Scottish Intercollegiate Guidelines Network

Prophylaxis of Venous Thromboembolism

A national clinical guideline

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October 2002

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

LEVELS OF EVIDENCE

1^{++}	High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
1^{+}	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews of RCTs, 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, e.g. 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 of RCTs, 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 EPIDEMIOLOGY OF VENOUS THROMBOEMBOLISM

Deep vein thrombosis (DVT) of the lower limbs is a common disease, often asymptomatic, but presenting with clinical symptoms (leg pain or swelling) in about 1 per 1,000 people per year in the general population. Complications include **pulmonary thromboembolism** (PE) and **post-thrombotic leg syndrome** (PLS). DVT has multiple causes (*see Table 1*).

Asymptomatic DVT is defined as DVT detected by screening with ^{125}I fibrinogen scanning, ultrasound, or ascending venography.[1-5]

Symptomatic DVT (leg pain or swelling) results from occlusion of a major leg vein. It requires specific investigation and treatment[6] which in hospitalised patients may delay discharge, or require readmission to hospital.

Pulmonary embolism, which in 90% of cases results from an asymptomatic DVT,[6,7] may present as sudden death, breathlessness, faintness, collapse, or chest pain.[6] **Nonfatal PE** in hospitalised patients may delay discharge, or require readmission to hospital. **Fatal PE** is under-diagnosed, because of the non-specificity of symptoms and signs prior to death, which may be attributed to myocardial infarction, pneumonia, or other pathology. About 10% of hospital deaths (1% of all admissions) were attributable to PE in the UK in one study from the 1980s.[7] More recent studies have continued to highlight the significant contribution of PE to in-hospital mortality,[8-13] especially after emergency surgery when prophylaxis is often omitted.[9]

Post-thrombotic leg syndrome (chronic leg pain, swelling, dermatitis, ulcers) is a consequence of destruction of leg vein valves by DVT. Leg ulcers are observed in 2-10% of patients approximately 10 years after their first symptomatic DVT.[14-18] About 0.2% of the general population have venous leg ulcers.

Venous thromboembolism (VTE) is defined as DVT ± PE.

1.2 RATIONALE FOR PROPHYLAXIS

The risk of VTE is increased tenfold in patients who are hospitalised after trauma, surgery or immobilising medical illness, and also in pregnant and puerperal women. Screening studies for asymptomatic DVT, using contrast venography or radiolabelled fibrinogen scanning, as well as autopsy studies have shown that DVT is common in such patients. In many of these patients, DVT remains asymptomatic but in others it can cause morbidity and mortality.[1,7,19,20] 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.[18-24] Clinical diagnosis is difficult,[6] and treatment with full-dose anticoagulant therapy has risks, especially of bleeding.[6]

There is evidence that routine prophylaxis reduces morbidity, mortality and costs in hospitalised patients at risk of DVT and PE, as highlighted in national and international guidelines.[19-22] In contrast, screening for asymptomatic DVT, and its treatment, are expensive, insensitive and not cost-effective compared to routine prophylaxis in at-risk patients.[19-22]

1.3 DEVELOPMENT AND REVIEW OF THE SIGN GUIDELINE

The need for a national guideline on prophylaxis was highlighted by a study of fatal PE in surgical patients in Scotland up to 1995, which showed that 56% of patients who died of PE did not receive antithrombotic prophylaxis, despite having major risk factors and no contraindications to standard antithrombotic regimens.[8] VTE is probably an escalating public health problem, due to the increasing age of the population.[19,25]

Following publication of the SIGN guideline in 1995,[22] studies have reported high interest from hospital trusts in implementation of the guideline[26] and high compliance with the trust local protocol/guideline.[27-29]

The original SIGN guideline[22] recommended prophylaxis primarily according to efficacy in reducing risk of asymptomatic DVT (detected by routine screening), a widely accepted "surrogate" endpoint frequently employed in randomised clinical trials (RCTs). Further reasons to consider this endpoint in developing the guideline were that asymptomatic DVT is the usual precursor of both fatal PE[7,12] and PLS;[15] and that prophylactic methods which reduce the incidence of asymptomatic DVT also reduce the incidence of symptomatic DVT[30,31] and of symptomatic PE, including fatal PE, to a similar extent.[2-5,30,31]

Since the publication of this guideline,[22] concern has been raised, especially by UK orthopaedic surgeons, as to the appropriateness of routine pharmacological antithrombotic prophylaxis. The validity of asymptomatic DVT as a surrogate endpoint in RCTs has been questioned because of the discrepancy between high incidence of venographic DVT and low risk of clinical outcomes such as death, e.g. in elective hip and knee replacement surgery.[31-39] The risks and benefits of anticoagulant prophylaxis in orthopaedic patients need to be balanced. For instance, low molecular weight heparins (LMWHs) have been associated with an increased risk of vertebral canal haematoma after spinal and epidural block in recent reports from North America.[40-42] Recent analyses of the efficacy of heparin prophylaxis in medical patients with acute myocardial infarction[43] or acute ischaemic stroke,[44] have also raised questions as to the role of routine heparin in addition to routine aspirin therapy in such patients.[6]

1.4 MAJOR CHANGES TO THE GUIDELINE

The revised guideline includes new evidence, systematic reviews, and consensus statements published from 1994-2001. In addition:

Patient groups are no longer categorised as high, moderate and low risk.[22] Instead:

- where possible the incidences of asymptomatic and symptomatic DVT and PE and mortality in patients given no antithrombotic prophylaxis are defined. These baseline incidences of thromboembolic risk are established from observational studies, as well as control groups in randomised trials (which constitute a selected population)[45]
- The efficacy of prophylaxis on a range of outcome measures is considered, including

  1. asymptomatic DVT
  2. symptomatic VTE
  3. total mortality (multifactorial and hence insensitive to change in only one component)

- The balance of average bleeding risk versus average reduction in thromboembolic morbidity and mortality is considered.

1.5 HOW TO USE THE GUIDELINE

The guideline begins by identifying patient groups at risk of VTE (*section 2*) and describing the available methods of prophylaxis (*section 3*), with general recommendations about efficacy, safety, and how they should be used. Appropriate methods of prophylaxis for specific patient groups are considered in subsequent sections.

All recommendations apply only in the absence of contraindications.

This guideline is not intended to be construed or to serve as a standard of medical 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. The ultimate judgement regarding a particular clinical procedure or treatment plan must be made in light of the clinical data presented by the patient and the diagnostic and treatment options available. However, it is advised 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.

1.6 DIFFERENCES FROM OTHER NATIONAL GUIDELINES

This guideline differs significantly from the most recent North American guideline[19] in recommending aspirin as an effective prophylaxis in surgical patients (*section 3.3*). The North American guideline[19] does not recommend aspirin because other prophylactic methods (e.g. heparins) are more effective in reducing asymptomatic DVT. The SIGN guideline development group notes that aspirin is as effective as heparins in reducing the risk of fatal pulmonary embolism, which is the most clinically relevant endpoint in prophylaxis of VTE. Both aspirin (*Table 3*) and heparins (*Table 5)* reduce the overall absolute risk of fatal PE in surgical patients from 0.6% to 0.2%. Furthermore, aspirin carries a lower relative risk of major bleeding *(1.24, 95% CI 1.12 - 1.37)* compared to heparin *(1.75, 95% CI 1.43-2.01: Tables 3 and 5).*

2 Risk factors for venous thromboembolism

D **All patients admitted to hospital for major trauma** *(e.g. fracture causing immobilisation)*, **major surgery** *(e.g. duration over 30 mins)*, **or acute medical illness** *(e.g. likely to require bed rest for three days or more)* **should be individually assessed for risk of VTE.**

D **Assessment of individual risk should include:**

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

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

D **Within local guidelines, individual prophylaxis should be chosen according to the balance of efficacy and risks** *(especially bleeding)*, **and the patient's preferences.**

D **Routine screening for thrombophilias prior to risk situations such as prescription of oral contraceptives or hormone replacement therapy, pregnancy, or elective major surgery is not recommended.**[61,62]

Table 1: Risk factors for venous thromboembolism[1,46,54,55,59,60]

Age[1, 46-51]	Exponential increase in risk with age. In the general population - <40 years annual risk 1/10,000 60-69 years annual risk 1/1,000 >80 years annual risk 1/100 May reflect immobility and coagulation activation[52,53]
Obesity[1,46,50,51,54-56]	3 × risk if obese (body mass index ≥30 kg/m^2) May reflect immobility and coagulation activation[52,53]
Varicose veins[50,51]	1.5 × risk after major general / orthopaedic surgery But low risk after varicose vein surgery[15,57]
Previous VTE[1,17]	Recurrence rate 5% / year, increased by surgery
Thrombophilias[58-62]	Low coagulation inhibitors (antithrombin, protein C or S) Activated protein C resistance (e.g. factor V Leiden) High coagulation factors (I, II, VIII, IX, XI) Antiphospholipid syndrome High homocysteine
Other thrombotic states[59,60]	Malignancy 7 × risk Heart failure Recent myocardial infarction / stroke Severe infection Inflammatory bowel disease, nephrotic syndrome Polycythaemia, paraproteinaemia Bechet's disease, paroxysmal nocturnal haemoglobinuria
Hormone therapy	Oral combined contraceptives, HRT, raloxifene, tamoxifen[63,64] 3 × risk High-dose progestogens 6 × risk *(see section 10)*
Pregnancy, puerperium	10 × risk *(see section 9)*
Immobility	Bedrest >3 days, plaster cast *(see section 5)*, paralysis *(see sections 5 &7)* 10 × risk; increases with duration
Prolonged travel	*see section 11*
Hospitalisation	Acute trauma, acute illness, surgery, 10 × risk
Anaesthesia	2× general vs spinal / epidural[65]

3 Methods of prophylaxis

This section discusses the interventions which reduce the incidence of VTE and provides generic recommendations for their use. Recommendations for specific patient groups or circumstances are made in following sections. The prophylactic effect of spinal or epidural anaesthesia is reviewed in section 7.

3.1 GENERAL MEASURES

3.1.1 MOBILISATION AND LEG EXERCISES

Immobility increases the risk of DVT about tenfold.[46,59] A meta-analysis of RCTs of bed rest for several medical conditions found no evidence of benefit of bed rest for any condition.[66] In immobilised patients, leg exercises reduce venous stasis and should be encouraged.[1,15] 2+ 1+

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

3.1.2 HYDRATION, HAEMODILUTION AND VENESECTION

Haemoconcentration increases blood viscosity and reduces blood flow, especially in the deep veins of the leg in immobile patients.[67] 4

D **Adequate hydration should be ensured in immobilised patients.**

There is insufficient evidence regarding the balance of risks and benefits to support recommendations about the use of either haemodilution,[68,69] or venesection *(apart from primary proliferative polycythaemia)*.[70]

3.2 MECHANICAL METHODS

Mechanical methods of antithrombotic prophylaxis increase mean blood flow velocity in leg veins and reduce venous stasis. They include:

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

There are few trials of mechanical methods in medical patients. Unlike pharmacological methods, mechanical methods do not increase the risk of bleeding and may be preferred in patients in whom bleeding risks may outweigh the antithrombotic efficacy of pharmacological prophylaxis. Mechanical methods are contraindicated in patients at risk of ischaemic skin necrosis, e.g. those with critical limb ischaemia or severe peripheral neuropathy.[71,72] Cross-infection is a risk when devices are re-used.

☑ Adequate precautions must be taken to prevent cross-infection when mechanical devices are re-used by subsequent patients (*see manufacturer's instructions*).

