevention and management of VTE during pregnancy.

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 4)*. These have been reviewed in recently updated guidelines in the United Kingdom and North America.[229,230] Cohort studies have shown that the presence of multiple risk factors increases the risk of VTE.[229,231, 232] Over 70% of women who suffer a fatal or non-fatal antenatal PE in the United Kingdom have identifiable risk factors,[233] hence many PEs are potentially preventable with the appropriate use of thromboprophylaxis. 2+ 4

Table 4: Risk factors for VTE in pregnancy (adapted from RCOG 2009).[230]

Pre-existing risk factors
Previous VTE (DVT or PE)
Thrombophilia (heritable and acquired, including antiphospholipid syndrome) (*see Table 1*)
Family history of VTE in a first degree relative
Age over 35 years
Obesity (body mass index (BMI) > 30 kg/m^2) either pre-pregnancy or in early pregnancy
Parity >3
Gross varicose veins
Paraplegia
Sickle cell disease
Inflammatory disorders, eg inflammatory bowel disease
Some medical disorders, eg nephrotic syndrome, certain cardiac diseases, active cancer, stroke
Myeloproliferative disorders, eg essential thrombocythaemia, polycythaemia vera
Smoking
Anaemia
Intravenous drug misuse, including femoral vein stenosis
Obstetric risk factors
Multiple pregnancy
Pre-eclampsia
Excessive blood loss (>1 litre) or blood transfusion
Prolonged labour
Mid-cavity instrumental delivery
Caesarean section
New onset or transient risk factors
Surgical procedure in pregnancy or puerperium, eg evacuation of retained products of conception, postpartum sterilisation
Hyperemesis
Dehydration
Ovarian hyperstimulation syndrome
Systemic infection, eg pyelonephritis
Immobility (>3 days bed rest), including hospital admission
Long-distance travel (>4 hours)

7.2 ANTENATAL THROMBOSIS RISK ASSESSMENT

During pregnancy and the puerperium, the presence of multiple risk factors increases the risk of VTE.[231] Women with a personal history of VTE are at increased risk of recurrence during pregnancy and the puerperium.[234] Recurrence rates of 1.4% to 11.1% have been reported.[235]

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.[235] 2 3

The reported risks of VTE in pregnancy associated with thrombophilic defects vary considerably, both between defects and between studies.[69,236] Women who are heterozygotes for the most common heritable thrombophilias in the United Kingdom (factor V Leiden and prothrombin G20210A) and who have no prior history of VTE, are at low absolute risk of VTE in pregnancy (<1%).[237,238] Pregnant women with a family history of unprovoked VTE in a first degree relative or VTE in a first degree relative which was pregnancy- or combined oral contraceptive- or HRT-related, may be at increased risk. Testing for heritable thrombophilia may be helpful in quantifying the risk but mainly when the affected relative has a known thrombophilia.

There is a lack of evidence of antithrombotic intervention to prevent antenatal VTE in women with asymptomatic thrombophilia.[69]

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

☑ Women should be asked about a personal and family history of VTE and whether an objective diagnosis was made.

D **Routine testing for thrombophilia in pregnancy is not indicated.**

7.3 METHODS OF THROMBOPROPHYLAXIS

7.3.1 ANTICOAGULANTS

Systematic reviews have concluded that LMWH is a safe alternative to UFH as an anticoagulant during pregnancy and LMWH has a preferable safety profile.[239-241] 1^{++} 2^{++}

The largest of these systematic reviews included 64 studies reporting 2,777 pregnancies in which LMWH was used for thromboprophylaxis or treatment of VTE.[239] No studies were found comparing the safety or efficacy of LMWH with either no anticoagulation or with VKA anticoagulation. Although no RCTs comparing LMWH with UFH were available for inclusion in this systematic review, the authors compared studies describing the use of LMWH in pregnancy with historical data where UFH was employed. The risk of heparin induced thrombocytopenia (HIT) was substantially lower with LMWH (there were no cases of HIT in the 2,777 pregnancies reported) compared with UFH. The incidence of allergic skin reactions with LMWH was 1.8% (95% CI, 1.34 to 2.37), and of osteoporotic fractures was 0.04% (95% CI, 0.01 to 0.2). Clinically significant haemorrhage occurred in 1.98% of patients (95% CI, 1.5 to 2.57) and was usually attributable to an obstetric cause.[239] 2^{++}

In patients who are unable to tolerate heparin, usually because of skin allergy, and where there is no evidence of HIT, an alternative to LMWH can be considered. Where the problem persists or in women with HIT the use of danaparoid may be considered. A review of 91 pregnancies in 83 women concluded that danaparoid is an effective and safe antithrombotic in pregnancy for women who are intolerant of heparin.[242]

Vitamin K antagonists, such as warfarin, are known to be teratogenic during pregnancy and may also cause fetal haemorrhage.[243-246] 2^{+} 2^{-} 3

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%).[247] However, in a multicentre prospective cohort study of vitamin K antagonists and pregnancy outcome, there were only two cases of coumarin embryopathy in 356 live births (0.6%) suggesting that the teratogenic effect of warfarin may be less than previously thought.[245] The substitution of heparin prior to six weeks gestation appears to eliminate the risk of embryopathy, although this may increase the risk of valve thrombosis in women with mechanical heart valves.[248] 2++ 2+

Breast feeding is not contraindicated with either heparin or vitamin K antagonist therapy.[230,249,250]

Cohort studies have shown that over 40% of antenatal VTE occurred in the first trimester of pregnancy.[251-253] The Confidential Enquiries into Maternal Deaths in the United Kingdom (2003-5) found that two thirds of antenatal fatal PE occurred in the first trimester,[19] resulting in the recommendation that, where possible, antenatal thromboprophylaxis should be commenced in the first trimester of pregnancy.[230] 3 4

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

D **Antenatal thromboprophylaxis should generally be commenced in the first trimester of pregnancy.**

C **Vitamin K antagonists have adverse fetal effects and should generally be avoided in pregnancy. In women with mechanical heart valves, however, the risks and benefits of VKA and heparin should be assessed on an individual basis.**

C **Women of childbearing age using VKA should be clearly informed of the risk of teratogenesis associated with these agents and should be advised to 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.**

7.3.2 MECHANICAL PROPHYLAXIS

Expert opinion recommends that all women with previous VTE or a previously identified thrombophilia should wear AES throughout pregnancy and for at least six weeks postnatally.[48] 4

D **Pregnant women considered to be at increased risk of VTE should be advised to wear AES when immobilsed/hospitalised.**

7.4 SELECTION FOR 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 trials comparing one method of thromboprophylaxis with placebo or no treatment, and trials comparing combined methods of thromboprophylaxis, concluded that there was insufficient evidence on which to base recommendations for thromboprophylaxis during pregnancy and the puerperium.[254] 1-

Recommendations in UK and US guidelines for selection of patients 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.[107,229,230] There is a risk of overuse of pharmacological thromboprophylaxis in pregnancy and this should be borne in mind when assessing risk. 4

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

D **Women with a previous unprovoked VTE; or VTE linked to oestrogen** *(including pregnancy)* **; or minimally provoked VTE** *(related to travel)***; or previous recurrent VTE; or other additional risk factors for VTE; should be offered antenatal thromboprophylaxis with LMWH.**

D **Women considered to be at high risk of VTE because of multiple risk factors** *(three or more)* **should be offered thromboprophylaxis with LMWH antenatally.**

D **Women with inherited or acquired thrombophilia and no previous history of VTE do not routinely require pharmacological thromboprophylaxis antenatally. Exceptions include women with:**

- **multiple thrombophilic defects** *(including homozygosity for factor V Leiden)*
- **antithrombin deficiency**
- **heritable thrombophilia and a strong family history of VTE, especially if pregnancy-related.**

7.4.1 RECURRENT VTE

Non-pregnant patients with recurrent VTE are at increased risk of further episodes.[107,255] It is expected that these individuals would have a high risk of VTE during pregnancy, though data to support this are lacking.[230] 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.[229] In this situation, higher prophylactic doses of LMWH ('intermediate dose') or therapeutic doses of LMWH may be appropriate. Some suggested dosing schedules are included in the RCOG Green-top guideline number 37.[230] Women with a history of recurrent VTE and not normally anticoagulated, should commence LMWH once the pregnancy is confirmed.[230] 4

D **Women with a history of recurrent VTE, who are normally anticoagulated with a VKA, should switch to intermediate or therapeutic dose LMWH as soon as pregnancy is confirmed.**

☑ Women with a history of prior VTE, who are normally anticoagulated with a VKA, should be referred to a consultant obstetrician or haematologist with expertise in pregnancy-related thrombosis.

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.[230,256] 4

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 *(See Table 6, section 15.1.4)*.[184]
- When a woman presents while on an intermediate or therapeutic regimen of LMWH, regional techniques should not be employed for at least 24 hours after the last dose of LMWH.[184]
- 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.[184]
- 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.[230]

4

There is an increased risk of wound haematoma following Caesarean section of around 2% with both UFH and LMWH.[239]

Women at high risk of haemorrhage, including those with major antepartum haemorrhage, may be managed better with UFH or AES. 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 SELECTION FOR POSTNATAL THROMBOPROPHYLAXIS

The highest risk period for VTE, and PE in particular, is during the puerperium *(see Table 1, section 3.2)*.[238, 257] It has been recommended that the threshold for prescribing thromboprophylaxis should be lower in the postnatal period than in the antenatal period since the risk of developing VTE per day is higher and the duration of exposure shorter.[229,230]

4

In women who are normally anticoagulated with warfarin outwith pregnancy, recommencement of warfarin should be avoided until at least the third postnatal day.[256]

The following recommendations for selection for postnatal thromboprophylaxis are based on guidelines from the Royal College of Obstetricians and Gynaecologists[230] and the American College of Chest Physicians.[229]

D **All women should be assessed after delivery for risk factors for VTE.**

D **Women with multiple risk factors for VTE should be considered for postnatal thromboprophylaxis.**

☑ Women with two or more risk factors should receive LMWH for seven days after delivery; women with three or more risk factors should be offered AES in addition to LMWH.

D **All women who have had an emergency Caesarean section and those who have an elective Caesarean section who have one or more additional risk factors for VTE, should receive thromboprophylaxis with LMWH for seven days.**

D
- **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.**

D
- **Women receiving prophylaxis antenatally should continue thromboprophylactic doses for six weeks following delivery.**
- **Warfarin is an alternative to LMWH in this situation.**
- **Women who are normally anticoagulated with warfarin outwith pregnancy can recommence warfarin three days after delivery.**

8 Travel-related thrombosis

8.1 RISK OF VTE

Epidemiological data indicate that the absolute risk of VTE associated with long-haul air travel (>4 hours) applies equally to other modes of passive transport, including by car and rail.[258]

A reliable estimate of relative risk from epidemiological data is 2 to 3-fold.[258] 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.[259] The increased risk persists for up to eight weeks after travel.[260,261]

The risk of flight-related VTE is increased in both shorter and taller individuals and in the overweight and is associated with location in a window seat.[258,262] Use of the combined oral contraceptive pill and carriage of factor V Leiden also increase risk.[258] No evidence was identified to suggest that dehydration plays a role in increasing risk.[263]

2^+
3

Although hypobaric hypoxia simulating airliner cabin conditions does not cause coagulation activation,[264] there is evidence from a study of pathogenesis of air travel-related VTE that blood coagulation is activated during long-haul flight in women with factor V Leiden who use the combined oral contraceptive pill.[265]

8.2 METHODS OF THROMBOPROPHYLAXIS

8.2.1 EXERCISE

Popliteal venous blood flow appears to be enhanced by seated exercises,[266,267] although their efficacy in the prevention of travel-related VTE has been questioned in an epidemiological study.[262]

2^+

8.2.2 MECHANICAL PROPHYLAXIS

There is no direct, high quality, admissable evidence that AES prevent clinical VTE during long-haul travel, although there are limited data suggesting a reduction in subclinical events using Class 1 stockings.[268] The use of AES 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 also differ. Full length AES are ineffective in VTE prevention after stroke *(see section 6.3)* and their apparent efficacy in other hospitalised medical patients is limited *(see section 6.2)*. Inappropriately fitted AES may cause adverse effects.[218,268]

1^{++}
1^-

8.2.3 PHARMACOLOGICAL PROPHYLAXIS

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

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.

☑ The risks and possible benefits of any intervention should always be discussed with the patient before travelling.

D
- **Travellers should be advised to remain as ambulant as safely possible before, during and after journeys.**
- **Leg exercise whilst seated may be recommended.**

D
- **The use of AES 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.

☑ In people deemed to be at especially high risk of travel-related VTE, pharmacological prophylaxis can be considered. LMWH has been used for this purpose.

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 and/or signs. Most patients with confirmed PE do not have clinically evident DVT and around 30% of patients with symptomatic DVT have asymptomatic PE.

- Suggestive symptoms and signs:

  DVT: unilateral leg pain, swelling, tenderness, increased temperature, pitting oedema, prominent superficial veins

  PE: breathlessness, chest pain, haemoptysis, collapse, tachycardia, hypotension, tachypnoea, raised jugular venous pressure, focal signs in chest, hypoxia/cyanosis.

- Predisposing factors *(see Table 1)*

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9.2 DIAGNOSTIC ALGORITHMS

A variety of clinical decision rules (CDRs) can be used to assess the clinical probability of having DVT and PE (*see Annexes 3-5 for examples*). Most commonly used are the Wells score for DVT and PE, and the Geneva score and the revised Geneva score for PE. In assessment of suspected PE the Wells score and the revised Geneva score can be simplified and dichotomised. These changes may facilitate clinical use.

☑ 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 the CDR for assessment of PE.

The use of combinations of CDRs and testing for D-dimer has been evaluated extensively, particularly to determine their clinical utility in excluding a diagnosis of DVT or PE. It is important that CDRs are only used in the assessment of appropriate pre-defined groups of patients. For example, the original Wells score (Annex 5a) for DVT is not validated for use in patients with previous DVT, and neither the original (Annex 5a) or the revised Wells score for DVT (Annex 5b) are validated for use in patients with suspected DVT at sites other than the lower limb, hospitalised patients or pregnant women. The Geneva score and the revised Geneva score for PE and the Wells rule for PE include patients with previous VTE but are also less well validated for use in patients who are already hospitalized at the time of presentation with suspected PE. The use of combinations of CDRs and D-dimer is therefore generally applicable to ambulatory, non-hospitalised patients presenting with suggestive symptoms or signs of VTE; it should not be applied to the investigation of hospitalised patients and pregnant women in whom initial investigation should be by appropriate imaging.

A systematic review of cohorts of patients presenting with suspected VTE who were prospectively assessed using a CDR and D-dimer testing, and where a defined end point was the occurrence of objectively proven VTE at three months of follow up, showed 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.[269] 2++

These results compare favourably with conventional imaging methods used to diagnose suspected VTE.[270-276]

In individuals in whom DVT was excluded by a combination of a low Wells score and a negative D-dimer the rate of symptomatic and fatal PE was found to be 1 in 2,222 and 1 in 10,000 respectively.[277] 2++

The three month incidence of DVT in suspected cases where the diagnosis was initially excluded using standard imaging techniques was 1.9% with venography[270] and 0.9% with repeat compression ultrasonography (CUS).[271-273] Similarly, where PE was initially excluded the three month incidence after pulmonary angiography was 0.8%[274] and after perfusion scanning 1.2%.[275, 276] Patients not excluded by the combination of CDR and D-dimer testing should proceed to appropriate imaging.[269,277] 3 4

A systematic review of the accuracy of point of care D-dimer tests concluded that these assays can be used to safely exclude a diagnosis of VTE in patients with a low risk score on CDR.[278] A variety of D-dimer tests can be used in the exclusion of suspected VTE in low probability patients. Sensitivities and specificities of different tests vary. Quantitative enzyme linked immunosorbent assays (ELISAs) have the highest sensitivities and lowest specificities compared to 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.[269] 1-2++

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 to 6.9%), while for patients with a normal computed tomography pulmonary angiogram (CTPA) it was 0.8% (95 CI 0.02% to 4.3%).[279] 3

D-dimer use is limited by the lack of specificity for VTE. False positive tests are common in hospitalised patients, cancer patients, post-surgical patients and pregnant women. The duration of symptoms of VTE also affects the sensitivity of the assay. These considerations should be borne in mind when diagnostic algorithms are being designed.

☑ The diagnosis of suspected DVT or PE in hospitalised patients and pregnant women should be by the appropriate imaging.

B **A validated CDR should be used in the initial assessment of outpatients presenting with suspected deep vein thrombosis or pulmonary embolism.**

☑ The results of the initial assessment should be used to determine the diagnostic strategy.

B **The Wells score, in either its 3 level** *(low, moderate or high)* **or 2 level** *(likely or unlikely)* **format, the Geneva or revised Geneva score in its 3 level format, or the Wells rule for PE in its 2 or 3 level format can be used to assess the clinical probability of a diagnosis of venous thromboembolism. In all cases it is important to follow the chosen protocol precisely and to apply it only to those patients and situations for which it has been validated.**

B **In patients with a first episode of VTE, the combination of a low probability CDR or 'DVT or PE unlikely' and a negative D-dimer test can be used to exclude a diagnosis of VTE.**

B **Patients with high clinical probability or 'DVT or PE likely' should not have D-dimer performed prior to imaging as it is of no value in the diagnostic process for this group.**

☑ Patients with high clinical probability or 'DVT or PE likely' should proceed to imaging to confirm or exclude VTE.

B **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.**

D **Patients assessed as low or 'unlikely' clinical probability and with a negative D-dimer should be informed that a diagnosis of VTE may become apparent during three months of follow up.**

☑ 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.

9.3 CONFIRMATION OF CLINICALLY SUSPECTED DEEP VEIN 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.[280,281] Sensitivity and specificity are considerably lower for asymptomatic above-knee DVT[282] and for below-knee (calf) DVT.[281,283] 1+ 3 4

The negative predictive value of a single normal ultrasound for exclusion of a proximal DVT in a symptomatic patient is high.[280] In moderately large population studies the outcome of patients with a negative initial scan appears to be similar to control populations[284] and the evidence for a general policy of repeat US at one week is not strong. There is evidence, however, to support the contention that distal DVT may propagate and subsequently become clinically relevant.[285] 2- 3 4

In a systematic review, five studies were evaluated to determine whether, following a normal ultrasound, a negative D-dimer could be used to exclude DVT in moderate or high probability groups. A negative test using a high sensitivity D-dimer assay combined with an initial negative US is associated with a less than 1% risk of missed DVT obviating the need for repeat scanning. The value of the test falls off, however, in patients with prolonged symptoms or who have had heparin for more than 24 hours.[277] 2++

The preferred initial imaging test for patients with suspected upper extremity DVT is duplex ultrasound because of its non-invasive nature and high sensitivity and specificity for upper extremity DVT.[286] However false-negative studies do occur and if clinical suspicion remains high, contrast venography may be required to confirm a diagnosis of upper extremity DVT.[287] 2+ 3

US is the recommended imaging test for diagnosing DVT in pregnant patients due to the absence of radiation exposure.[288,289]

C **Venous ultrasound is the imaging investigation of choice for patients with suspected DVT.**

C **Patients who have a negative or inadequate initial scan but who have a persisting clinical suspicion of DVT or whose symptoms do not settle should have a repeat US scan.**

☑ Patients who have an initial negative ultrasound scan should be considered for repeat ultrasound scanning at 5-7 days if:

- they have a high probability clinical decision rule (CDR) *(see section 9.2)*
- they have moderate or 'likely' CDR with a positive D-dimer result
- on clinical review the suspicion of DVT remains high or increases.

9.4 CONFIRMATION OF CLINICALLY SUSPECTED PULMONARY EMBOLISM

CTPA is the gold standard for detecting acute pulmonary embolus with a high sensitivity (83-100%) and specificity (89-97%).[290-292] Assessment of right ventricular/left ventricular (RV/LV) ratio as seen during CTPA is a useful indicator of severity of PE in the acute situation. In suspected PE, a good quality negative CTPA on a multidetector CT scanner effectively excludes pulmonary embolus.[293,294] 1+

Isotope lung scintigraphy (ILS) scanning, once the principal imaging investigation for suspected acute pulmonary embolism, has been largely superseded by CTPA.[295] ILS still has a place in the investigation of suspected PE.[296,297] It can be used as an alternative in patients with contraindications to CTPA, and is particularly useful in patients with a normal chest X-ray without underlying lung disease.[298] In patients with an abnormal chest X-ray, ILS scanning gives a definitive diagnosis in only 52% of patients and is not recommended.[298] 1+ 3

In high-risk PE *(see section 11.1.1)*, abnormalities in right ventricular function give a strong clue to the diagnosis. In unusual situations where CTPA is not available but echocardiography is, this can be used as the initial diagnostic tool.