3.2.1 GRADUATED ELASTIC COMPRESSION STOCKINGS

A meta-analysis of RCTs of GECS in prevention of asymptomatic DVT observed that asymptomatic DVT occurred in 8.6% of active patients compared to 27% of controls *(OR 0.34, 95% CI 0.25, 0.46)*.[72] These results are consistent with an earlier meta-analysis,[73] and with historical reports of efficacy of elastic stockings in PE prophylaxis.[74,75] 1+

A **GECS are effective in prophylaxis of asymptomatic DVT and symptomatic PE in surgical patients.**

GECS are commercially available as both below-knee and above-knee stockings. Most controlled trials have used above-knee stockings.[1,19,20,72-74] Studies comparing above-knee and below-knee stockings have been too small to determine whether or not they are equally effective.[76-79] Hence

current evidence supports the preferential use of above-knee stockings unless contraindicated *(e.g. thigh circumference >81 cm, incontinence)*. A large study of above-knee versus below-knee stockings versus no stockings in stroke patients (CLOTS) is currently in progress.

☑ Above-knee GECS are preferred to below-knee stockings for prophylaxis of DVT.

Table 2 summarises contraindications and cautions for GECS. It has been suggested that 15-20% of patients cannot effectively wear GECS because of unusual limb size or shape.[19] An educational programme for appropriate use of GECS was found to be useful in one Scottish acute trust.[28]

Table 2: Contraindications and cautions for use of GECS

CONTRAINDICATIONS	CAUTIONS
– Massive leg oedema – Pulmonary oedema (e.g. heart failure) – Severe peripheral arterial disease – Severe peripheral neuropathy – Major leg deformity – Dermatitis	– Select correct size – Apply carefully, aligning toe hole under toe[3] – Check fitting daily for change in leg circumference – Do not fold down – Remove daily for no more than 30 minutes

3.2.2 GECS PLUS PHARMACOLOGICAL PROPHYLAXIS OR INTERMITTENT PNEUMATIC COMPRESSION

A meta-analysis of RCTs[72] and the preliminary results of another meta-analysis found that GECS combined with pharmacological prophylaxis or IPC increases efficacy in reducing the incidence of asymptomatic DVT in surgical patients (OR 0.24; CI 95 0.15-0.37). 1+

A multicentre observational study of elective hip replacement patients found that the combination of GECS with pharmacological prophylaxis appeared to be more effective in reduction of asymptomatic DVT than pharmacological prophylaxis alone.[51] 2+

Increased efficacy may reflect a combined effect on venous stasis and hypercoagulability. The combined approach is currently commonly employed in Scotland,[29] and the rest of the UK.[80]

A **GECS may be combined with pharmacological prophylaxis or IPC in surgical patients, to increase efficacy in reducing the incidence of DVT.**

3.2.3 INTERMITTENT PNEUMATIC COMPRESSION

IPC devices periodically compress the calf and/or thigh muscles of the leg *(inflation pressures 35-40 mmHg at about 10s/min)*,[19,20] and stimulate fibrinolysis.[81] Compression devices are usually applied immediately before or during surgery and are often replaced by GECS following surgery as they can cause discomfort in the conscious patient.

Pooled analyses of trials of IPC in prevention of asymptomatic DVT after non-orthopaedic surgery showed a relative risk reduction of around 68%.[20] Similar results have been demonstrated following orthopaedic *(mostly elective hip)* surgery.[20] A recent observational study found that IPC reduced the risk of re-hospitalisation for symptomatic VTE after elective hip surgery.[82] One RCT observed that the addition of IPC devices to unfractionated heparin (UFH) reduced the risk of PE following cardiac surgery from 4% to 1.5% *(risk reduction 62%)*.[83] 1+, 2+

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

A **IPC plus low dose heparin reduces the risk of symptomatic PE in cardiac surgery patients.**

3.2.4 MECHANICAL FOOT PUMPS AND FOOT IMPULSE TECHNOLOGY

The A-V impulse system foot pump has been developed to provide mechanical prophylaxis in patients who are unable to weight bear and has only been used in orthopaedic surgery. RCT data suggest efficacy in prevention of asymptomatic DVT.[84-93] 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.[92] 1+

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

3.3 ANTIPLATELET AGENTS (ASPIRIN)

3.3.1 EFFICACY AND SAFETY IN SURGICAL PATIENTS (*see Table 3*)

A meta-analysis of 53 RCTs of antiplatelet agents (usually aspirin) in prophylaxis of VTE in general or orthopaedic surgery reported significant reductions in risks of asymptomatic DVT (26% vs. 35%), pulmonary embolism (0.6% vs. 1.6%) and fatal PE (0.2% vs. 0.6%); with a non-significant trend to lower mortality and a significant increase in major bleeding.[3,4] These results were confirmed by a further large trial, the Pulmonary Embolism Prevention (PEP) Trial.[31] In this study, 13,356 patients undergoing surgery for hip fracture and 4,088 patients undergoing elective hip arthroplasty were randomised to aspirin *(160 mg daily, started preoperatively and continued for 35 days)* or placebo; in addition to "any other thromboprophylaxis thought necessary". Patients were not screened for asymptomatic DVT. Combining the results from all trials revealed no significant reduction in total mortality *(3.9% vs. 4.0%)*, while confirming a significant increase in major bleeding *(7.7% vs. 6.2%)* which was similar to the reduction in symptomatic DVT or PE *(see Table 3)*. There was a significant reduction in fatal PE *(0.2% vs. 0.6%; NNT 250)*. 1++

3.3.2 EFFICACY AND SAFETY IN MEDICAL PATIENTS

The efficacy of aspirin in reduction of total cardiovascular events (myocardial infarction; MI, stroke, PE, cardiovascular death) is now clearly established in acute MI and in acute ischaemic stroke[6] and outweighs the increased risk of bleeding (*see section 8*).

3.3.3 DOSE OF ASPIRIN, CONTRAINDICATIONS AND CAUTIONS

The PEP trial used aspirin 160 mg/day.[31] The standard preparations available in the UK are 75 mg and 300 mg, hence 150 mg is recommended. Aspirin 75-300 mg/day is licensed in the UK for prevention of cardiovascular events in acute MI and in acute ischaemic stroke but not for VTE prophylaxis in surgical patients *(see the SIGN guideline on antithrombotic therapy)*.[6]

A **Aspirin 150 mg/day started preoperatively and continued for 35 days is effective prophylaxis of asymptomatic and symptomatic VTE in surgical patients. Aspirin also reduces cardiovascular events in acute MI and acute ischaemic stroke.**

Cautions and contraindications to aspirin are summarised in Table 4.

Table 3: Summary of meta-analyses of RCTs of antiplatelet drugs (usually aspirin) in prophylaxis of VTE in surgical patients[3,4,31]

Patient group	**Asymptomatic DVT**		**Symptomatic DVT**		**All PE**		**Fatal PE**		**Total Mortality**		**Major bleeding**	
	Active	*Control*	*Active*	*Control*	*Active*	*Control*	*Active*	*Control*	*Active*	*Control*	*Active*	*Control*
Non-orthopaedic surgery	278/1434	396/1459			16/3408	58/3419	2/3408	15/3419	32/3408	29/3419		
	(19.4%)	(27.1%)			(0.5%)	(1.7%)	(0.06%)	(0.4%)	(0.9%)	(0.8%)		
Elective orthopaedic surgery	160/427	232/436			23/2576	39/2578	1/2576	4/2578	9/2576	13/2578		
	(37.5%)	(53.2%)			(0.9%)	(1.5%)	(0.04%)	(0.15%)	(0.35%)	(0.5%)		
Traumatic orthopaedic surgery	163/454	189/444	69/6679	97/6677	60/7183	115/9171	27/7183	60/7171	470/7183	488/7171		
	(35.9%)	(41.9%)	(1.0%)	(1.5%)	(0.8%)	(1.6%)	(0.38%)	(0.84%)	(6.5%)	(6.8%)		
All surgery	601/2315	814/2339	69/6679	97/6677	99/13167	212/13168	30/14067	79/13168	511/13167	530/13168	845/10995	684/11024
	(26.0%)	(34.8%)	(1.0%)	(1.5%)	(0.6%)	(1.6%)	(0.2%)	(0.6%)	(3.9%)	(4.0%)	(7.7%)	(6.2%)
Relative risk (95% CI)												
Non-orthopaedic surgery	0.71 (0.62-0.82)				0.28 (0.16-0.48)							
Orthopaedic surgery	0.77 (0.69-0.86)		0.71 (0.52-0.97)		0.65 (0.50-0.85)		0.44 (0.28-0.68)					
Total surgery	0.75 (0.68-0.82)		0.71 (0.52-0.97)		0.47 (0.37-0.59)		0.36 (0.23-0.54)		0.96 (0.86-1.09)		1.24 (1.12-1.37)	

Table 4: Contraindications and cautions for aspirin and heparins in prophylaxis of VTE

CONTRAINDICATIONS	CAUTIONS
▪ Uncorrected bleeding disorders, e.g. – haemophilias – oral anticoagulants – platelet count <70x10^9/L ▪ Bleeding or potentially bleeding lesions – oesophageal varices – active peptic ulcer – recent (3 months) GI or intracranial bleed – intracranial aneurysm or angioma ▪ Allergy ▪ Heparin associated thrombocytopenia or thrombosis (heparin)	▪ Asthma (aspirin) ▪ Severe liver impairment, alcoholism ▪ Severe kidney impairment ▪ Major trauma or surgery to brain, eye or spinal cord *(see section 4)* ▪ Spinal or epidural block *(see section 7)* ▪ Anaemia (Hb <10g/dl)

Aspirin is commonly used to prevent MI in the older population.[6] 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.[3,4,31] Stopping aspirin in such patients prior to giving perioperative heparin will not reduce perioperative bleeding (because the antiplatelet effect of aspirin lasts a week) and carries the risk that aspirin may not be re-prescribed after surgery. In general therefore, perioperative low-dose heparin is not contraindicated in patients already taking aspirin.

3.4 UNFRACTIONATED AND LOW MOLECULAR WEIGHT HEPARINS

Unfractionated heparin (UFH) and several LMWHs (dalteparin, enoxaparin, reviparin and tinzaparin) are currently licensed in the UK for prophylaxis of VTE.[94-96] They vary in their manufacture, chemistry and biology, but it is not clear whether or not these characteristics affect clinical efficacy or safety equivalence.[97]

For prophylaxis of VTE, heparins are usually given subcutaneously, in lower doses than are used for the treatment of established thromboembolism. In such doses, they have little effect on the activated partial thromboplastin time (APTT). LMWHs have a longer half-life than UFH, so can be given as once daily subcutaneous injections for prophylaxis, compared to 8-12 hourly for UFH. Heparin prophylaxis is usually given for at least five days (the minimum duration of prophylaxis in RCTs) or until hospital discharge if earlier. Prolonged prophylaxis may be indicated in patients with continued illness and immobility, and in orthopaedic patients (*see section 5.1.3*).

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

3.4.1 EFFICACY AND SAFETY OF UFH IN SURGICAL PATIENTS

A meta-analysis of RCTs[2] (including a large trial[30]) found that low-dose subcutaneous UFH significantly reduces the incidence of asymptomatic DVT, symptomatic DVT and PE, fatal PE, and total mortality. A significant increase in major bleeding (from about 4% to 6%) was also observed; however there was no increase in fatal bleeding (n = 8 vs. n = 6) (*see Table 5*). 1++

Table 5: Summary of meta-analyses of RCTs of low-dose subcutaneous heparins in prophylaxis of VTE in surgical patients

Intervention and Group	Asymptomatic DVT		Symptomatic DVT[33]		Symptomatic PE		Fatal PE		Total Mortality		Major bleeding	
	Active	Control	Active	Control	Active	Control	Active	Control	Active	Control	Active	Control
UFH vs. control[2]												
non-orthopaedic	373/4095 (9.1%)	813/3525 (23.1%)			72/7188 (1.0%)	173/6574 (2.6%)	14/6568 (0.2%)	40/6631 (0.6%)	214/5627 (3.8%)	260/5696 (4.6%)	400/6484 (6.2%)	229/5980 (3.8%)
elective orthopaedic	78/371 (21%)	171/368 (46.5%)			43/450 (9.6%)	42/437 (9.6%)	0/498 (0%)	8/489 (1.6%)	0/498 (0%)	8/489 (1.6%)	16/336 (4.8%)	9/322 (2.8%)
traumatic orthopaedic	73/264 (27.7%)	123/251 (49.9%)			9/241 (3.7%)	7/228 (3.1%)	5/241 (2.0%)	7/228 (3.1%)	22/241 (9.1%)	16/241 (6.6%)	4/106 (3.8%)	6/94 (6.4%)
total orthopaedic	151/635 (23.8%)	294/619 (47.5%)			52/691 (7.5%)	49/665 (7.3%)	5/739 (0.7%)	15/717 (2.1%)	22/739 (3.0%)	24/730 (3.3%)	19/543 (3.5%)	15/524 (2.8%)
Total	524/4730 (11.1%)	1107/4144 (26.7%)	33/2045 (1.6%)	122/2076 (5.9%)	124/7879 (1.6%)	202/7910 (2.8%)	19/7307 (0.3%)	55/6777 (0.8%)	236/6366 (3.7%)	284/6426 (4.4%)	419/7027 (6.0%)	244/6504 (3.8%)
LMWH vs. control[98,99]												
non-orthopaedic	4/145 (2.8%)	17/138 (12.3%)			(see text)		2/2399 (0.08%)	4/2398 (0.17%)	9/2349 (0.38%)	20/2348 (0.85%)	123/2247 (5.5%)	48/2251 (2.1%)
orthopaedic	87/348 (25%)	169/349 (48%)			3/495 (0.6%)	6/501 (1.2%)	0/495 (0%)	3/501 (0.6%)	0/495 (1.8%)	9/501 (1.8%)	13/93 (14.0%)	7/97 (7.2%)
Total	91/493 (18.5%)	186/487 (38.2%)					2/2894 (0.07%)	7/2899 (0.24%)	18/2844 (0.6%)	29/2849 (1.0%)	136/2340 (5.8%)	55/2348 (2.3%)
UFH or LMWH vs. control[2,98,99]												
non-orthopaedic	377/4240 (8.9%)	830/3663 (22.7%)			72/7188 (1.0%)	173/6574 (2.6%)	16/8967 (0.18%)	44/9029 (0.49%)	223/7976 (2.8%)	280/8044 (3.5%)	523/8731 (6.0%)	277/8231 (3.4%)
orthopaedic	238/983 (28.8%)	463/968 (47.8%)			55/1186 (4.6%)	55/1166 (4.7%)	5/1234 (0.4%)	18/1218 (1.5%)	31/1234 (2.5%)	33/1231 (2.7%)	32/636 (5.0%)	22/621 (3.5%)
Total	615/5223 (11.8%)	1293/4631 (27.9%)	33/2045 (1.6%)	122/2076 (5.9%)	127/8374 (1.5%)	228/7740 (2.9%)	21/10201 (0.2%)	62/10247 (0.6%)	254/9210 (2.8%)	313/9275 (3.4%)	555/9367 (5.9%)	299/8852 (3.4%)
Relative Risk (95% CI)												
non-orthopaedic	0.39 (0.35-0.44)				0.38 (0.29-0.50)		0.37 (0.21-0.65)		0.80 (0.68-0.96)		1.78 (1.54-2.05)	
orthopaedic	0.51 (0.45-0.58)				0.98 (0.68-1.42)		0.27 (0.10-0.74)		0.94 (0.58-1.52)		1.42 (0.84-2.42)	
Total	0.42 (0.39-0.46)		0.49 (0.34-0.71)		0.52 (0.42-0.64)		0.34 (0.21-0.56)		0.82 (0.69-0.96)		1.75 (1.53-2.01)	

3.4.2 EFFICACY AND SAFETY OF LMWHS IN SURGICAL PATIENTS

Meta-analyses of RCTs have shown that subcutaneous LMWHs have similar prophylactic efficacy and risk of bleeding to UFH (*see Table 5*).[98,99] Once UFH had been shown to significantly reduce both fatal postoperative PE and mortality,[2,30] 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.

Combining the results of all RCTs of UFH or LMWH versus controls (*Table 5*), there was a significant reduction in fatal PE which was very similar to that with aspirin prophylaxis (0.2% vs 0.6%; NNT 250). Heparin prophylaxis was more likely to increase major bleeding compared to aspirin; but unlike aspirin reduced total mortality in non-orthopaedic surgery (2.8% vs. 3.5%; NNT 150) but not in orthopaedic surgery. 1++

3.4.3 EFFICACY AND SAFETY OF UFH AND LMWHS IN MEDICAL PATIENTS

A meta-analysis of RCTs in general medical patients[5] showed similar reductions in asymptomatic DVT and symptomatic PE to those in surgical patients *(see section 8)*. 1++

A **Subcutaneous low dose heparin (UFH or LMWH) is effective in prophylaxis of asymptomatic and symptomatic VTE in surgical and medical patients.**

3.4.4 ADMINISTRATION, DOSAGE AND COAGULATION MONITORING

Cautions and contraindications to heparin prophylaxis are summarised in Table 4 (see also section 7).

When administered for thromboprophylaxis, both UFH and LMWH are given subcutaneously. The risk of wound haematomas can be minimised by avoiding injection sites close to wounds.[30] The dose of UFH is 5,000 IU 8-12 hourly or 7,500 IU 12 hourly. Consult the appropriate manufacturer's data sheet for the dose of LMWH.

In general, monitoring of the anticoagulant effect of low dose UFH or LMWH is not required. As LMWHs have little effect on the APTT, plasma anti-Xa activity should be measured instead.[96,100] Monitoring of plasma APTT or anti-Xa levels should be performed:

- in high-risk pregnancy *(see section 9)*
- if there are complications such as haemorrhage or accidental overdose
- in patients with renal failure given higher (therapeutic) doses of LMWH.[100]

See the SIGN guideline on antithrombotic therapy.[6]

3.4.5 MONITORING PLATELET COUNT

Clinically important heparin associated thrombocytopenia (HAT) is immune mediated and usually occurs between five and 10 days (up to 20 days) after initiation of heparin. It can occur at any dose of either UFH or LMWH. LMWH is less likely than UFH to be associated with antiplatelet antibodies. HAT should be considered in any patient whose platelet count falls by 50% or more. It may present as, or be complicated by, thrombosis.[94, 96] 2+

Lepirudin was shown in an RCT to be more effective than dextran.[96] 1+

B **In order to detect heparin associated thrombocytopenia, a baseline platelet count should be obtained and platelet count monitored in all patients receiving heparins for five days or more.**

A **Heparin should be stopped if thrombocytopenia develops, or if the platelet count drops by 50% or more. Possible alternative initial antithrombotics include lepirudin.[96]**

B **Warfarin is a suitable alternative antithrombotic to heparin following heparin associated thrombocytopenia, once the platelet count has recovered to >100 x 10^9/L.[96]**

3.4.6 MONITORING BONE DENSITY

Prolonged *(over 12 weeks)* use of prophylactic heparin, e.g. in pregnancy, has been associated with increased risk of osteoporosis and bone fractures.[96] Long term LMWH may carry a lower risk of bone fractures than UFH in older patients.[101] 2++

3.4.7 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.[94,96] Protamine is less effective in reversal of LMWH anticoagulation *(consult manufacturer's data sheet)*.

3.5 HEPARINOIDS

The heparinoid, **danaparoid**, is effective in prophylaxis of DVT in patients undergoing general or orthopaedic surgery.[102] Provided there is no evidence of cross-reactivity, it is also effective in treatment of patients with heparin associated thrombocytopenia[94,96,103] and can be used as short-term prophylaxis in patients with a history of this condition.[94]

3.6 HIRUDINS

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

Desirudin administered subcutaneously has been found to be safe and superior to UFH[104,105] or to the LMWH, enoxaparin,[106] in the prevention of asymptomatic deep vein thrombosis after total hip or knee replacement. There are no data to indicate that it is more effective in reduction of either PE or mortality. It is not presently licensed in the UK.

Lepirudin is effective in treatment of patients with VTE in patients with heparin associated thrombocytopenia.[96]

3.7 PENTASACCHARIDES

The synthetic pentasaccharide **fondaparinux** is a highly selective, indirect inhibitor of activated factor Xa. A meta-analysis of trials recruiting orthopaedic patients has shown that it was more effective than LMWH in reduction of asymptomatic DVT.[107] It was not more effective in reduction of symptomatic DVT, PE or mortality.

3.8 ORAL ANTICOAGULANTS

Warfarin is effective in prophylaxis of asymptomatic DVT.[19,108] However, it is not widely used for this indication in the UK[27,80] because its use requires daily monitoring by the International Normalised Ratio (INR) of the prothrombin time, and because it increases the risk of bleeding after trauma or surgery,[6,19,20] as well as after spinal or epidural anaesthesia (*see section 7)*.

Contraindications and cautions include:[6]

- bleeding disorders *(see Table 4)*
- bleeding or potentially bleeding lesions *(see Table 4)*
- spinal or epidural anaesthesia *(see section 7)*
- pregnancy, due to fetal toxicity *(see section 9)*.

In patients on long term oral anticoagulant therapy (e.g. for atrial fibrillation or heart valve disease/ prosthesis) who are immobilised by illness, trauma or surgery, continuation of oral anticoagulants may be appropriate prophylaxis of VTE. However, the INR should be checked and the dose of anticoagulant adjusted according to the perceived balance of risks of thrombosis and bleeding, especially after trauma or surgery.[6] 4

D **In patients receiving long term oral anticoagulant therapy who are immobilised by illness, trauma or surgery, continuation of oral anticoagulants** (target INR 2.0-2.5) **may be appropriate prophylaxis.**

Where the risks of bleeding during or after surgery give rise to concern, oral anticoagulant therapy may be discontinued pre-operatively provided that alternative, effective prophylaxis *(e.g. the combination of UFH or LMWH with mechanical prophylaxis)* is instituted once the INR is less than 2.[6] 4

D **The combination of UFH or LMWH with mechanical prophylaxis may be an effective alternative to continuing oral anticoagulants in selected surgical patients.**

3.9 DEXTRANS

Intravenous dextrans appear less effective than heparins in prophylaxis of asymptomatic DVT, but may be equally effective in prophylaxis of PE.[19] However, dextrans are not widely used in the UK[27,80] because of cumbersome administration and adverse effects including allergic reactions *(rarely anaphylaxis)*, bleeding, and fluid overload (especially in patients with renal or cardiac insufficiency).[108]

☑ 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.[109] Thus, dextrans should be avoided peripartum.

☑ Dextrans should be avoided peripartum.

4 General and gynaecological surgery

4.1 RISK OF VTE

Patients undergoing major (e.g. duration over 30 minutes) general or gynaecological surgery, who are aged 40 years or over, or who have other risk factors *(see Table 1)* have a significant risk of both asymptomatic and symptomatic VTE. The risk of VTE increases with the number of risk factors.