There are no good trials on the optimal imaging of suspected PE in pregnancy and management depends on a balance between limiting the radiation dose to mother and fetus and diagnostic accuracy.[299] The Royal College of Obstetricians and Gynaecologists (RCOG) recommends chest X-ray and bilateral lower limb Doppler ultrasound examination as initial investigations.[256] If both are negative ILS or CTPA should be performed. ILS results in a substantially lower radiation dose to the mother than CTPA and can be considered when a chest X-ray is normal; the ventilation component can be omitted to further reduce radiation exposure. 4

Most data suggest that the radiation dose to the fetus from CTPA is similar to or lower than that from ILS, however the maternal breast tissue receives a relatively high radiation burden during CTPA.[300] The safety of iodinated contrast media in pregnancy is unclear. Current guidance suggests that they can be used with CTPA but that the neonatal thyroid function should subsequently be assessed.[301]

A **Computed tomography pulmonary angiography using multidetector computed tomography should be the first line investigation of pulmonary embolism.**

B **When interpreting the computed tomography pulmonary angiography the right ventricular/left ventricular ratio should be assessed as an indicator of severity.**

C **Isotope lung scintigraphy may be considered if computed tomography pulmonary angiography is unavailable and the patient is clinically stable** (*ie, no right heart strain and no hypotension)***, and is of most use in:**

- **patients with a normal chest X-ray and no underlying chronic lung disease**
- **patients with a contraindication for computed tomography pulmonary angiography.**

D
- **pregnant women who have a normal chest X-ray.**

☑ In patients with suspected high-risk PE, echocardiography should be considered where immediate access to multislice computed tomography pulmonary angiography is not available

9.4.1 BIOCHEMICAL MARKERS

Non-high-risk patients with PE *(see section 11.1)* may benefit from escalation of therapy and should be assessed for markers of right ventricular dysfunction and/or myocardial injury (B-type natriuretic peptide (BNP) and troponin), and if present should continue to be monitored for evidence of deterioration.[302-304] 2+ 4

D **Non-high-risk pulmonary embolism patients** *(cardiovascularly stable)* **should be assessed for markers of myocardial injury, such as BNP and troponin, and right ventricular dysfunction.**

10 Preliminary assessment

10.1 CLINICAL AND LABORATORY INVESTIGATIONS

Before embarking upon anticoagulant therapy following a diagnosis of VTE consideration needs to be given to:

- investigating disorders underlying the development of DVT or PE
- ensuring it is safe to anticoagulate the patient
- ensuring that monitoring of anticoagulation can be carried out safely and accurately
- monitoring for side effects of anticoagulant drugs
- clinical assessment of the risks of anticoagulation.

Good clinical history taking and examination are 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.[305] 1++

Due to their pharmacology the anticoagulants which are most often used in the management of VTE require assessment of baseline coagulation and renal function prior to embarking on therapy.[306] LMWHs are principally metabolised by the kidney and manufacturers' advice is that dose reduction should be considered in patients with glomerular filtration rate (GFR) of <30 mls/min. 3

Fatal bleeding due to accumulation of LMWH has been described in patients with impaired renal function.[307,308]

Poor renal function is also a risk factor for bleeding in patients on warfarin.[309] 2+

The prothrombin time (PT) is used to monitor the anticoagulant effect of warfarin and the activated partial thromboplastin time (APTT) is used to monitor the anticoagulant effect of UFH. A baseline assessment of PT and APTT is required to identify prolongation of clotting times which might contraindicate anticoagulation or complicate monitoring.

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 a baseline platelet count performed before starting.

The outpatient bleeding risk index indicates the annual risk of major bleeding in patients being treated with warfarin. This involves a simple clinical assessment combined with a full blood count and assessment of serum creatinine. Patient age, a history of gastrointestinal (GI) bleeding, a history of stroke (haemorrhagic or ischaemic) and a history of concomitant medical illness (recent MI, renal impairment, anaemia or diabetes mellitus) are important in the assessment of bleeding risk.[309] 2+

A systematic review of clinical prediction rules (CDRs) to estimate the risk of bleeding on warfarin concluded that no available CDR, including the outpatient bleeding risk index, exhibited sufficient predictive accuracy to recommend widespread use in practice.[310] 2++

There is a well documented association between cancer and VTE. Many episodes of VTE occur in patients with cancer and in those undergoing treatment for cancer *(see Table 1, section 3.2)*. A full clinical history and physical examination for symptoms and signs of underlying malignancy should be performed in patients presenting with apparently unprovoked VTE.

A systematic review addressing whether or not patients presenting with apparently unprovoked VTE should be screened for clinically occult malignancy using a combination of laboratory based tests and imaging found that compared with history taking, physical examination, and performing routine tests, extensive cancer screening by tumour markers and imaging scans reveals more cancers.[311] The prevalence of cancer in patients presenting with unprovoked VTE was 6% at the time of diagnosis of VTE and 10% between diagnosis of VTE and one year. In patients with unprovoked VTE, extensive screening by abdominal and pelvic CT scanning increased the proportion of previously undiagnosed cancers detected from 49% to 70% compared with less intensive screening (standard blood tests and chest X-rays). The cost effectiveness and effect on mortality and morbidity of detecting malignancy is unknown.[311] 2^+

D **All patients presenting with VTE should have a full clinical history and examination undertaken with the aim of detecting underlying conditions contributing to the development of thrombosis and assessing suitability for antithrombotic therapy.**

A **Testing for inherited forms of thrombophilia** *(AT, PC, PS deficiency and factor V Leiden and prothrombin G20210A)* **does not influence initial management of VTE and should not be performed routinely.**

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

☑ Patients commencing treatment with UFH, 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
- assess bleeding risk.

☑ Patients for whom anticoagulation is planned should be assessed for their risk of anticoagulant induced bleeding.

C **Unselective screening for cancer in patients with DVT or PE is not recommended.**

11 Initial management of venous thromboembolism

11.1 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 < 90 mmHg for > 15 minutes) should be regarded as high risk PE with a 15% early (< 30 days) mortality rate. Non-high-risk patients who are initially cardiovascularly stable, can be subclassified into low risk (PE with 30 day mortality < 1%) or intermediate risk (PE with 30 day mortality 3-15%) based on evidence of myocardial injury and/or right ventricular dysfunction.[304]

Despite evidence from RCTs demonstrating the superiority of LMWH over UFH for treatment of DVT, this has not been shown for treatment of PE. A Cochrane review comparing fixed dose LMWH with adjusted dose UFH for acute PE found an OR of 0.88 (95% CI 0.48 to 1.63) for risk of recurrent VTE.[312] A systematic review of fondaparinux 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.[151] LMWH, UFH and fondaparinux can all be regarded as suitable agents for initial anticoagulation in patients presenting with PE. | 1+

For the majority of patients, heparin therapy can be discontinued once therapeutic anticoagulation with a vitamin K antagonist has been established (usually 6-10 days) and the INR is ≥ 2 *(see section 12.1)*.[255] | 4

In patients deemed to have intermediate-risk PE, thrombolysis carries a significant risk of major haemorrhage and there is no clear evidence of improved survival benefit or reduced PE recurrence.[255] | 4

Given the potential for early improvement in haemodynamic function, however, 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.

Patients deemed to have low-risk PE are suitable for outpatient management or early discharge *(see section 14.2)*.

A **Patients with suspected PE should be treated with therapeutic doses of heparin or fondaparinux until the diagnosis has been deemed very unlikely.**

D **Once confirmed the heparin or fondaparinux should be continued until the INR is at least 2.0 on a vitamin K antagonist, and for at least 5 days**

D **Patients with intermediate-risk PE should not routinely receive thrombolytic therapy.**

☑ Patients with intermediate-risk PE should be monitored in hospital and be considered for thrombolysis should they deteriorate.

☑ Patients with low-risk PE can be considered for outpatient management or early discharge.

11.1.1 HIGH-RISK PE

Initial management of the shocked patient with PE includes haemodynamic (dobutamine, epinephrine) and respiratory (oxygen) support.[304] 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. | 4

There are few RCTs addressing management of this high-risk group of PE patients and a Cochrane review identified only one small RCT (8 patients) in unstable PE.[313] 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%, OR1.61, 95% CI 0.91 to 2.86).[313] | 1++

Thrombolysis did, however, result in early improved haemodynamic outcomes (pulmonary artery pressures) and perfusion lung scanning, pulmonary angiography and echocardiographic assessments compared to heparin alone.[313] None of the studies reported on potential late benefits of thrombolytic therapy (eg reduced risk of developing chronic thromboembolic pulmonary hypertension). 1+

☑ Patients with high-risk PE should be managed in a coronary care unit or high dependency unit.

11.1.2 COINCIDENTAL FINDING OF PE OR VTE

With improvements in imaging techniques the incidental detection of thrombosis is relatively common *(see section 11.7)*. The appropriate management strategies for dealing with such findings are, however, unclear and research is needed to clarify what is the most appropriate approach.

11.1.3 VENA CAVA FILTERS

Use of inferior vena cava (IVC) filters is rarely appropriate. No evidence was identified to support the routine placement of an IVC filter when a patient is able to be anticoagulated.

If anticoagulation therapy is not possible for patients with acute deep vein thrombosis then placement of an IVC filter can lead to reduction in radiologically diagnosed PE but no difference in symptomatic PE and no overall mortality benefit.[314] Once any contraindication to anticoagulation has passed, it should be reinstituted. Whenever possible the filter should be retrieved.[315] Filter insertion is not without complications and frequently filters cannot be retrieved. 4

There is no evidence to support or refute long term anticoagulation merely to prevent IVC filter thrombosis.[315]

IVC filters significantly reduce the number of PEs suffered by patients who present with proximal DVT (1.1% v 4.8%, OR 0.22, 95% CI 0.05 to 0.90) but they are associated with an increase in the development of recurrent DVT (20.8% v 11.6%, OR 1.87, 95% CI 1.10 to 3.20) at two years follow up.[316] This is the major complication of IVC filter insertion in patients with proximal DVT. Other complications are shown in Table 5. 1- 4

Table 5: Complications of IVC filter insertion[315]

Immediate	
Misplacement	1.3%
Haematoma	0.6%
Pneumothorax	0.02%
Air embolus	0.2%
Carotid artery puncture	0.04%
Atrioventricular fistula	0.02%
Early	
Insertion site thrombosis	8.5%
Infection	(rare but documented)
Late	
DVT	21%
IVC thrombosis	2-10%
Post-thrombotic syndrome	15-40%
IVC penetration	0.3%
Filter migration	0.3%
Entrapment of guidewires	(rare but documented)
Filter tilting	(rare but documented)
Fracture	(rare but documented)

☑ If a device is used, retrievable IVC filters should be used although successful retrieval cannot be guaranteed

D **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.**

11.2 LOWER LIMB DVT

11.2.1 ANTICOAGULATION

Meta-analyses have demonstrated the superiority of LMWH over UFH in the initial treatment of DVT.[317, 318] A Cochrane review included 22 studies of over 8,000 patients of which 75% had DVT and 25% PE without evidence of DVT.[312] 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).[312] When analyses were confined to nine studies treating proximal DVT the same superiority of LMWH was seen. The survival advantage with LMWH was 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 review identified four studies comparing once daily with twice daily LMWH.[319] 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). | 1^{++} 1^{+}

Few studies have directly compared different LMWH preparations. However, a review of the data available suggests they have similar efficacy, as does outpatient compared to inpatient administration.[255] | 4

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.[151] | 1^{+}

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) and the INR is ≥2 *(see section 12.1)*.[255] | 4

There is evidence, however, that cancer patients with VTE benefit from reduced risk of VTE recurrence and of bleeding through use of continued LMWH therapy (durations in studies ranged from three to six months) rather than vitamin K antagonist therapy.[320-322] | 1^{+}

This option is also a suitable alternative for patients intolerant of, or unsuitable for, vitamin K antagonist therapy. Examples are intravenous drug users versus ileofemoral DVT, in whom there may be difficulties with venous access and compliance with oral therapy,[323, 324] and pregnant women with a history of prior VTE *(see section 7.4)*. | 3

Use of vitamin K antagonists is generally contraindicated in pregnancy *(see sections 4.9 and 7.3.1)*.