In the absence of specific thromboprophylaxis, the average risk of VTE endpoints in observational studies of such patients is as follows *(see Tables 3 and 5)*:[1-3,19,20,30,110]

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

In many of these studies patients were screened for asymptomatic DVT *(using radiolabelled fibrinogen scanning or venography)* and some patients with asymptomatic DVT were treated with full-dose anticoagulants, resulting in an under-estimate of the incidences of proximal DVT and of PE.

Most trials of antithrombotic prophylaxis in surgical patients have been performed in general *(mainly abdominal)* and gynaecological surgery.[1,3,19,20,30,110]

4.2 HEPARINS

4.2.1 UNFRACTIONATED HEPARIN

In patients undergoing major surgery, meta-analyses of controlled trials,[2,110] have shown that subcutaneous low-dose UFH *(5,000 IU, 8-12 hourly)* is effective in reducing the risks of DVT and PE, as well as mortality *(Table 5)*. The large International Multicentre Trial also observed reductions in the need for full-dose anticoagulant treatment for symptomatic DVT or PE.[30] 1++

Adverse effects include an increase in the risk of wound haematomas *(from 3.8% to 6.2%, see Table 5)*.[1] However, this can be minimised by avoiding subcutaneous injection near to wounds.

4.2.2 LOW MOLECULAR WEIGHT HEPARINS

Due to the ethical problems of using untreated control groups in trials after the demonstration that UFH was effective in reducing PE and mortality,[2,110] most studies of LMWH have used UFH as the control intervention. Two meta-analyses, published since the previous version of this guideline, concluded that there is no difference between LMWH and UFH in efficacy for thromboprophylaxis against DVT or PE in general surgery, nor is there any difference in increased risk of bleeding[98,99] *(see Table 5)*. 1++

An RCT reported only in abstract[111] also found no difference in the rate of fatal PE or bleeding when comparing a LMWH with UFH in 23,078 patients undergoing general or orthopaedic surgery.

LMWHs have two advantages over UFH[94,112]

(1) they can be administered once daily (saving staff time)

(2) they are less likely to cause heparin-associated thrombocytopenia.

LMWHs are more expensive than UFH. Certoparin, dalteparin, enoxaparin, reviparin and tinzaparin are currently licensed for DVT prophylaxis in non-orthopaedic surgery.[94] Their relative efficacy has recently been reviewed.[97]

A **The preferred methods of prophylaxis** *(because they reduce mortality as well as fatal PE)* **in patients undergoing major general or gynaecological surgery who are at significant risk of VTE are:**

subcutaneous low-dose UFH *(5,000 IU, 8-12 hourly)*

or

subcutaneous LMWH *(dose as per manufacturer's instructions)*.

4.3 MECHANICAL METHODS

4.3.1 GRADUATED ELASTIC COMPRESSION STOCKINGS

Above-knee GECS appear similarly effective to UFH or LMWH in prophylaxis of asymptomatic DVT in patients undergoing general or gynaecological surgery *(see section 3.2.1)*. They may also reduce the risk of symptomatic PE, but this awaits confirmation. Their effect on mortality is unknown. 1+

A **In patients undergoing major general or gynaecological surgery GECS can be substituted for UFH or LMWH when these agents are contraindicated.**

In patients undergoing general or gynaecological surgery the addition of above-knee GECS to UFH or LMWH increases the efficacy of prophylaxis against asymptomatic DVT *(see section 3.2.1)*.[72] The addition of GECS to UFH or LMWH should therefore be considered in patients at a significantly increased risk of VTE, e.g. in patients with multiple risk factors such as cancer. 1++

A **GECS can be combined with UFH or LMWH in patients undergoing general or gynaecological surgery who are at high risk due to the presence of multiple risk factors.**

4.3.2 INTERMITTENT PNEUMATIC COMPRESSION

There is evidence that IPC is as effective as UFH or LMWH in prophylaxis of asymptomatic DVT.[19] IPC also reduces the risk of PE in cardiac surgery.[83] 1+

When IPC is discontinued mechanical prophylaxis is usually continued with GECS.

A **In patients undergoing major general or gynaecological surgery, IPC followed by above-knee GECS can be substituted for UFH or LMWH when these agents are contraindicated.**

4.4 ANTIPLATELET DRUGS (ASPIRIN)

Antiplatelet therapy is less effective than other agents in prophylaxis of asymptomatic DVT after major general or gynaecological surgery *(risk reduction 37%)*, although a meta-analysis suggested that it may be similarly effective in prevention of PE *(risk reduction 71%, see Table 3)*.[3,4] This is confirmed by the PEP study in orthopaedic patients.[31] There is no evidence for a reduction in total mortality with aspirin, which increased the risk of bleeding *(usually wound haematoma) from 5.6% to 7.8% (Table 3)*. Oral *(or nasogastric or rectal)* antiplatelet agents may not be practical immediately prior to general or gynaecological surgery. For these reasons, antiplatelet agents should be reserved for patients in whom UFH or LMWH are contraindicated. 1++

A **Aspirin** *(150 mg/day orally, rectally or by nasogastric tube)* **is an alternative to UFH or LMWH when these agents are contraindicated in patients undergoing major general or gynaecological surgery who are at significant risk of VTE.**

Although no studies of combined prophylaxis were identified, in view of the limited efficacy of aspirin in prevention of asymptomatic DVT, its combination with IPC/GECS may be logical in patients in whom UFH or LMWH are contraindicated.

There is some evidence to suggest that the combination of antiplatelet drugs with UFH or LMWH may be more effective in prophylaxis of PE than either agent alone[2,3,31] but the combination may also increase the risk of bleeding. Since the combined use of aspirin and heparin is not yet

supported by reliable evidence, the balance of risk and benefit remains unclear. As discussed in section 3.3.3, perioperative low dose heparin is not contraindicated in patients already taking aspirin.

4.5 DEXTRANS

Intravenous dextran 40 or 70 is less effective than other agents in prophylaxis of asymptomatic DVT after major general or gynaecological surgery, but may be similarly effective in prevention of PE *(see section 3.9)*. It also carries a risk of allergic reactions and anaphylaxis. It may be considered as alternative prophylaxis of VTE in patients undergoing major general or gynaecological surgery who are at high risk.[19] 1+

A **Intravenous dextran 40 or 70 is a possible alternative prophylaxis of VTE in high risk patients undergoing major general or gynaecological surgery.**

4.6 ORAL ANTICOAGULANTS

Warfarin is rarely used for prophylaxis of postoperative VTE due to the increased risk of bleeding and need for regular monitoring.

In patients who are on long term oral anticoagulant therapy *(e.g. for atrial fibrillation or heart valve disease/prosthesis)* and who are immobilised by illness, trauma or surgery, continuation of oral anticoagulants may be appropriate prophylaxis *(see section 3.8)*. 4

5 Orthopaedic surgery and trauma

The pilot SIGN guideline,[22] considering published evidence up to early 1994, identified major elective *(e.g. total hip or knee replacement)* or traumatic *(e.g. hip fracture)* orthopaedic surgery as "high risk", for both asymptomatic DVT *(incidence 40-80%)* and fatal PE *(incidence 1-10%)* in the absence of prophylaxis. As discussed in section 1.3, the recent literature has established that fatal PE is uncommon after total hip or knee replacement in the absence of routine anticoagulant prophylaxis.[113]

5.1 TOTAL HIP OR KNEE REPLACEMENT

Table 6 combines data from control groups *(placebo injections or no specific prophylaxis)* in meta-analyses of randomised trials of antiplatelet drugs *(Table 3)* or low-dose subcutaneous heparins *(Table 5)* with recent data from UK cohort studies in major elective orthopaedic surgery *(total hip or knee replacement)*. Without specific anticoagulant prophylaxis, there is a high incidence of asymptomatic DVT *(50% detected by routine venography 7-14 days after surgery)* at the site of surgery *(femoral vein at hip replacement, popliteal vein at knee replacement)* and a significant incidence of nonfatal, clinical DVT and PE *(up to 5% in hip replacement; up to 14% in knee replacement)*. The overall risk of fatal pulmonary embolism is about 0.4%*(95% CI 0.1-1.0%)*.[113] These risks of clinical and fatal VTE are similar to those in major general or gynaecological surgery *(Tables 3,5 and 6)*, despite the higher incidence of asymptomatic DVT in major orthopaedic surgery *(total DVT 50%; proximal DVT 16%)*.[114]

Recent data suggests that total mortality after total hip or knee replacement in the absence of pharmacological prophylaxis may be lower than the estimate from the control groups in antiplatelet or heparin trials *(1% in Table 6)*, at 0.3%.[113,114] Obviously the incidence of fatal PE must be lower than the incidence of total mortality.[114]

More randomised trials have been performed in total hip replacement compared to total knee replacement. The effects of prophylaxis appear similar in both groups of patients and have been combined as "major elective orthopaedic surgery" in meta-analyses *(Tables 4-6)*, and in this guideline. Detailed references are given in recent reviews.[19,20,113] The Scottish national arthroplasty register may provide additional information on VTE risk and prophylaxis in the future.

☑ All patients undergoing hip or knee arthroplasty should be enrolled in the Scottish national arthroplasty register.

Table 6: Summary of incidence of VTE events, mortality and major bleeding in control groups in meta-analyses of antiplatelet drugs (Table 3) or low-dose subcutaneous heparins (Table 5); and in recent UK cohort studies without routine heparin prophylaxis; in major elective orthopaedic surgery (total hip or knee replacement).

	Asymptomatic DVT	Symptomatic DVT	Nonfatal PE	Fatal PE	Total mortality	Major bleeding
Control groups						
Antiplatelet trials	232/436 (53.2%)		35/2578 (1.4%)	4/2578 (0.15%)	13/2578 (0.5%)	
Heparin trials	171/368 (46.5%)		42/437 (9.6%)	8/489 (1.6%)	33/1231 (2.7%)	9/322 (2.8%)
Total	403/804 (50.1%)		77/3012 (2.6%)	12/3067 (0.4%)	46/4809 (1.0%)	
Cohort studies [114] (95% confidence intervals)						
Hip replacement [34,39]		1.9% (1.1-2.8)	1.2% (0.6-2.2)	0.3% (0.1-0.8)		
Knee replacement [115,116]		9% (7-11)	1.9% (1.2-3.0)	0.4% (0.1-1.1)		

5.1.1 MECHANICAL PROPHYLAXIS

As noted in section 3.2, there is evidence from pooled analyses of small randomised trials that GECS, IPC or foot pumps reduce the risk of asymptomatic DVT in elective orthopaedic surgery, including both hip and knee replacement. IPC may be less effective in reducing the risk of proximal DVT,[113] while foot pumps may be more effective in reducing the risk of proximal DVT. [86-93] 1++ 2++

A **Patients undergoing total hip or knee replacement (or other elective major orthopaedic surgery) can be considered for mechanical prophylaxis (GECS ± IPC or foot pumps).**

5.1.2 ANTIPLATELET DRUGS (ASPIRIN)

In a meta-analysis of randomised trials,[31] antiplatelet drugs (usually aspirin) reduced the risk of asymptomatic DVT and of PE by about one-third in patients undergoing elective orthopaedic surgery, as in all surgical trials *(see Table 3)*. While not statistically significant, there was a similar reduction in total mortality. Aspirin may be more effective in reduction of proximal DVT than warfarin.[117] The excess risk of bleeding after total hip replacement appears low and there appears to be no significant increased risk of wound haematoma or infection.[31] 1++

A recent cohort study observed low risks of fatal PE (0.13%), nonfatal PE (0.94%) and symptomatic DVT (1%) in patients with THR receiving aspirin and mechanical prophylaxis *(GECS or IPC)*.[118] 2

A **Patients undergoing total hip or knee replacement (or other elective major orthopaedic surgery) can be considered for aspirin** *(150 mg orally, started before surgery and continued for 35 days)*.