A **Patients with suspected DVT should be treated with therapeutic doses of LMWH or fondaparinux until the diagnosis has been deemed very unlikely or confirmed.**

D **In confirmed DVT the heparin or fondaparinux should be continued until the INR is at least 2.0 on a vitamin K antagonist, and for at least 5 days.**

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

A **Patients with cancer and VTE should be offered treatment with LMWH** *(rather than vitamin K antagonist)* **for three to six months and reviewed thereafter.**

11.2.2 THROMBOLYSIS AND PHARMACOMECHANICAL THERAPY

Few studies were identified which specifically address the management of 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%. Carefully selected patients with low bleeding risk (often younger patients) with extensive proximal iliofemoral DVT may benefit from thrombolysis, particularly catheter-directed thrombolysis, in which the systemic thrombolytic effect and bleeding rates are less.[314,325-327] 1++ 1+

High success rates for clot lysis have been reported in studies assessing the effect of combining catheter-directed thrombolysis with percutaneous mechanical thrombectomy.[328,329] Effectively the clot is isolated between two balloons where it is subjected to thrombolysis by pharmacological and mechanical means. 3

It is hoped the high rate of patency following the procedure will lead to long term improved valve function, fewer symptoms of post-thrombotic syndrome and lower recurrence rates. Long term data from RCTs are required before clear recommendations for this mode of treatment can be made.

D

- **Thrombolysis is not routinely recommended for patients with lower limb DVT.**
- **Thrombolysis, preferably catheter-directed thrombolysis or catheter-directed thrombolysis with percutaneous mechanical thrombectomy, can be considered on an individual basis, particularly in patients at low bleeding risk with limb threatening or massive iliofemoral DVT.**

11.3 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 10-21% of patients with STP will already have DVT at presentation and a further 3-4% will progress to it if untreated.[330]

Patients with at least 5 cm of thrombus in a superficial vein were more likely to have underlying DVT if the STP was in the proximal long saphenous vein (within 10 cm of the saphenofemoral junction). STP within a varicose vein was less likely to be associated with underlying DVT.[331] In 42% of cases of STP with coexisting DVT, however, the DVT was non-contiguous with the STP.

A Cochrane review and a guideline on treatment options for STP found that while topical gels and sprays containing heparin, heparinoids or non-steroidal anti-inflammatory drugs (NSAIDs) can reduce local symptoms there is no evidence that they reduce the risk of STP extension, recurrence or progression to DVT.[255,332] Oral NSAIDs, however, significantly reduced STP extension and/or recurrence by 67% compared to placebo (OR 0.33, 95% CI 0.16 to 0.68). 1+ 4

Several RCTs have also addressed the efficacy of subcutaneous LMWH in prophylactic and therapeutic doses compared to each other, to placebo or to oral NSAIDs.[332] In most of these studies all patients and controls also wore AES. As with oral NSAIDs, extension and/or recurrence of STP was significantly reduced (range, 67-84% reduction) with LMWH, even with short term treatment for 8-12 days.[333] This benefit remained significant at three month follow up. This study may have been underpowered to detect differences in DVT rate and differences between subcutaneous LMWH and oral NSAIDs. There was a non-significant trend to fewer early DVT events in the heparin arm, 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; a result also seen in another study comparing low-dose LMWH versus therapeutic dose LMWH treatment for 30 days.[334] Five out of 21 patients with STP extension in the long saphenous vein towards the spheno-femoral junction subsequently developed DVT. In an RCT of fondaparinux, 2.5 mg daily for 45 days, in patients with acute symptomatic superficial thrombophlebitis of the legs, the primary efficacy outcome (combination of death, symptomatic VTE, extension of STP to the saphenofemoral junction or symptomatic STP recurrence at day 47) was present in 5.9% of patients on placebo and 0.9% on fondaparinux (relative risk reduction 85%, 95% CI 74 to 92%, $p < 0.001$.[335] There was no difference in death rate and the calculated number needed to treat to prevent an episode of PE or DVT was 88.

1+
2+

Early surgical treatment of STP can reduce STP extension and/or recurrence, but this approach is no better than LMWH and has a higher complication rate.[332]

1+

D **Patients with clinical signs of superficial thrombophlebitis affecting the proximal long saphenous vein should have an ultrasound scan to exclude concurrent DVT.**

B

- **Patients with superficial thrombophlebitis should have anti-embolism stockings and can be considered for treatment with prophylactic doses of LMWH for up to 30 days or fondaparinux for 45 days.**
- **If LMWH is contraindicated, 8-12 days of oral NSAIDs should be offered.**

☑ Patients with superficial thrombophlebitis at, or extending towards, the sapheno-femoral junction can be considered for therapeutic anticoagulation for 6-12 weeks.

11.4 UPPER EXTREMITY DVT

Upper extremity DVT is relatively unusual and most cases are secondary to the presence of a venous catheter, malignancy or compression of the vein. There may also be a history of unaccustomed upper limb exercise.[336]

The studies available are heterogeneous case series and many included a mixed population without discriminating those with an underlying mechanical cause of DVT. There are no trials evaluating methods of initial anticoagulation separately for upper limb thrombosis. The role of thrombolysis was also described only in case series.[337]

In patients with upper extremity DVT 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 upper extremity DVT, compared to 19%, 95% CI 16 to 22, in leg DVT).[337] Prolonged anticoagulation for these patients is generally not indicated.[337]

3

There was no good quality evidence that the initial treatment of upper limb thrombosis should differ from that for lower limb thrombosis.

☑ Management of upper extremity DVT needs to be on an individual patient basis and should include management of any underlying condition.

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

11.5 CEREBRAL VEIN THROMBOSIS

11.5.1 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 although there is an early in-hospital fatality rate of around 5%, and an overall mortality rate of approximately 10%.[338] Cerebral haemorrhage, secondary to cerebral vein thrombosis, has been noted in 39% of patients.[339]

A Cochrane review identified two small RCTs including 79 patients randomised to anticoagulation (heparin with or without warfarin) or no anticoagulation.[340] 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, patients showed no new or enlarging cerebral haemorrhage with anticoagulation. 2+

Long term cohort follow-up studies indicate that recurrent cerebral vein thrombosis is uncommon (2-3%), as is thrombosis at other sites (4-5%), perhaps because many initial cerebral vein thrombosis events occur in young patients with temporary precipitating factors.[339,341] In excess of 80% of patients show recanalisation of the thrombosed cerebral vein after six months. Furthermore, the presence of heritable thrombophilia does not appear to influence recurrence risk, all suggesting that long term anticoagulation should be unnecessary in most patients. The use of steroid therapy in acute cerebral vein throbosis demonstrated no outcome benefits in a modestly sized retrospective case control study.[342] 2-

11.5.2 THROMBOLYSIS

A Cochrane review of thrombolysis for cerebral venous thrombosis identified no RCTs.[343]

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.[344] It may be indicated in selected cases where there is ongoing clinical deterioration despite other therapy.[345,346] 2++ 4

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

11.6 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.[338]

A review identified no randomised trials of treatment of splanchic vein thrombosis,[338] but found case series and observational cohort studies, one of which indicated a mortality rate of around 10% and a recurrence rate of 18.5% at 41 months in non-anticoagulated patients.[347] Thirty nine per cent of patients with underlying myeloproliferative disease suffered a recurrent venous thrombosis.[347] Anticoagulation appeared to reduce recurrence and was associated with recanalisation in 45% of patients.[347] The presence of sequelae to splanchnic vein thrombosis (portal hypertension with oesophageal varices and hypersplenism with thrombocytopenia) increases the risk of bleeding should anticoagulation be prescribed. 3

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.**

11.7 INCIDENTAL VTE

With improvements in imaging techniques and their wide application, the identification of clinically unsuspected VTE on scans performed for another purpose, typically staging for malignancy, is increasingly common. For example, in one study of patients referred for routine contrast-enhanced thoracic CT there was unsuspected thrombus in 12 of 785 patients (1.5%), mostly in inpatients with cancer.[348] High rates of incidental DVT in other vascular beds have also been reported in patients with cancer, again predominantly in inpatients.[349] The natural history of incidental VTE is unclear.[350] Although short term outcome without anticoagulant therapy was generally good in one study of incidental PE, this was an observational study involving only a small number of patients.[351]

3

D **In patients with incidental VTE detected by imaging, treatment decisions should be made on an individual basis taking account of the thrombus burden and the presence of additional risk factors for VTE as well as bleeding risk.**

11.8 PREGNANCY

The management of pregnancy-related venous thromboembolism is covered in a national guideline.[256]

12 Further management of venous thromboembolism

12.1 CHOICE OF ANTICOAGULANT

Small RCTs confirmed the need for extended anticoagulation, usually with VKA, beyond the initial few days of heparin therapy.[352,353] It was subsequently demonstrated that therapeutic doses of VKA were superior to prophylactic doses of UFH for extended anticoagulation.[354] Large prospective studies have shown that the risk of recurrent VTE is reduced for the duration of VKA therapy (*see section 12.1.2)*, however, throughout VKA therapy the risk of bleeding is increased *(see section 15.1)*, with an annual risk of around 1-7% for organ or life threatening bleeds.[355-357] 1+ 3

Use of VKA is contraindicated in pregnancy *(see sections 4.9 and 7.3.1)*.

The use of LMWH for the prevention of recurrent VTE was addressed in three systematic reviews.[358-360] LMWH is at least as effective as warfarin for preventing recurrent VTE and appears to be more effective than warfarin in patients with cancer.[320-322] A Cochrane review and meta-analysis of six randomised controlled trials comparing LMWH with an oral anticoagulant and two studies comparing other treatment modalities in patients with cancer found no statistically significant difference in mortality but identified a significant reduction in recurrent symptomatic venous thromboembolic disease in favour of treatment with LMWH.[224] 1+

The efficacy of aspirin against VTE is inferior to that of VKA and LMWH in all situations studied.[361] Evidence is lacking for the efficacy of aspirin for the prevention of recurrent VTE after discontinuation of VKA therapy.