5.1.3 HEPARINS

In a meta-analysis of randomised trials, both UFH and LMWH reduced the risk of asymptomatic DVT by about 50% in patients undergoing elective orthopaedic surgery, as in all surgical trials. They had no effect on symptomatic PE or mortality and there was a non-significant trend to increased risk of major bleeding *(see Table 5)*. There was a statistically significant reduction in fatal PE (as in all surgical trials); however the incidence of fatal PE in the control groups of these studies (1.5%) was appreciably higher than that in recent studies without routine pharmacological prophylaxis (0.1-1.0%).[114] 1++

In recent UK cohort studies of total hip replacement and total knee replacement in which there was a high incidence of spinal and epidural anaesthesia, and routine mechanical prophylaxis, use of heparin prophylaxis was not associated with significant reductions in clinical VTE or mortality.[113,114] The additional benefit of UFH or LMWH compared to routine early mobilisation, mechanical prophylaxis and aspirin is therefore unclear.[114] 2+

A **Patients undergoing total hip or knee replacement (or other elective major orthopaedic surgery) can be considered for UFH or LMWH**.

See section 7 for timing of initial dose for patients undergoing spinal or epidural blocks.

The routine duration of UFH or LMWH prophylaxis is until discharge from hospital (usually 7-15 days). However, in contrast to non-orthopaedic surgery, there is a high risk of recurrent asymptomatic DVT when venography is repeated at 4-5 weeks after surgery.[119] This may explain why heparin prophylaxis is no more effective than mechanical prophylaxis or aspirin, which can be readily continued for 35 days after surgery.[31]

LMWH prophylaxis can also be continued for 4-5 weeks after surgery, and was more effective than conventional LMWH *(or warfarin)* prophylaxis for 7-15 days in reducing risks of asymptomatic DVT and symptomatic VTE in a recent meta-analysis.[119] However, the risks of symptomatic VTE *(1.5% with 4-5 weeks LMWH and 3.3% with 7-15 days LMWH)* in this meta-analysis were higher than those observed in cohort studies using routine mechanical prophylaxis ± aspirin.[114,118] The role of extended LMWH prophylaxis is therefore unclear. Because of its logistic problems and costs, it should be reserved for very high-risk patients (*e.g. previous VTE and/or multiple risk factors)*.[19] 2+

A **The duration of UFH or LMWH prophylaxis should be 7-15 days after lower limb arthroplasty, extended to 4-5 weeks in very high-risk patients.**

5.1.4 ORAL ANTICOAGULANTS

Warfarin *(commenced before or immediately after surgery and adjusted to target INR 2.5 [range 2.0-3.0])* is similarly effective to UFH or LMWH prophylaxis in prevention of asymptomatic DVT and symptomatic VTE after elective total hip or knee replacement, and is widely used in North America.[19,113] Problems include the need for regular monitoring of the INR, and increased risk of postoperative bleeding. It is not widely used in the UK,[80] but could be considered in high-risk patients as an alternative to UFH or LMWH *(e.g. in patients on long term warfarin: see section 3.8)*. 1+

A **Patients undergoing major orthopaedic surgery** *(e.g. total hip or knee replacement)* **can be considered for warfarin** *(target INR 2.0-3.0)***, e.g. those already receiving warfarin.**

5.1.5 SUMMARY

A **Patients undergoing total knee or hip replacement** *(or other elective major orthopaedic surgery)* **should receive thromboprophylaxis: mechanical** *(GECS ± IPC, foot pumps)*, **pharmacological** *(aspirin or heparin or warfarin)*, **or both.**

5.2 HIP FRACTURE SURGERY

Hip fracture surgery (see SIGN guideline 56: Prevention and management of hip fracture in older people)[120] carries high risks of asymptomatic DVT (45%), symptomatic DVT (1-11%), symptomatic PE (3-13%) and fatal PE (1-7%) in the absence of VTE prophylaxis *(see Tables 3 and 5)*.[114]

The risks of fatal PE and total mortality (7%)[31] are higher than in elective arthroplasty, probably due to the higher mean age of hip fracture patients. Early surgery *(within 24 hours)* reduces the risk of DVT[121] and of fatal PE.[25] 2+

C **Early surgery (within 24 hours) is recommended where possible to reduce the risk of DVT and fatal PE after hip fracture.**

5.2.1 MECHANICAL PROPHYLAXIS

A meta-analysis of four randomised controlled trials of mechanical methods *(two trials of IPC and two of foot pumps; no trials of GECS were identified)* involving 422 patients observed that the incidence of asymptomatic DVT was reduced from 19% to 6%.[84] There was insufficient data to establish the effects of these devices on symptomatic VTE or mortality. In the PEP trial,[31] use of GECS *(by 30% of patients, non-randomised)* was not associated with reduction in symptomatic VTE. 1+

A **Mechanical prophylaxis (IPC or foot pumps) should be considered to reduce the risk of asymptomatic DVT after hip fracture. There is no evidence for the efficacy of GECS in hip fracture patients.**

5.2.2 ANTIPLATELET DRUGS (ASPIRIN)

A meta-analysis of randomised controlled trials *(mainly the PEP study of aspirin[31])* in patients undergoing surgery for hip fracture observed that aspirin reduced the risk of asymptomatic DVT (42% to 36%), symptomatic DVT (1.5% to 1.0%), all PE (1.6% to 0.8%), and fatal PE (0.8% to 0.4%), with no effect on total mortality *(see Table 3)*. 1++

The excess risk of bleeding was small *(one additional transfused bleed per 1,000 patients who were not receiving concomitant heparin prophylaxis)*.[31]

A **All patients with hip fracture should receive aspirin** *(150mg orally, started on admission and continued for 35 days)* **unless contraindicated.**

5.2.3 HEPARINS

A meta-analysis of UFH and LMWH in hip fracture surgery showed that heparins reduced the risk of asymptomatic DVT from 39% to 24% (NNT = 6.5). Unlike elective arthroplasty *(see section 5.1)*, no studies of recurrent asymptomatic DVT *(venography at 4-5 weeks)* or prolonged prophylaxis were identified. There was insufficient data to establish the effects of heparins on symptomatic VTE, mortality, or bleeding[84] *(see Table 5)*. 1++

In a multivariate analysis of predictors of death in a multicentre regional audit, mortality was lower among patients receiving pharmacological prophylaxis for VTE.[122] However, use of heparin prophylaxis *(18% UFH, 26% LMWH, non-randomised)* was not associated with reduction in symptomatic VTE in the PEP trial.[31] As with elective arthroplasty, the additional benefit of UFH or LMWH compared to routine early mobilisation, mechanical prophylaxis and aspirin is therefore unclear.[114] 2+

A **Heparin should be reserved for selected patients at high risk of VTE after hip fracture due to:**

- **multiple risk factors** *(see section 2)*
- **contraindications to routine mechanical prophylaxis and/or aspirin.**

5.2.4 ORAL ANTICOAGULANTS AND DEXTRANS

These methods also reduce the risk of VTE after hip fracture surgery,[19] but are not widely used in the UK due to logistic problems, and to risks of bleeding *(oral anticoagulants)* and anaphylaxis *(dextrans)*.

5.3 KNEE ARTHROSCOPY

The incidence of asymptomatic DVT after knee arthroscopy is not well defined.[123-126] At present there is insufficient evidence to justify routine prophylaxis in patients undergoing knee arthroscopy.

5.4 TRAUMA

The risk of DVT and fatal PE varies greatly among trauma patients; those with spinal cord injury, multiple trauma or lower limb fractures have high risks of asymptomatic DVT on screening *(about 50%) and fatal PE (0.5-2.0%)*.[19]

A recent meta-analysis[127] observed no significant efficacy for UFH in prophylaxis of VTE in trauma patients. There are limited randomised trials of LMW heparins in trauma patients.[19] LMWH *(enoxaparin)* reduced the risk of asymptomatic DVT compared to control or UFH[128,129] in patients with major trauma, without increased overt intracranial bleeding. Mechanical prophylaxis *(IPC or foot pump)* may be almost as effective in prophylaxis of asymptomatic DVT.[130,131] 1+

Two studies have shown that outpatient LMWH reduced the incidence of asymptomatic DVT in patients with plaster cast immobilisation.[132,133] 1+

At present, there is no evidence that any prophylactic method reduces the risk of clinical VTE or mortality in trauma patients. Following the PEP trial,[31] future trials of aspirin in trauma patients should also be considered. Aspirin should be considered in patients in whom LMWH and mechanical prophylaxis are not possible.

A **In patients with spinal cord injury, major lower limb fractures or multiple trauma, LMWH prophylaxis can be considered, unless contraindicated** *(e.g. by risk of intracranial bleeding)*.

A **In patients with contraindications to LMWHs, mechanical prophylaxis can be considered** *(e.g. IPC or foot pump)*.

C **In patients in whom LMWH is contraindicated and mechanical prophylaxis is not feasible** *(e.g. patients in plaster casts)*, **aspirin** *(150mg/day)*, **started on admission and continued for 35 days can be considered.**

6 Other types of surgery

6.1 UROLOGICAL SURGERY

6.1.1 MAJOR OR OPEN UROLOGICAL PROCEDURES

Patients undergoing major or open urological procedures appear to have a similar risk of DVT and PE to patients undergoing general or gynaecological surgery and should receive similar prophylaxis.[2,19,20,98,99] The efficacy of UFH or LMWH appears similar to that in general surgery.[2] 1+

A **The preferred method of prophylaxis in patients undergoing major or open urological procedures who are at significant risk of VTE** *(age over 40 or other risk factors)* **is:**

subcutaneous low-dose UFH *(5,000 IU, 8-12 hourly)*

or

subcutaneous LMWH *(dose as per manufacturer's instructions).*

In patients in whom UFH or LMWH are contraindicated, mechanical prophylaxis can be considered, in view of its efficacy in prophylaxis of asymptomatic DVT in general surgery. 1+

B **In patients in whom UFH or LMWH are contraindicated, mechanical prophylaxis (GECS ± IPC) can be considered.**

6.1.2 TRANSURETHRAL RESECTION OF THE PROSTATE

Transurethral resection of the prostate (TURP) is a lower risk procedure, with an incidence of asymptomatic DVT on screening of about 10%.[1] Although fatal PE is rare, it is the third commonest cause of death after TURP.[134] 2+

Low dose subcutaneous UFH is not used routinely because of fear of bleeding, although one trial showed no evidence of increased bleeding.[135]

No trials of LMWH, GECS or IPC were identified.