In a non-inferiority randomised controlled trial a fixed twice daily dose of dabigatran was compared to warfarin, dose-adjusted according to INR, in the treatment of acute VTE after initial parenteral anticoagulation. In relation to symptomatic confirmed VTE after six months, dabigatran was as effective as warfarin with a similar safety profile.[362] 2++

Some studies have suggested that statin use is associated with a reduced incidence of VTE.[363,364] In a large RCT fewer first episodes of VTE were found among older patients treated with rosuvastatin compared to placebo.[365] 1+ 2+

No data were identified, however, to support the use of statins to reduce the risk of recurrence of VTE after discontinuation of VKA therapy.

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

For the management of VTE, RCTs support the use of a target INR of 2.5 (range 2.0-3.0).[180,354,366,370] Retrospective descriptive studies have shown a higher risk of recurrence when INR values are below 1.9, and a higher risk of bleeding when the INR is more than 3.0.[355,371,372] 2++ 3

Although reduced-intensity warfarin (INR 1.5-2.0) is more effective than placebo for preventing recurrent VTE,[373] reduced-intensity treatment (INR 1.5-1.9) is associated with a higher rate of recurrent VTE than standard-intensity treatment with no reduction in clinically important bleeding.[374] 2++

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

D **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 patients with antiphospholipid syndrome, two RCTs have refuted this.[375, 376] In antiphospholipid syndrome a target INR of 2.5 is at least as effective as a higher target INR in prevention of recurrent VTE. 1++

B **In patients with 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 AND PULMONARY EMBOLISM

Four systematic reviews have addressed the duration of anticoagulation with a VKA, principally warfarin, after an episode of lower limb proximal DVT or PE.[356, 377-379] The risk of recurrent VTE remains low whilst treatment is continued but there is an inevitable increased risk of bleeding. 1++ 2+

A meta-analysis including 15 studies revealed that 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).[356] In the DURAC 1 trial, in patients with a first episode of VTE, treatment with a VKA for six months was associated with a lower risk of recurrence than treatment for six weeks at both two years and six years of follow up, without a statistically significant increased risk of bleeding.[75,380] In two studies comparing six months and three months of treatment with VKA in patients with VTE which was unprovoked or provoked by a reversible risk factor there was no difference in risk of recurrence.[381,382] One RCT suggested that treatment for six weeks is as effective as 12 weeks in isolated calf DVT (n = 105 v 92 and recurrence 2 v 3 for six and 12 weeks, respectively).[382] 1+

The risk of recurrent VTE after discontinuation of VKA therapy may be higher in patients with antiphospholipid antibodies.[375,376] 1++

An elevated plasma concentration of D-dimer measured shortly after the discontinuation of a course of VKA treatment for VTE identifies patients at higher risk of recurrence. In the PROLONG study only patients with an abnormal D-dimer level one month after discontinuation of anticoagulant for treatment of unprovoked VTE were randomised to resume warfarin or not. Thirty seven per cent of 608 patients recruited had abnormal D-dimer. When the primary end-point of recurrent VTE and major bleeding was assessed there were three events among the 103 patients who resumed warfarin therapy and 18 among the 120 who did not (adjusted hazard ratio 4.26, 95% CI 1.23 to 14.6, p = 0.02). In addition, there was an excess of events in the cohort with abnormal D-dimer who did not resume warfarin compared with the cohort with normal D-dimer (adjusted hazard ratio 2.27, 95% CI 1.15 to 4.46, p = 0.02).[383] 1+

Randomised trials have also suggested that residual vein occlusion detected by compression ultrasound after a course of VKA therapy for lower limb DVT may be a useful guide to duration of treatment.[384,385] In a post hoc analysis of the PROLONG study, however, abnormal D-dimer was not associated with residual vein occlusion and in the presence of abnormal D-dimer residual vein occlusion did not contribute to the risk of recurrent VTE.[386] This, combined with the lack of agreed criteria for the definition of residual vein occlusion, suggests that further research is required before the presence of residual vein occlusion can be used to determine theduration of VKA therapy 1+

A **After a first episode of proximal limb deep vein thrombosis or pulmonary embolism, treatment with a VKA should be continued for at least three months.**

☑ Uninterrupted, long term continuation of VKA therapy after a first episode of VTE may be appropriate in some patients and can be based on individual assessment of risk factors, including:

- an unprovoked first event
- the site and severity of the first event
- the presence of persistent comorbidities, eg cancer
- the presence of persistent antiphospholipid antibodies
- male sex *(see Table 2)*
- bleeding risk on anticoagulant treatment
- patient compliance and preference.

A **Measurement of D-dimer concentration one month after discontinuation of a course of VKA therapy after a first episode of unprovoked VTE can be considered for the identification of patients who may benefit from resumption of VKA therapy and continuation in the long term.**

☑
- 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.

12.2 GRADUATED ELASTIC COMPRESSION STOCKINGS

A systematic review identified three RCTs assessing the effect of use of below-knee graduated elastic compression stockings for the prevention of post-phlebitic syndrome.[387] The use of below-knee graduated elastic compression stockings (eg providing 40 mm Hg at the ankle) on the affected leg for two years after lower limb DVT reduced the incidence of the syndrome from 54% to 25.2% (RR 0.47, 95% CI 0.36 to 0.61) with a number needed to treat of four (95% CI 2.7 to 5.0). 1+

A **After deep vein thrombosis affecting a lower limb, the use of well fitted below-knee graduated elastic compression stockings for two years should be encouraged to reduce the risk of post-phlebitic syndrome.**

13 Monitoring the anticoagulant effect

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. The British Committee for Standards in Haematology recommends assays should be calibrated locally to establish an appropriate target APTT ratio.[388] 4

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

13.2 LOW MOLECULAR WEIGHT HEPARIN

LMWH does not require routine monitoring since weight-adjusted dosing for treatment, or a fixed dose for thromboprophylaxis, have been shown in clinical trials to provide a predictable clinical response.[116,209,312] 1^{++} 1^{+}

Such dosing may be unreliable, however, in patients at extremes of weight, those 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 around four hours after a subcutaneous dose of LMWH.[388] 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.[388] 4

C **Routine laboratory monitoring of LMWH is not recommended.**

13.3 WARFARIN

Warfarin has a narrow therapeutic window and there is considerable inter-individual as well as temporal intra-individual variability which necessitates regular monitoring. The PT, with the result expressed as INR, is the best measure of intensity of VKA therapy. A moderately sensitive INR reagent (with an International Sensitivity Index (ISI) <1.7) is recommended, as is assay validation within the individual laboratory.[389] 4

13.3.1 INR CONTROL

Cohort studies have established that high quality INR control, as assessed by a high percentage of time spent in the 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 episodes (RR 5.96, 95% CI 3.68 to 9.67, $p<0.0001$) while periods of INR <2 are associated with increased thrombotic events (RR 1.88, 95% CI 1.16 to 3.07, $p<0.05$).[355, 390] Poor quality INR control, as assessed by the percentage of 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 to 5.25, $p=0.003$).[391] 2^{+}

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.[392] Within specialised anticoagulant services computer-assisted dosing is at least as effective as manual dosing, and one randomised study demonstrated fewer adverse clinical events, primarily bleeding events, in VTE patients in the computer-assisted dosing arm compared to the manual dosing arm.[393] 2^{+}

Once a patient is stabilised on warfarin, more frequent INR monitoring has been associated with improved quality of INR control (time in target range) in retrospective studies of patients with atrial fibrillation.[394] This relationship has not been demonstrated in venous thrombosis patients.[395] The average interval between INR testing is 3-4 weeks in most UK anticoagulant services. Many stable patients, however, can be monitored less frequently, while more frequent testing may be advisable for patients who exhibit an unstable dose response.[396] | 2-4

In suitably selected and trained patients anticoagulation self management is a safe and effective, although more expensive, management option.[392,397] | 1+

☑ There are several models of care for management of VKA therapy. The optimal approach suitable for local conditions and which provides the most precise INR control should be selected.

A **Computer-assisted dosing algorithms are recommended.**

D **Patient self testing and self management supported by a dedicated and well trained anticoagulant team may be considered for selected patients.**

14 Outpatient management of acute VTE

The widespread use of LMWH (administered subcutaneously once daily and without requirement for laboratory monitoring) in the initial treatment of VTE has led to the increasing practice of managing acute DVT, or even PE, in the community setting. Any potential benefit must be balanced against the risks of early recurrent VTE (especially life threatening PE) or major haemorrhage occurring in outpatients. It is likely that patients who are clinically unstable, have significant comorbid disease or have severe mobility problems are best managed as inpatients.

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).[398] All six trials had limitations 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 fewer major bleeds (RR 0.67, 95% CI 0.33 to 1.36) and reduced mortality (RR 0.72, 95% CI 0.45 to 1.15), but a higher minor bleeding rate (RR 1.29, 95% CI 0.94 to 1.78). While some of the apparent benefit from outpatient treatment could have been due to the use of LMWH rather than UFH, the single study comparing LMWH in the two settings showed a similar pattern of results. Outpatient therapy is as safe and effective as inpatient treatment for DVT in appropriately chosen patients if support services are in place. 1+

Characteristics of patients who may be less suitable for outpatient management have been identified from the prospective Spanish register, Registro Informatizado de la Enfermedad Tromboembólica (RIETE).[399] 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 British Committee for Standards in Haematology guideline advises that DVT patients unlikely to be suitable for outpatient treatment include those with coexistent serious medical pathology, severe acute venous obstruction (phlegmasia cerulea dolens), severe pain, renal impairment, significant communication or mobility problems, poor social circumstances, known heparin allergy and those with active bleeding or at high risk of bleeding.[400] 4

B **Outpatient therapy of DVT may be considered for selected patients with appropriate support services in place.**

14.2 PULMONARY EMBOLISM

Initial management of PE is covered in section 11.1.

About 35% of patients with DVT managed as outpatients have subclinical PE. Patients presenting with PE who are unstable are unsuitable for outpatient management or even early discharge.