C **In patients undergoing TURP who are at increased risk of VTE due to multiple risk factors, antithrombotic prophylaxis with UFH, LMWH, or GECS ± IPC should be considered.**

6.2 NEUROSURGERY

VTE is common after neurosurgery.[136] Asymptomatic DVT can be demonstrated in 20-50% of all patients following neurosurgery. Autopsy studies indicate that 12% of postoperative deaths can be attributed to PE (with evidence of PE in 25% of all autopsies). Risk factors include intracranial surgery *(versus spinal),* malignancy, duration of surgery, and lower limb weakness or paralysis.[136] 1+

Given the risk of intracranial or intraspinal bleeding, mechanical prophylaxis is preferred. As in other types of non-orthopaedic surgery, IPC and/or GECS appear similarly effective in prevention of asymptomatic DVT and can be recommended routinely unless contraindicated.[19,20,136] 1+,4

A **Neurosurgical patients should receive antithrombotic prophylaxis using mechanical methods (GECS ± IPC).**

A recent meta-analysis of LMWH versus placebo[137] showed that LMWH was effective but at an increased risk of bleeding *(relative risk increase 71%).* 1+,4

A **LMWH can also be considered in neurosurgical patients, but there is an increased risk of haemorrhage.**

6.3 CARDIOTHORACIC SURGERY

Patients undergoing major cardiothoracic surgery appear to have a similar risk of VTE to patients undergoing major general or gynaecological surgery,[83] and should receive similar prophylaxis. 2+

In patients undergoing cardiac surgery, the addition of IPC to low dose heparin prophylaxis reduced the risk of pulmonary embolism.[83] 1+

Aspirin should be discontinued prior to cardiac bypass surgery (when full-dose heparin is given) because it increases perioperative bleeding and does not appear to increase coronary graft or arterial patency.[6] It can be resumed six hours after bypass grafting, unless contraindicated by bleeding, and continued long term *(75-300 mg/day)* in patients with symptomatic arterial disease.[6] 1+

Clopidrogel increases postoperative bleeding and should be stopped five days before elective cardiac surgery *(see manufacturer's datasheet)*.

B **In patients undergoing major cardiothoracic surgery who are at significant risk of VTE, subcutaneous low-dose UFH or LMWH are recommended. Mechanical prophylaxis (GECS ± IPC) is an alternative.**

A **In patients undergoing cardiac surgery, the addition of IPC to heparin prophylaxis should be considered.**

A **Aspirin should be discontinued prior to elective cardiac bypass surgery because of the risks of bleeding, and resumed** (75-300 mg/day) **via nasogastric tube six hours following bypass grafting and continued long term in patients with symptomatic arterial disease.**

6.4 PERIPHERAL VASCULAR SURGERY

6.4.1 MAJOR VASCULAR SURGERY

Patients undergoing major peripheral vascular surgery appear to have a similar risk of VTE to patients undergoing major general or gynaecological surgery, and should receive similar prophylaxis.[20,138] The risk of VTE appears particularly high in patients immobilised following critical limb ischaemia or major amputation.[6,139,140] Mechanical prophylaxis is contraindicated in patients with severe peripheral arterial disease because of the risk of skin necrosis *(see section 3.3)*. Aspirin improves arterial patency following bypass grafting and should be given or resumed *(via nasogastric tube)* six hours following surgery *(unless contraindicated by bleeding)*.[6] 1++ 3,4

C **In patients with critical limb ischaemia or who are undergoing major peripheral vascular surgery** *(including amputation),* **subcutaneous low-dose UFH or LMWH is recommended.**

A **Aspirin** *(75-300 mg/day)* **should be given or resumed** *(via nasogastric tube)* **starting six hours following bypass grafting and continued long term.**

6.4.2 VARICOSE VEIN SURGERY

While the presence of varicose veins increases the risk of DVT after major abdominal, pelvic or orthopaedic surgery *(see section 2)*, the risk of VTE after varicose vein surgery appears low, in the absence of other risk factors *(e.g. previous DVT or PE, prolonged surgery or immobility)*.[57] GECS are commonly prescribed for such patients; the addition of LMWH or UFH is recommended in those with additional risk factors. 3

C **In patients undergoing varicose vein surgery who have no additional risk factors for VTE, postoperative GECS are recommended.**

C **In the presence of additional risk factors** *(e.g. previous DVT or PE, prolonged surgery or immobility)* **the addition of subcutaneous UFH or LMWH is recommended.**

6.5 MINIMAL ACCESS SURGERY

Minimal access surgery patients are usually mobilised and discharged earlier than patients in whom open surgery is performed. However, in this group of patients, venous blood flow in the legs is often reduced and there is significant activation of blood coagulation and inflammation.[141,142,] Further research is therefore required to establish the risk of VTE.

A survey of UK surgeons indicated that despite the perception of a lower risk following minimal access surgery, the majority used prophylaxis *(UFH, LMWH, GECS or IPC)* as for open surgery.[143] 4

C **In patients undergoing minimal access surgery who have additional risk factors, or who are undergoing major prolonged procedures, subcutaneous UFH or LMWH is recommended.**

C **In lower-risk patients mechanical prophylaxis (GECS ± IPC) is recommended.**

6.6 HEAD AND NECK SURGERY

The incidence of VTE in patients undergoing major head and neck surgery *(e.g. for cancer)* is unknown.[144] In the absence of specific data, prophylaxis is recommended as for general surgical patients.

6.7 EYE SURGERY

The incidence of PE after cataract surgery has been reported as very low.[145]

7 Spinal and epidural blocks

7.1 EFFICACY IN PROPHYLAXIS OF VTE IN SURGICAL PATIENTS

A meta-analysis of RCTs of spinal/epidural block versus general anaesthesia reported reduction in postoperative morbidity and mortality *(including VTE)*.[65] 1+

A **Spinal or epidural anaesthesia may be preferred to general anaesthesia where appropriate and feasible.**

7.2 RISK OF VERTEBRAL CANAL HAEMATOMA WHEN COMBINED WITH PHARMACOLOGICAL PROPHYLAXIS OF VTE

The increasing use of pharmacological prophylaxis for VTE has raised concerns amongst anaesthetists that spinal or epidural block may be followed by an increased risk of vertebral canal haematoma. Most cases of vertebral canal haematoma occur spontaneously, at an estimated incidence of only one per million population per year,[146] often associated with disordered coagulation,[147] which is also one of the major causal factors in the cases reported after spinal/epidural block.[148] Although this is a rare complication, its serious nature requires that some precaution is taken to minimise its incidence.[149] Advice on the use of spinal/epidural block in patients receiving pharmacological prophylaxis for thromboembolism has been published.[150] Technical difficulty during instrumentation of the vertebral canal is an associated factor, with epidural block *(especially with catheter insertion)* carrying a greater risk than spinal anaesthesia. Catheter removal is also a time of risk.[148] The skill and experience of the anaesthetist may therefore be important.

In 1997-98 American reports documented over 40 cases of vertebral canal haematoma occurring within a five year period in patients receiving the LMW heparin, enoxaparin.[40,41] Most followed spinal or epidural block, although a few followed diagnostic lumbar puncture. The report also confirmed the risk factors identified in the earlier review:[148] epidural catheters carried the highest risk at both removal and insertion. However, this is in direct contrast to the European experience, where, although enoxaparin has been available for much longer, only two cases of vertebral canal haematoma have been reported. In a further study, the incidence of vertebral canal haematoma after spinal or epidural block in patients receiving enoxaparin was estimated at 1 in 2,250,000 in Europe, but at 1 in 14,000 in the United States.[151] The main factor contributing to this variation was the difference in the recommended dose of enoxaparin used: 40mg once daily, starting 12 hours before surgery for high risk European patients, compared with 30mg twice daily, starting one hour after surgery for American patients. In the European patients, the peak effect of the drug *(occurring at four - six hours post-administration)* would be past at the time of block administration, minimising risk. In the American patients, although there would be no effect at the institution of a block, the long half life of enoxaparin *(10-12 hours)* could lead to accumulation, producing an overt effect on coagulation and leading to bleeding at the time of catheter removal.[152]

7.2.1 ORAL ANTICOAGULANTS *(see section 3.8)*

Full anticoagulation is an absolute contraindication to spinal or epidural block. Most authorities recommend that the INR be 1.5 or lower for institution of a block or removal of a catheter.[153-155] In most cases, the patient with a higher INR who is to undergo major elective surgery will have it delayed so that coagulation can revert to normal. Management is as outlined elsewhere[6,156] *(see also SIGN guideline on perioperative transfusion)*.[157]

7.2.2 UNFRACTIONATED HEPARIN *(see section 3.4)*

Thromboprophylaxis with low-dose subcutaneous heparin *(5,000 IU 8-12 hourly or 7,500 IU 12-hourly)* does not usually prolong the APTT and large numbers of patients have received spinal or epidural block without sequelae.[158] However, a transient elevation of the APTT may occur[159] and some anaesthetists prefer not to institute spinal or epidural block within 4-6 hours of a dose, and to administer heparin after institution of the block.[150] Similar considerations apply to catheter removal. The platelet count should be checked before the block is instituted or the catheter

removed if the patient has been receiving any heparin preparation for more than a few days, to exclude heparin-associated thrombocytopenia *(see section 3.4.5)*.

7.2.3 LOW MOLECULAR WEIGHT HEPARINS

Evidence suggests that standard European dosing regimens *(e.g. enoxaparin 20-40mg once daily)* are not associated with any increased risk as long as the block is instituted, or the catheter removed, 10-12 hours after drug administration. A first dose can be given immediately after block administration or catheter removal.[160]

7.2.4 ANTIPLATELET AGENTS (ASPIRIN)

There is little or no evidence that aspirin increases risk,[160] although interactions with other agents such as heparins or warfarins may occur.[149]

7.2.5 RECOMMENDATIONS

D **When instituting spinal/epidural block prior to elective surgery, epidural catheter removal or diagnostic lumbar puncture, the following precautions should be taken:**

- **Aspirin: proceed normally, but remember interactions**
- **UFH: proceed normally but exercise caution**
  - **or administer 4-6 hours before block**
  - **or delay first dose until after block performed or until after surgery**
- **LMWH: administer 10-12 hours before block**
- **Warfarin: if INR <1.5 proceed normally**
  - **if INR ≥1.5 delay surgery or consider alternative anaesthetic or anaesthetic technique if surgery is urgent.**

☑ When there is difficulty or bleeding during the block procedure it is essential that this is recorded and greater vigilance ensured during the postoperative period. It may also be advisable to omit or delay the next dose of thromboprophylactic agent.

☑ If perioperative pharmacological prophylaxis is to be omitted altogether in a patient who would normally receive it, a mechanical method should be used instead.

☑ In patients requiring emergency surgery who have already received a thromboprophylactic drug, the agent used, the dose, and the time interval since the last administration should be noted and related to the recommendations above.

☑ Any decision should be based on the balance of risks and benefits, will often require discussion with the patient, and should be documented fully.

Management and prophylaxis of the patient in labour are considered in section 9.

8 Medical patients

Most cases of VTE are triggered by causes other than surgery and most fatal PE occur in medical patients.[7,12,13,46-49] Despite this high risk in medical patients, there are a smaller number of medical patients in randomised trials compared with the number of surgical patients. In recent years, meta-analyses in myocardial infarction,[43] stroke[161,162] and other medical patients[5] have clarified the benefits and risks of prophylaxis in these patients.

8.1 ACUTE MYOCARDIAL INFARCTION

Prior to the introduction of routine antithrombotic therapy (aspirin, thrombolysis, anticoagulants) patients with acute myocardial infarction had a risk of asymptomatic DVT of about 24%, and a risk of clinical PE of 2.6-9.4%.[19,43] The risk increases with age and in the presence of heart failure.[163]

8.1.1 ANTIPLATELET DRUGS (ASPIRIN) AND THROMBOLYTIC THERAPY

Current evidence-based guidelines endorse the routine use of aspirin (and thrombolytic therapy) in selected patients in clinically suspected evolving acute myocardial infarction, because both interventions reduce mortality. Aspirin also reduces the rates of reinfarction and stroke. The following recommendations are taken from the SIGN guideline on antithrombotic therapy:[6] 1++

A **It is strongly recommended that all patients with clinically suspected evolving acute MI who are not already receiving aspirin should be given aspirin** (150-300 mg).

A **It is strongly recommended that all patients with clinically suspected evolving acute MI should be considered for thrombolytic therapy.**

8.1.2 ANTICOAGULANTS

A meta-analysis of randomised trials of anticoagulants in acute myocardial infarction[43] showed that routine intravenous or subcutaneous heparin reduced the risk of DVT *(asymptomatic or symptomatic)*, PE and mortality. In the absence of aspirin, anticoagulant therapy reduced mortality by 25%, representing 34 fewer deaths per 1,000. It also reduced PE by 49%, representing 18 fewer PE per 1,000.[43] However in the presence of aspirin, high dose heparin reduced mortality by only 6%, representing five fewer deaths per 1,000, and PE by 25%, representing one fewer PE per 1,000. High-dose heparin was associated with an excess of three major bleeds per 1,000.[43] 1++

The SIGN guideline on antithrombotic therapy[6] recommends the following:

A **Heparin should not be used routinely in addition to aspirin in acute MI, but reserved for patients at increased thromboembolic risk** *(and for certain patients undergoing thrombolysis).*

A **Patients with acute, established MI at increased risk of systemic or pulmonary thromboembolism due to:**
– large anterior Q-wave infarction
– severe left ventricular dysfunction
– congestive heart failure
– history of systemic or pulmonary embolism or thrombophilia
– echocardiographic evidence of mural thrombus
– persistent atrial fibrillation
– prolonged immobilisation
– marked obesity
should be considered for anticoagulation with full-dose heparin *(target APTT ratio 2.0, range 1.5-2.5)* **followed** *(if indicated by continuing risk)* **with warfarin** *(target INR 2.5, range 2.0-3.0)* **for up to three months, depending upon the physician's estimate of the risk: benefit ratio in the individual patient.**

A **In other patients with acute MI, and in patients as defined above in whom the bleeding risks of full-dose anticoagulation are judged to outweigh the benefits, prophylaxis of VTE with low-dose subcutaneous heparin** *(7,500 IU 12-hourly)* **for seven days or until ambulant, should be considered**.

8.1.3 GENERAL MEASURES

Early mobilisation appears to reduce mortality in acute myocardial infarction.[66]

8.1.4 MECHANICAL PROPHYLAXIS

In a small RCT of 80 patients with acute MI, all of whom received aspirin, the incidence of asymptomatic DVT was significantly reduced in the stockinged leg compared with the other (control) leg.[164] Taken in conjunction with good evidence for the efficacy of compression stockings in prevention of asymptomatic DVT and PE in surgical patients,[72,73] there is evidence to support the use of compression stockings in patients with MI. 1+

A **Compression stockings may be considered in patients with acute MI who are at increased risk of VTE, especially when heparin prophylaxis is contraindicated.**

8.2 ACUTE STROKE

Asymptomatic DVT occurs in up to 50% of patients with acute hemiplegic stroke, most often in immobile patients with paralysis of a leg. However, clinically apparent DVT or PE probably occurs in fewer than 5%. Autopsy series have identified PE in a large proportion of patients, and PE may account for up to 25% of early deaths.[165] See also SIGN guideline on Stroke Rehabilitation *(currently under review)*.[166]

8.2.1 GENERAL MEASURES

Early mobilisation and hydration should, in theory, reduce the risk of thrombosis, although no studies have been performed to evaluate the impact of these interventions on VTE. There is evidence from one RCT that early intravenous fluids improve stroke outcome,[167] perhaps by maintaining homeostasis.[168] A meta-analysis of RCTs of haemodilution showed that VTE was reduced, despite overall lack of benefit.[169]

☑ Patients with stroke should be mobilised as early as practicable and measures taken to ensure good hydration.

8.2.2 MECHANICAL PROPHYLAXIS

In small trials of patients with acute stroke, the incidence of asymptomatic DVT was significantly reduced by GECS.[170] Taken in conjunction with good evidence for the efficacy of compression stockings in prevention of asymptomatic DVT and PE in surgical patients,[72,73] they may therefore be effective in VTE reduction after stroke, although no large RCTs have evaluated their use in this context. 1+

C **Selected use of graduated compression stockings may be justified for some high risk patients.**

D **Compression stockings are preferred for patients with haemorrhagic stroke.**

There is no evidence that intermittent pneumatic compression is effective in stroke patients, although it is effective in patients undergoing neurosurgery.[171]

8.2.3 ANTIPLATELET DRUGS (ASPIRIN)

Eight trials involving 41,325 patients were included in a systematic review of the effect of aspirin on clinical outcome after acute stroke.[172] Two trials testing aspirin 160 to 300 mg once daily started within 48 hours of onset contributed 98% of the data. The maximum follow-up was six months. With treatment, there was a significant decrease in death or dependency at the end of follow-up. This corresponds to an additional 13 patients alive and independent at the end of follow-up for every 1,000 patients treated. 1++

The systematic review included two trials which reported on the effect of aspirin on DVT in patients with acute stroke.[172] Only 35 of 136 patients developed symptomatic or asymptomatic DVT during the treatment period; 29% of those allocated to control and 24% of those allocated to treatment: a non-significant 22% reduction in odds, but potentially of clinical significance since it represents the avoidance of about 40 DVTs per 1,000 patients treated.[172] Reliable data are available for the effects of aspirin on PE (over 40,000 patients). Aspirin significantly reduced pulmonary embolism from 0.5% in controls to 0.3% in treated patients, an odds reduction of 29%, i.e. avoiding PE in two patients for every 1,000 treated. This effect is similar to that in meta-analyses of surgical patients.[3,31] Under-ascertainment of events in both groups may mean that the absolute benefit has been underestimated; if the true rate of pulmonary embolism were 2% in the control group, and the same proportional reduction were applied, then aspirin might avoid PE in seven per 1,000 patients.

2+

1++

A **Early treatment with aspirin** *(initially 150-300 mg/day)* **is recommended in acute ischaemic stroke, starting as soon as intracranial haemorrhage is excluded by CT or MR brain scanning, for risk reduction in death and cardiovascular events, including DVT and PE.**

☑ Aspirin can be given by nasogastric tube or rectally (using 300mg suppositories) for those who are unable to swallow.

8.2.4 HEPARINS

Systematic reviews of RCTs of low dose subcutaneous heparins (including heparinoids and LMWHs) have shown that heparin reduces the risk of asymptomatic DVT after stroke.[160,161] It is less certain whether clinically apparent DVT is prevented by such regimens. Any benefit in terms of prevention of DVT, PE and early recurrence of ischaemic stroke is offset by an increase in haemorrhagic complications.[160,161,172] Routine heparin use in the first two weeks after a presumed ischaemic stroke has not been associated with any net reduction in the proportion of patients who are dead or dependent at six months.[160,161] The bleeding risk with UFH and LMWH is dose-related. Since there is no evidence of greater net benefit from higher dose regimens, if heparins are to be used after stroke, low dose regimens should be selected,[160,161] and LMWH may be preferred due to a lower risk of bleeding in medical patients.[5]

1++

A **UFH** *(e.g. 5,000 IU subcutaneously twice a day)* **or a LMWH may be considered in patients with ischaemic stroke who are judged to be at higher than average risk of VTE** *(e.g. history of previous VTE, known thrombophilia or active cancer)* **and lower than average risk of haemorrhagic complications.**

8.3 OTHER MEDICAL PATIENTS

Autopsy studies have highlighted the contribution of PE to deaths in other groups of immobilised patients in medical wards.[5,12,13] Most trials of prophylaxis have been performed in patients with heart failure, respiratory failure, or infections *(e.g. chest infections)*. Patients immobilised in intensive care units, or for diabetic coma, cancer, inflammatory bowel disease or nephrotic syndrome should also be considered for prophylaxis.

8.3.1 HEPARINS

A recent meta-analysis of seven trials of heparin versus control and eight trials of LMWH versus UFH observed a 56% decrease in asymptomatic DVT, and a 51% decrease in clinical PE with heparins.[5] The reduction in mortality was not statistically significant and the risk of major bleeding was higher. LMWH was similarly effective to UFH in reducing the risks of DVT, PE and mortality; but had a 55% lower risk of major bleeding.[5] These data are supported by a recent controlled trial of two doses of a LMWH in which the benefit was maintained at three month follow-up.[174]

1++

A **In general medical patients who are immobilised in hospital due to acute illness, especially those with heart failure, respiratory failure, infections, diabetic coma, inflammatory bowel disease, nephrotic syndrome, or in intensive care, prophylaxis of VTE with low dose UFH or LMWH should be considered. LMWH carries a lower risk of bleeding.**

8.3.2 MECHANICAL METHODS

No trials were identified. In medical patients at risk of VTE, graduated compression stockings may be considered (especially if heparin prophylaxis is contraindicated), extrapolating from a meta-analysis of trials in all groups of patients, including medical patients with acute myocardial infarction.[164] 1+

C **In general medical patients at significant risk of VTE in whom heparin prophylaxis is contraindicated, GECS may be considered.**

8.4 CANCER PATIENTS

As discussed in section 2, patients with cancer have an increased risk of VTE, including central venous line thrombosis and chemotherapy-induced thrombosis. As noted above, immobilised cancer patients in medical or surgical wards should be considered for prophylaxis. The SIGN guideline on antithrombotic therapy[6] includes the following additional recommendations:

A **Minidose warfarin** *(1 mg/day, no INR monitoring)* **is recommended for prophylaxis of thrombosis in cancer patients with central venous catheters.**

A **Low-dose warfarin** *(target INR 1.6, range 1.3-1.9)* **is recommended for prophylaxis of thrombosis during chemotherapy in stage IV breast cancer.**

8.5 PATIENTS RECEIVING ANTIPSYCHOTIC DRUGS

There is recent evidence that patients receiving antipsychotic drugs may have an increased risk of VTE,[175] possibly due to immobility.[176] It may be prudent to avoid strict bedrest and to encourage exercise in such patients, and to educate patients and carers about this potential risk.[176]

☑ Patients receiving antitpsychotic drugs may have an increased risk of VTE: education on risk and mobility is encouraged.

9 Pregnancy and the puerperium

There is a tenfold increase in thrombotic risk throughout pregnancy and the puerperium.[177,178] The same factors that increase thrombotic risk in non-pregnant patients e.g. obesity, immobility, dehydration, long-distance air travel (*see Table 1*) also increase the risk of thrombosis associated with pregnancy. During pregnancy additional risk factors such as pre-eclampsia and delivery, particularly operative delivery, must be considered.[179]

LMWH is preferred to UFH as it is safer in pregnancy[180-183] and is also preferable to warfarin during pregnancy *(because of the fetal toxicity of oral anticoagulants)*. 2++

B **Warfarin and other coumarins should be avoided if possible during pregnancy, at least between six and 12 weeks gestation and after 36 weeks' gestation.**

B **LMWH is preferred to UFH in pregnancy, as there is more safety data.**

D **All pregnant women should be regularly assessed for VTE risk factors.**

9.1 ANTENATAL THROMBOSIS RISK ASSESSMENT

Women attending for their first antenatal visit should be asked specifically about their personal and family history of VTE and whether any diagnosis was objectively confirmed. If this information is not available, investigate the history of anticoagulant treatment. Where prolonged anticoagulant therapy has been prescribed, in keeping with the management of VTE, it is prudent to assume that this has been a definite event. Patients with thrombophilias appear to be at particular risk of VTE in pregnancy.[184-186]

D **All pregnant women with a personal history of VTE, or a family history of VTE in first or second degree relatives, should be offered screening for thrombophilias.**

There is accumulating evidence linking congenital thrombophilia to other pregnancy complications, including miscarriage, pre-eclampsia, intrauterine growth restriction and fetal death.[177]

9.2 PREVIOUS VTE AND NO IDENTIFIABLE THROMBOPHILIAS

Where a patient has had a single previous VTE event associated with a temporary risk factor which is no longer present, antenatal anticoagulation is controversial because of the low risks of recurrence and the potential hazards of heparin.[187] Where the previous VTE event was oestrogen-related *(e.g. COC use or pregnancy),* there is a stronger case for LMWH prophylaxis throughout the pregnancy. The use of LMWH reduces these hazards.[178] Each case should therefore be judged on an individual basis taking into account any additional risk factors, and the patient counselled regarding the potential risks and benefits of antenatal pharmacological thromboprophylaxis. As events can occur early in pregnancy, it is important to assess risk at this time and start thromboprophylaxis if significant risk factors (such as hyperemesis with associated immobility) are present.