There is limited evidence regarding the safety of outpatient treatment for PE.[314] 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.[401] At three months follow up there were no deaths from PE and one death from bleeding in both the outpatient and early hospital discharge treatment categories. 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. 2++

The use of a prognostic prediction model may assist in selection of patients for early discharge. Five models for patients with acute PE (Geneva score, Pulmonary Embolism Severity Index, the Spanish score, the Davies criteria and the Home Management Exclusion criteria) were reviewed.[402] The Pulmonary Embolism Severity Index model, derived from the largest study (n = 10,354) included in the review,[403] takes account of 11 routinely available clinical parameters and categorises 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%.[403, 404] Sensitivity for overall mortality was 91% (95% CI 81 to 97%) and the negative predictive value was 99% (95% CI 97% to 100%).[405] 2++

Stable, low-risk PE patients may be identified by virtue of a low clinical prognostic score (eg Pulmonary Embolism Severity Index), normal right ventricular dimensions and normal biochemical markers of negative predictive value for early mortality (*see section 9.4.1*).[303]

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 33,813 patients in studies of pharmacological prophylaxis for major general surgery.[406] Different doses and preparations of heparins were used and patients were divided into five groups for analysis: high dose LMWH > 3,400 IU/day, low dose LMWH < 3,400 IU/day, high-dose UFH 5,000 U three times a day, low-dose UFH < 5,000 IU three times a day and placebo. Some patients also received mechanical thromboprophylaxis but this was 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, and subsequent operation required due to bleeding. In patients undergoing general surgery there was a higher rate of wound haematoma and drain site bleeding in those who received thromboprophylaxis with UFH or LMWH than placebo. The rate of re-operation to control bleeding in recipients of any heparin was, however, very low (0.7%) and was identical to the rate in 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.[406] 1++

A systematic review and meta-analysis of major bleeding after pharmaceutical prophylaxis for major orthopaedic surgery in 21 studies including 20,523 patients found that different drugs were associated with a different risk of major bleeding.[181] The analysis found that the relative risk of bleeding was lowest for warfarin, followed by LMWH followed by UFH and fondaparinux. One weakness of this analysis 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. 1+

The risk of bleeding while on warfarin is affected by features of the patient, the indication for anticoagulation, the duration of therapy and the target INR. A higher target INR is almost uniformly associated with a higher bleeding risk and bleeding is more common earlier in therapy.

In a meta-analysis of 10,757 patients on warfarin for the treatment of VTE the overall rate of major bleeding was 7.22 per 100 patient years with a rate of fatal bleeding of 1.3 per 100 patient years. Of 276 major bleeds, 37 were fatal giving a case fatality for major haemorrhage of 13.4%.[357] In an analysis of bleeding associated with different durations of anticoagulation for VTE, however, the annual rates of haemorrhage were 1.1% in those undergoing prolonged anticoagulation compared with 0.6% in those who had completed shorter courses.[356] Patients' risk of bleeding on warfarin should be assessed but, as indicated in section 10.1, none of the clinical prediction rules currently available reliably does this.[310] 1++ 2+

15.1.1 REVERSAL OF VKA INDUCED ANTICOAGULATION

A systematic review showed that reversal of VKA induced anticoagulation into the therapeutic range, using small doses (1-2.5 mg) of vitamin K given orally or intravenously, was achieved in around 80% of patients.[407] 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.[408] 1+

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. This is best achieved using prothrombin complex concentrate in a dose that is adjusted depending on the presenting INR.[409]

In a comparison of the rate of reversal of anticoagulation using different vitamin K preparations given by different routes (oral or intravenous), intravenous vitamin K was shown to reverse anticoagulation with a more rapid onset than oral vitamin K and, therefore, in such cases larger doses of vitamin K (5-10 mg) should be given intravenously.[410] 3

15.1.2 REVERSAL OF HEPARIN ANTICOAGULATION

Reversal of heparin anticoagulation is covered in section 4.4.2.

15.1.3 RECOMMENDATIONS

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

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

D **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.

☑ Monitoring of patients should be more intensive during the first months of treatment when anticoagulant control tends to be less stable.

15.1.4 BLEEDING RISK DURING REGIONAL ANAESTHESIA/ANALGESIA

Compared with general anaesthesia, both spinal and epidural anaesthetic techniques have been shown to reduce the incidence of VTE.[72,411] This reduction in VTE is, however, less than that seen when antithrombotic pharmacological prophylaxis is administered. Antithrombotic drugs increase the risk of vertebral canal bleeding in patients who undergo central neuraxial block and this may result in permanent neurological injury due to compression of the spinal cord or cauda equina. This complication of neuroaxial block is very rare but exposure to antithrombotic drugs is a significant risk factor.[412,413] 1-4

Consensus guidelines on the risks of regional anaesthesia in the anticoagulated patient have been published by the American Society of Regional Anesthesia and Pain Medicine.[414] Modified consensus guidance based on these guidelines is shown in Table 6.

Table 6: Guidance for central neural axial block in patients taking drugs affecting haemostasis

Aspirin and NSAIDS	Clopidogrel	Unfractionated heparin prophylaxis (subcutaneous)	Unfractionated heparin treatment (intravenous)	LMWH**	Warfarin	Rivaroxaban Dabigatran
No issue	Stop 7 days preop if possible. If not, proceed with caution	Wait at least 4hr after a dose before block or catheter removal. Wait at least 1hr before dosing after procedure (catheter insertion or withdrawal)	Stop infusion 2-4 hr before block. Start infusion >1 hr after block. Remove epidural catheter no sooner than 2-4 hr after discontinuation of infusion	Wait at least 12 hrs after a prophylactic dose and 24 hr after a therapeutic dose before block.* Wait at least 10 hours after dose before removing catheter. After catheter removal wait 2-4 hr before next dose	Proceed if INR ≤1.5	These are started postoperatively. Wait 12-18 hrs after dose for epidural catheter removal. Wait 6 hrs before next dose

**Adapted from the American Society of Regional Anesthesia and Pain Medicine guidelines on the risks of regional anesthesia in the anticoagulated patient.[414]*

*** With fondaparinux the period between administration and procedure should be greater than for LMWH due to its longer half-life.*

15.2 HEPARIN INDUCED THROMBOCYTOPENIA

Heparin induced thrombocytopenia (HIT) is an important complication of the use of heparins. It is 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 heparin (UFH or 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 days 5-10 of exposure although recently exposed patients (within previous 100 days) may develop HIT within the first 24 hours of re-exposure.[415] 4

Porcine heparins are associated with a lower incidence of HIT than bovine heparins and should be used in preference to them.[416] Low molecular weight heparins are associated with a lower incidence of HIT than UFH.[417] 1+ 4

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 patients using laboratory tests to detect the anti-heparin/anti-platelet factor 4 (PF4) antibodies which result in the disorder.[418]

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.[419,420] Two drugs, lepirudin[421,422] and danaparoid,[419] are currently licensed in the UK for immediate management of this condition. 3

Documentation of the occurrence of HIT in clinical records is essential.

Detailed guidance on the management of HIT is given in the British Committe for Standards in Haematology guideline on this topic.[415]

A **To minimise the incidence of HIT, LMWH should be used in preference to UFH.**

D **To minimise the incidence of HIT, porcine heparins should be used in preference to bovine heparins.**

☑ All patients who are receiving treatment doses of UFH or LMWH and all surgical and medical patients who are receiving UFH or LMWH for thromboprophylaxis should be monitored for the development of thrombocytopenia.

☑ 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.

D **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 before receiving treatment.**

D
- **Monitoring patients for the development of HIT should be by performing serial platelet counts.**
- **Patients who have previously received UFH or LMWH within 100 days or in whom the 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 two to three days from day four to day14 of exposure.**

☑ HIT should be suspected if the platelet count falls by 30% or more or if there is thrombocytopenia ($< 150 \times 10^9$/l).

☑ HIT should be considered in patients who develop a new thrombosis or in whom thrombosis extends and in patients who develop typical skin lesions or features of a systemic response such as fever, chills, or shivering whilst receiving any form of heparin.

D
- **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.**

D **Whether or not there is evidence of a new thrombotic episode related to HIT, patients should receive therapeutic, as opposed to prophylactic, doses of lepirudin or danaparoid.**

D
- **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 warfarin therapy is introduced it should be at a low dose** *(5 mg daily)* **and danaparoid or lepirudin should be withdrawn only after the INR has been > 2 on two consecutive days.**

☑ A history of HIT should be carefully documented in the clinical record.

15.3 REDUCED BONE MINERAL DENSITY

Prolonged exposure to unfractionated heparin (UFH) may result in an excess of osteoporosis in pregnant women.[423] There is evidence, however, that the risk is lower with LMWH than with UFH.[239,424] An RCT of long-term dalteparin in pregnancy indicated that women with prolonged exposure to dalteparin in pregnancy did not have significantly lower bone densities than controls.[424] In a systematic review of the safety and efficacy of LMWHs for thromboprophylaxis and treatment of VTE in pregnancy, only one osteoporotic fracture was observed among the 2,777 pregnant women exposed to LMWHs.[239] 1+ 2+

C **Monitoring of bone density in pregnant women exposed to LMWHs is not recommended.**

There is some evidence for warfarin-associated osteoporosis in long term users of warfarin. In a large observational study of osteoporotic fractures the OR of fracture for men using warfarin for more than a year was 1.63 (95% CI 1.26 to 2.10) and for women was 1.05 (95% CI 0.88 to1.26).[425] It is not possible to make recommendations on monitoring and treatment based on the evidence currently available.

15.4 VITAMIN K ANTAGONISTS, EMBRYOPATHY AND FETAL HAEMORRHAGE

Use of vitamin K antagonists in pregnancy is covered in section 7.

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 VTE with patients and carers and in guiding the production of information leaflets.

16.1 CHECKLIST FOR PROVISION OF INFORMATION

This section gives examples of the information patients/carers may find helpful at key stages. 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.

Initial presentation/assessment.
▪ Explain what VTE is and the causes. Discuss risk factors including family history. ▪ Explain the symptoms and signs. ▪ Explain that confirmation of VTE is necessary using clinical examination, a blood test and imaging. ▪ Explain to patients who have tested negative for VTE using clinical examination and a blood test why further tests are unnecessary. Explain that they should seek urgent advice and further assessment if they have relevant symptoms (*see section 9.1*), and provide a leaflet describing the symptoms *(see Annex 6)*. Indicate any alternative diagnosis. ▪ Explain to patients who had a suspected DVT but negative ultrasound that they should seek urgent advice and further assessment if they have the following symptoms: - increased limb pain or swelling - sudden onset of breathlessness - chest or back pain - coughing or spitting up blood - any episode of collapse. ▪ Explain to patients who have tested positive for VTE (especially if unprovoked) that the thrombotic tendency may run in the family in some cases. Advise patients to make adult first degree relatives aware of the symptoms and encourage them to seek medical help immediately should they experience them and provide a leaflet describing the symptoms. *(See Annex 7)*
Treatment
▪ Explain treatment options to patients and discuss the benefits and risks. ▪ Explain the importance of early mobilisation and encourage patients confined to a chair or bed to perform regular leg exercises. ▪ Encourage the use of properly fitted compression stockings on the lower limb affected by DVT. ▪ Advise women of the need to consider alternative contraception if the combined oral contraceptive (COC) is to be discontinued. ▪ Advise patients on warfarin of the requirement for regular blood tests to inform dosing, on the potential for other drugs to interact (including some over-the-counter medications and supplements), on the implications of trauma (especially to the head), and on the need to seek urgent advice should unexpected bleeding occur.
Prevention
▪ Advise about the risks of recurrence after discontinuing anticoagulant treatment for VTE and about actions to reduce the risk as appropriate (eg, weight reduction in the obese, avoidance of unnecessary immobility, use of thromboprophylaxis during high-risk periods). ▪ Explain the risks of VTE to patients using COC or HRT and advise them to seek medical help immediately if they experience relevant symptoms.

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

An example of an advice leaflet for patients discharged from the emergency department following attendance with a possible DVT is shown in Annex 6.

An example of an advice leaflet for patients discharged from the outpatient DVT service is shown in Annex 7.

An example of a general patient information leaflet on DVT is available on the SIGN website at **www.sign.ac.uk**.This leaflet has been developed as an aid to standardising information giving. The guideline development group recommends that one general patient information leaflet should be available across NHSScotland and paper copies of this leaflet made available in areas to which the general public have easy access.

☑ One general patient information leaflet should be available across NHSScotland and paper copies of this leaflet made available in areas to which the general public have easy access.

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.

Implementation of this guideline will be encouraged and supported by SIGN. The implementation strategy for this guideline is available on the SIGN website at w**ww.sign.ac.uk**.

17.1 RESOURCE IMPLICATIONS OF KEY RECOMMENDATIONS

No recommendations are considered likely to reach the £5 million threshold which warrants full cost impact analysis.

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.

The guideline development group has identified the following as key points to audit to assist with the implementation of this guideline.

- Compliance with and recording of risk assessment in all patients admitted to or presenting acutely at hospital.
- Compliance with appropriate prescription of mechanical and pharmacological prophylaxis.
- Percentage of time in range for INR for patients receiving VKA and percentage INR tests <1.5 and >4.5 as measures of likely poor efficacy and bleeding risk.
- The rate of healthcare-associated VTE should be recorded and monitored routinely to identify areas where the risk assessment policy may need to be reviewed.
- National condition-specific audits should use available linked datasets to monitor readmission or death associated with a VTE episode.

17.3 ADDITIONAL ADVICE TO NHSSCOTLAND FROM NHS QUALITY IMPROVEMENT SCOTLAND AND THE SCOTTISH MEDICINES CONSORTIUM

On 8 December 2008, the Scottish Medicines Consortium (SMC) advised that:
rivaroxaban (Xarelto®) is accepted for use within NHS Scotland for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery.

On 9 June 2008, the Scottish Medicines Consortium (SMC) advised that:
dabigatran etexilate (PradaxaÒ) is accepted for use within NHS Scotland for the primary prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

NHS QIS validated NICE MTAs
TA157 Dabigatran etexilate is recommended as an option for the prevention of VTE in adults undergoing elective total hip or knee replacement surgery.

TA170 Rivaroxaban is recommended as an option for the prevention of VTE in adults undergoing elective total hip or knee replacement surgery.

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 the prevention and management of venous thromboembolism (VTE). 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

The guideline development group was not able to identify sufficient evidence to answer all of the key questions *(see Annex 1)* asked in this guideline. The following areas for further research have been identified:

- A head-to-head comparison of aspirin and LMWH as thromboprophylaxis in surgical, particularly orthopaedic, patients.
- An evaluation of the effectiveness of AES in non-stroke medical patients.
- An evaluation of the relative effectiveness of full and knee length AES in non-stroke patients.
- An evaluation of the effectiveness of thromboprophylaxis in patients in the ICU setting.
- An evaluation to determine which women benefit from thromboprophylaxis during pregnancy and the puerperium, the effectiveness of the methods currently employed and the optimum timing of administration.
- An evaluation of the role of negative D--dimer in excluding DVT in high and moderate risk patients with a first negative ultrasound scan.
- A comparison of heparin and thrombolysis in high-risk PE patients.
- A comparison of standard initial treatment with LMWH versus catheter-directed thrombolysis in proximal lower limb DVT.
- An evaluation to determine which cases of STP require imaging to exclude concurrent DVT.
- An evaluation to determine the optimal dose and duration of anticoagulant therapy for STP.
- A study to determine the natural history of incidental VTE.
- A randomised controlled trial of outcomes in incidental VTE (an observational study and follow-up RCT of treatment versus no treatment if indicated).

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

Professor Mike Greaves *(Chair)*	*Professor of Haematology, University of Aberdeen*
Ms Julie Blythe	*Orthopaedic Pharmacist, Royal Infirmary of Edinburgh*
Dr Adrian Brady	*Consultant Cardiologist, Glasgow Royal Infirmary*
Ms Beatrice Cant	*Programme Manager, SIGN*
Dr Matthew Checketts	*Consultant Anaesthetist, Ninewells Hospital, Dundee*
Mr John Duncan	*Vascular Surgeon, Raigmore Hospital, Inverness*
Miss Tracey Gillies	*General Surgeon, Royal Infirmary of Edinburgh*
Dr Roberta James	*Acting Programme Director, SIGN*
Ms Joan Lawson	*Lay Representative, Caithness*
Mr Gordon McPherson	*Lay Representative, Renfrewshire*
Dr John Murchison	*Consultant Radiologist, Royal Infirmary of Edinburgh*
Mr Paul Rogers	*Vascular Surgeon, Gartnavel General Hospital, Glasgow*
Mrs Lynne Smith	*Information Officer, SIGN*
Dr Campbell Tait	*Consultant Haematologist, Glasgow Royal Infirmary*
Dr Andrew Thomson	*Consultant Obstetrician and Gynaecologist, Royal Alexandra Hospital, Paisley*
Professor Isobel Walker	*Consultant Haematologist, Glasgow Royal Infirmary*
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.

Ms Mary Deas	*Distribution and Office Coordinator*
Mrs Karen Graham	*Patient Involvement Officer*
Mrs Lesley Forsyth	*Events Coordinator*
Mr Stuart Neville	*Publications Designer*
Ms Gaynor Rattray	*Senior Guideline Coordinator*

19.2.1 PATIENT INVOLVEMENT

In addition to the identification of relevant patient issues from a broad literature search, SIGN involves patients and carers throughout the guideline development process in several ways. SIGN recruits a minimum of two patient representatives to guideline development groups by inviting nominations from the relevant 'umbrella', national and/or local patient-focused organisations in Scotland. Where organisations are unable to nominate, patient representatives are sought via other means, eg from consultation with NHS Board public involvement staff.

Further patient and public participation in guideline development was achieved by involving patients, carers and voluntary organisation representatives in the peer review stage of the guideline and specific guidance for lay reviewers was circulated. Members of the SIGN patient network were also invited to comment on the draft guideline section on provision of information.

19.3 ACKNOWLEDGEMENTS

SIGN is grateful to the following former members of the guideline development group.

Dr Daniel Franks	*General Practitioner, Stanley Medical Centre, Perth*
Professor Steffen Breusch	*Consultant Orthopaedic Surgeon, Royal Infirmary of Edinburgh*
Mr Colin Howie	*Consultant Orthopaedic Surgeon, Royal Infirmary of Edinburgh*

SIGN is grateful to Professor Steffen Breusch and Mr Colin Howie for their contribution to the development of the guideline. Professor Steffen Breusch and Mr Colin Howie wish to register their disagreement with the recommendations made in section 5.5.

19.4 CONSULTATION AND PEER REVIEW

19.4.1 NATIONAL OPEN MEETING

A national open meeting is the main consultative phase of SIGN guideline development, at which the guideline development group presents its draft recommendations for the first time. The national open meeting for this guideline was held on 29th September 2009 and was attended by 118 representatives of all the key specialties relevant to the guideline. The draft guideline was also available on the SIGN website for a limited period at this stage to allow those unable to attend the meeting to contribute to the development of the guideline.

19.4.2 SPECIALIST REVIEW

This guideline was also reviewed in draft form by the following independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. The guideline group addresses every comment made by an external reviewer, and must justify any disagreement with the reviewers' comments.

SIGN is very grateful to all of these experts for their contribution to the guideline.

Dr Roopen Arya	*Consultant Haematologist and Director, King's Thrombosis Centre, London*
Professor Edwin van Beek	*SINAPSE Chair of Clinical Radiology, University of Edinburgh*
Mr Ivan Brenkel	*Consultant Orthopaedic Surgeon, Queen Margaret Hospital, Dunfermline*
Professor Julie Brittenden	*Reader in Vascular Surgery, University of Aberdeen*
Dr Alexander Gatt	*Consultant Haematologist, Royal Free Hampstead NHS Trust, London*
Dr Ron Kerr	*Consultant Haematologist, Ninewells Hospital, Dundee*
Professor Gordon Lowe	*Emeritus Professor (formerly Professor of Vascular Medicine), University of Glasgow*
Dr Mark McColl	*Consultant Haematologist, Crosshouse Hospital, Kilmarnock*
Mr David Paul	*Lay Representative, Glasgow*
Dr Scott Ramsay	*Consultant Physician and Geriatrician, St John's Hospital, Livingston*
Mrs Jennifer Ross	*Medication Safety Officer, Aberdeen Royal Infirmary*
Dr Abel Wakai	*Locum Consultant in Emergency Medicine, St James' Hospital, Dublin*
Professor Tony Wildsmith	*Professor of Anaesthesia, Ninewells Hospital, Dundee*

19.4.3 SIGN EDITORIAL GROUP

As a final quality control check, the guideline is reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers' comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. The editorial group for this guideline was as follows.

Mr Andrew de Beaux	*The Royal College of Surgeons of Edinburgh*
Dr Keith Brown	*Chair of SIGN; Co-Editor*
Dr Roberta James	*Acting Programme Director, SIGN*
Professor John Kinsella	*The Royal College of Anaesthetists*
Mrs Fiona McMillan	*The Royal Pharmaceutical Society of Great Britain (Scottish Department)*
Dr Graeme Simpson	*The Royal College of Physicians of Edinburgh*
Dr Sara Twaddle	*Director of SIGN; Co-Editor*

Abbreviations

ACCP	American College of Chest Physicians
ACS	acute coronary syndromes
AES	anti-embolism stockings
APTT	activated partial thromboplastin time
ARR	absolute risk reduction
AT	antithrombin
BMI	body mass index
BNF	British National Formulary
BNP	B-type natriuretic peptide
CABG	coronary artery bypass graft
CCT	controlled clinical trial
CDR	clinical decision rule
CDT	catheter-directed thrombolysis
CI	confidence interval
CLOTS 2	Clots in Legs Or sTockings after Stroke
COC	combined oral contraceptive
CPR	clinical prediction rule
CT	computed tomography
CTPA	computed tomography pulmonary angiogram
CUS	compression ultrasonography
CVC	central venous catheter
CVP	central venous pressure
DVT	deep vein thrombosis
ECG	electrocardiogram
ELISA	enzyme linked immunosorbent assay
ESC	European Society of Cardiology
GFR	glomerular filtration rate
GI	gastrointestinal
HIT	heparin induced thrombocytopenia
HR	hazard ratio
HRT	hormone replacement therapy
HTA	Health Technology Assessment
ICU	intensive care unit
ILS	isotope lung scintigraphy
INR	International Normalised Ratio
IPC	intermittent pneumatic compression
IQR	interquartile range
ISI	international sensitivity index
IU	international unit

IVC	inferior vena cava
LEDVT	lower extremity DVT
LMWH	low molecular weight heparin
LR	likelihood ratio
MI	myocardial infarction
MTA	multiple technology appraisal
NHS QIS	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
PAD	peripheral arterial disease
PC	protein C
PE	pulmonary embolism
PEP	Pulmonary Embolism Prevention trial
PESI	Pulmonary Embolism Severity Index
PF4	anti-platelet factor 4
PMT	percutaneous mechanical thrombectomy
PT	prothrombin time
PS	protein S
PTS	post-thrombotic syndrome
RAM	risk assessment method
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	randomised controlled trial
RIETE	Registro Informatizado de la Enfermedad Tromboembólica
RR	relative risk
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
UFH	unfractionated heparin
UK	United Kingdom
US	ultrasound
VKA	vitamin K antagonist
VTE	venous thromboembolism

Annex 1

Key questions used to develop this guideline

RISK FACTORS	
Key question	*See guideline section*
1. What are the risk factors for venous thromboembolism (VTE) (first and recurrent)? 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.	3
PREVENTION	
Key question	*See guideline section*
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)? 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), dextrans, direct thrombin inhibitors, factor-Xa inhibitors.	4,5
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.	4,6
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.	7
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.	8

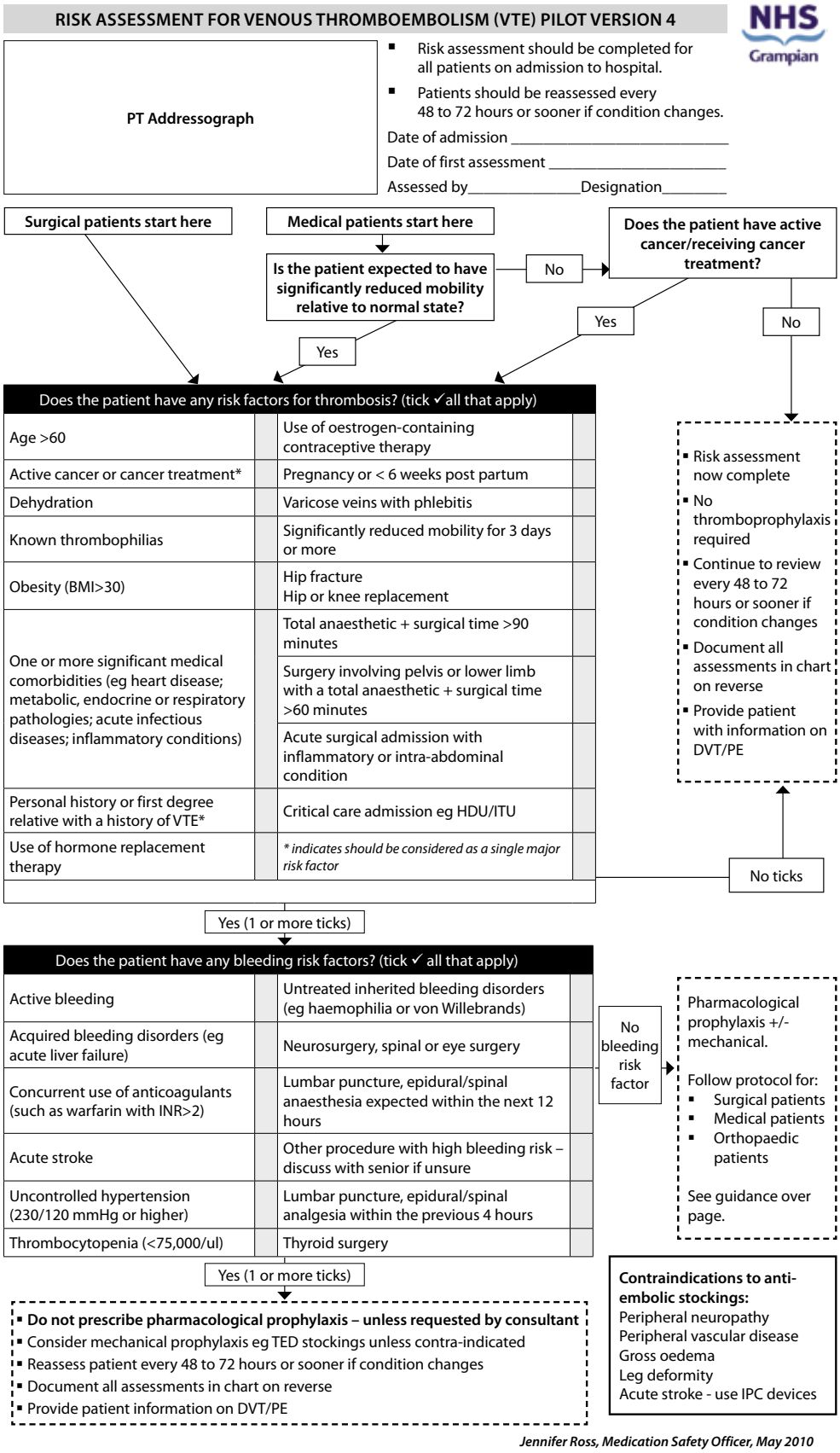
6. What investigations predict risk of VTE, and in whom should they be performed? First VTE and recurrent VTE. Consider: thrombophilia testing, factor V Leiden, prothrombin G20210A, Protein C antithrombin deficiency, Factor VIII, homocysteine, MTHFR, antiphospholipid, CD14, CD 16, CD55, CD59, lipoprotein A, Protein S, JAK-2, D-dimer, ultrasound? Consider the following populations: pregnancy, contraception users, HRT users, preoperative patients, long-haul travel, family history.	10
ADVERSE EFFECTS	
Key question	*See guideline section*
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.	15
INVESTIGATION	
Key question	*See guideline section*
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.	9
9. What diagnostic techniques should be used to diagnose clinically suspected DVT? Consider: duplex scan, venography, ultrasound (compression or duplex), MRI, plethysmography.	9.3
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).	9.4
MANAGEMENT OF VTE	
Key question	*See guideline section*
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.	11
12. In patients with acute severe and non-severe PTE what is the optimal initial management? Consider: thrombolysis, anticoagulants, IVC filter.	11.1

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? a. Renal function, clotting screen, assessment of bleeding risks, full blood count b. Cancer screening.	10
14. Which patients with VTE can be managed successfully in an outpatient setting?	14
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, graduated compression stockings.	12
16. What monitoring is required for patients on anticoagulant therapies? Outcome: warfarin – INR levels; heparins - APTT, anti-Xa.	13

Annex 2

Algorithm for assessing the risk of venous thromboembolism (VTE)

Grampian risk assessment tool



Annex 3

The Geneva score for assessment of probability of PE

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

The Geneva score	
Parameter	**Score** (points)
Age:	
▪ 60-79 years	1
▪ over 80 years	2
Previous DVT or PE	2
Recent surgery within four weeks	3
Heart rate > 100 beats per minute	1
$PaCO_2$ (partial pressure of CO_2 in arterial blood):	
▪ < 35 mmHg	2
▪ 35-39 mmHg	1
PaO_2 (partial pressure of O_2 in arterial blood):	
▪ < 49 mmHg	4
▪ 49-59 mmHg	3
▪ 60-71 mmHg	2
▪ 72-82 mmHg	1
Chest X-ray findings:	
▪ Band atelectasis	1
▪ Elevation of hemidiaphragm	1
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.

Revised Geneva score	
Parameter	**Score** (points)
Age 65 years or over	1
Previous DVT or PE	3
Surgery or fracture within one month	2
Active malignant condition	2
Unilateral lower limb pain	3
Haemoptysis	2
Heart rate:	
▪ 75 to 94 beats per minute	3
▪ 95 or more beats per minute	5
Pain on deep palpation of lower limb and unilateral oedema	4
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 5a

The Wells score or criteria for assessment of suspected DVT

Wells score or criteria: (possible score -2 to 8)

Wells score or criteria	
Criteria	**Score** (points)
1. Active cancer (treatment ongoing or within last six months or palliative)	1
2. Calf swelling >3 cm compared to other calf (measured 10 cm below tibial tuberosity)	1
3. Collateral superficial veins (non-varicose)	1
4. Pitting oedema (greater in the symptomatic leg)	1
5. Swelling of entire leg	1
6. Localised tenderness along distribution of deep venous system	1
7. Paralysis, paresis, or recent plaster cast immobilisation of lower extremities	1
8. Recently bedridden >3 days, or major surgery in past four weeks	1
9. Alternative diagnosis at least as likely as DVT	subtract 2
Interpretation: For evaluation (low v moderate v high)	
Score of 0 or less	low probability of deep vein thrombosis.
Score of 1 or 2	moderate probability of deep vein thrombosis.
Score of 3 or higher	high probability of deep vein thrombosis.

Philip S Wells, David R Anderson, Janis Bormanis, Fred Guy, Michael Mitchell, Lisa Gray, Cathy Clement, K Sue Robinson, Bernard Lewandowski. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. Lancet 1997; 350: 1795–98

Annex 5b

The revised Wells score or criteria for assessment of suspected DVT

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

Wells score or criteria	
Criteria	**Score** (points)
1. Active cancer (treatment within last six months or palliative)	1
2. Calf swelling ≥3 cm compared to asymptomatic calf (measured 10 cm below tibial tuberosity)	1
3. Collateral superficial veins (non-varicose)	1
4. Pitting oedema (confined to symptomatic leg)	1
5. Swelling of entire leg	1
6. Localised tenderness along distribution of deep venous system	1
7. Paralysis, paresis, or recent cast immobilisation of lower extremities	1
8. Recently bedridden ≥3 days, or major surgery requiring regional or general anesthetic in the previous 12 weeks	1
9. Previously documented deep-vein thrombosis	1
10. Alternative diagnosis at least as likely as DVT	subtract 2
Interpretation: For dichotomised evaluation (likely v unlikely)	
Score of 2 or higher	Deep vein thrombosis is “likely”.
Score of less than 2	Deep vein thrombosis is “unlikely”.

Philip S. Wells, M.D., David R. Anderson, M.D., Marc Rodger, M.D., Melissa Forgie, M.D., Clive Kearon, M.D., Ph.D., Jonathan Dreyer, M.D., George Kovacs, M.D., Michael Mitchell, M.D., Bernard Lewandowski, M.D., and Michael J. Kovacs, M.D. Evaluation of d-Dimer in the Diagnosis of Suspected Deep-Vein Thrombosis N Engl J Med 2003;349:1227-35

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]

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