☑ Management options should be discussed with each patient.

C **In all women with VTE events during previous pregnancy or COC use, antenatal thromboprophylaxis should be started as early as possible in pregnancy.**

C **In all women with previous idiopathic VTE, antenatal prophylaxis should be started as early as possible in pregnancy.**

B **Women in whom a previous VTE occurred in association with other temporary risk factors, which are no longer present** *(e.g. surgery or trauma)***, and who have no identifiable thrombophilia or current risk factors other than pregnancy, do not routinely require antenatal LMWH prophylaxis, but should be considered for GECS.**

C **Where antenatal thromboprophylaxis is appropriate, it should be:**
- **subcutaneous LMWH** *(e.g. 40mg enoxaparin daily or 5,000 IU dalteparin daily)*. **The platelet count should be checked before and one week after the introduction of LMWH**
- **at low body weight, e.g. <50kg, lower doses of LMWH may be required** *(e.g.20mg enoxaparin daily or 2500 IU dalteparin daily)*
- **in obese patients,** *(e.g. BMI >30 in early pregnancy)*, **higher doses of LMWH may be required**
- **GECS may be combined with LMWH. Clinical surveillance for evidence of VTE should also be considered.**

C **All women with a past history of VTE should receive thromboprophylaxis postpartum** *(see section 9.5)*.

9.3 LONG TERM ANTICOAGULANTS OR KNOWN HERITABLE THROMBOPHILIA

Women on long term anticoagulant drugs or with a known heritable thrombophilic defect usually merit referral to a unit experienced in management of pregnancy in thrombophilic women.[61] The risk of VTE associated with thrombophilic defects varies considerably. Patients should be stratified according to the level of risk associated with their thrombophilia.[61] All patients with heritable thrombophilia should be considered for GECS during pregnancy and for six weeks postpartum (*see section 9.5*).

9.3.1 HIGH RISK OF CLINICAL VTE (>1:40)

– *women on long term anticoagulant thromboprophylaxis for VTE*
– *women who have antithrombin deficiency (whether or not they have had a previous symptomatic thrombosis*)

These women should be considered at very high risk of antenatal VTE and must be considered for anticoagulant prophylaxis throughout pregnancy. They should be advised of the need to switch from warfarin to LMWH *(or to start LMWH)* as soon as pregnancy is confirmed. The dose of heparin given should be closer to that used for the treatment of VTE rather than that used for prophylaxis. [61]

C **In pregnant women at high risk of VTE, prophylaxis should be subcutaneous LMWH,** *(e.g. enoxaparin 0.5-1mg/kg 12 hourly or dalteparin 50-100 IU/kg 12 hourly)*, **based on the early pregnancy weight. The platelet count should be checked before and one week after the introduction of LMWH.**

Where a LMWH is used, 12 hourly injections may be preferable to once daily injections in view of the increased clearance of LMWH in pregnancy. Women who are receiving long term anticoagulant thromboprophylaxis because of a prosthetic heart valve also require intensive anticoagulation in pregnancy. Such women should be referred to a specialist unit with the experience of management of these problems.

9.3.2 MODERATELY INCREASED RISK OF CLINICAL VTE (1:40 -1:200)

– *women with a previous thromboembolic event who have an underlying thrombophilia and who do not belong to the previous high risk category*
– *women with no personal history of VTE but who have been found (e.g. because of a family history) to be protein C deficient, to have combinations of defects, or to be homozygous for a defect*

LMWH prophylaxis should be started in these women as soon as the pregnancy is confirmed.[61]

C **In pregnant women at moderately increased risk of VTE, prophylaxis can be given as LMWH** *(e.g. enoxaparin 40mg daily or dalteparin 5,000 IU daily)*. **The platelet count should be checked before and one week after the introduction of LMWH.**

9.3.3 SLIGHTLY INCREASED RISK OF CLINICAL VTE (1:200 -1:400)

– *women with no personal history of venous thrombosis but who have had a defect identified, e.g. because of a family history, and who do not belong to the categories described in 9.3.1 or 9.3.2.*

These women do not usually require routine anticoagulant thromboprophylaxis antenatally but should be offered anticoagulant prophylaxis following delivery. The risk of thrombosis should be discussed with the patient antenatally, and GECS considered *(see section 9.2)*. If LMWH thromboprophylaxis is requested, the patient should be treated with LMWH in prophylactic doses *(as in section 9.3.2)*.[61]

9.4 ANTIPHOSPHOLIPID SYNDROME

Women with antiphospholipid syndrome (lupus anticoagulants or anticardiolipin antibodies) and recurrent miscarriage should receive thromboprophylaxis with LMWH and low-dose aspirin from the point of diagnosis of pregnancy.[187-189] Although such therapy is aimed at preventing pregnancy loss, which is related to placental thrombosis, these women are likely to be at risk of other thromboembolic events and pregnancy complications. Similar prophylaxis should be given to women with antiphospholipid syndrome and a previous thrombotic event. 1+

Women with antiphospholipid syndrome and no previous thrombotic event or recurrent miscarriage should be considered for low dose aspirin (75 mg/day), to reduce the risk of pregnancy complications and postpartum heparin thromboprophylaxis.[178]

A **Women with antiphospholipid syndrome and recurrent miscarriage should receive thromboprophylaxis from the diagnosis of pregnancy with LMWH** *(e.g. enoxaparin 40 mg daily or dalteparin 5,000 IU daily)* **and low dose aspirin** (75 mg/day).

C **Women with antiphospholipid syndrome who have already had a thrombotic event should receive low dose aspirin** (75 mg/day) **and LMWH** *(e.g. enoxaparin 40mg daily or dalteparin 5,000 IU daily)* **from the diagnosis of pregnancy.**

C **Other women with antiphospholipid syndrome should receive low dose aspirin** (75 mg/day) **antenatally to reduce the risk of pregnancy complications, and postpartum heparin prophylaxis** *(see section 9.5)***.**

9.5 DELIVERY AND THE PUERPERIUM

9.5.1 MANAGEMENT OF DELIVERY

Patients on LMWH antenatally and who wish epidural anaesthesia in labour, or epidural or spinal anaesthesia for caesarean section, should stop pharmacological prophylaxis when labour starts. In general terms, an epidural or spinal block should not be given for 10-12 hours after LMWH administration *(see section 7)*. However, the risk benefit ratio must be taken into account in the decision regarding timing of epidural or spinal anaesthesia. LMWH should not be given within two hours of epidural or spinal anaesthesia or of catheter removal.

C
- **In pregnant women who have requested epidural anaesthesia during labour, stop the administration of LMWH when labour starts.**
- **LMWH can be administered or readministered three hours after atraumatic epidural or spinal anaesthesia, or removal of an epidural catheter.**

☑ Patients should be warned to discontinue self-injections of LMWH as soon as they believe themselves to be in labour, and not restart until evaluation in hospital.

9.5.2 MANAGEMENT OF THE PUERPERIUM

In addition to previous VTE and thrombophilias, other risk factors that merit consideration of postpartum prophylaxis include:

- age >35 years
- caesarean section (particularly if carried out as an emergency procedure during labour)
- operative vaginal delivery
- obesity *(BMI >30 kg/m²)* either pre-pregnancy or in early pregnancy
- parity ≥4
- labour >12 hours
- gross varicose veins
- pre-eclampsia
- lower limb paralysis
- immobilisation *(>4 days bed rest)*
- current infection
- extended major pelvic or abdominal surgery
- major current medical conditions.

C **Postpartum thromboprophylaxis is recommended in women with:**
- **previous VTE (or family history)**
- **known thrombophilias**
- **other thrombotic risk factors.**

C **Postpartum, the first dose of subcutaneous LMWH** *(enoxaparin 40mg daily or dalteparin 5,000 u daily)* **should be given 3-6 hours after delivery.**

C **Postpartum anticoagulation should be continued for a minimum of six weeks in patients with previous VTE or thrombophilias. In other patients, prophylaxis should continue until discharge from hospital; review need for prophylaxis if hospital stay continues beyond five days.**

C **Where the patient does not wish to continue self-injecting, LMWH can be replaced by warfarin starting on the first or second postpartum day. The LMWH can be withdrawn when the INR has been within the target range** *(usually 2.0 - 3.0)* **for two consecutive days.**

C **There is no contraindication to breast feeding when the mother is being treated with LMWH, warfarin or other coumarins.**

C **GECS can be added to LMWH in high risk patients and should be used where LMWH is contraindicated.**

9.6 HEPARIN CONTRAINDICATIONS IN PREGNANCY AND PUERPERIUM

9.6.1 SKIN REACTIONS

Where LMWH is contraindicated because of skin reactions, consider changing:

- to another LMWH
- to danaparoid if cross-reactivity is excluded
- to low dose aspirin plus GECS.

9.6.2 HEPARIN ALLERGY

In patients with heparin allergy warfarin may be used during pregnancy. However, it must be replaced with LMWH at least four weeks ahead of the expected delivery date. If possible the gestation period 6-12 weeks and post 36 weeks should also be avoided.

9.6.3 HEPARIN ASSOCIATED THROMBOCYTOPENIA

A LMWH or danaparoid may be considered in patients who have heparin associated thrombocytopenia if cross-reactivity has been excluded. Warfarin may be considered in those at high thrombotic risk. Postpartum, warfarin or recombinant hirudin may be considered.

9.6.4 HAEMORRHAGE

Patients with antepartum or postpartum haemorrhage may be at considerable risk of deep venous thrombosis. Clearly while there is a coagulation defect, it would be inappropriate to prescribe UFH or LMWH. These patients should be treated with GECS. Pharmacological thromboprophylaxis can be employed once any coagulation defect has subsided and the haemorrhagic complication has resolved.

C **Where anticoagulants are contraindicated, GECS should be worn for at least six weeks following delivery. This may be combined with low dose aspirin** (75 mg/day).

10 Oral contraceptives and hormone replacement therapy

10.1 ORAL CONTRACEPTIVES

The background rate of spontaneous VTE in healthy women who are not pregnant and who do not use the combined oral contraceptive (COC) pill is around five cases per 100,000 women per year. The risk is increased threefold *(15/100,000 women per year)* in users of second generation contraceptives,[190] and six fold *(30/100,000 women per year)* in users of third generation oral contraceptives *(i.e. containing desogestrel or gestodene)*.[191]

The **absolute** risk of thrombosis in women taking third generation pills is small *(an excess risk of 10-25 cases of VTE per 100,000 women years)* and is less than the risk associated with pregnancy *(estimated at 100 cases per 100,000 maternities)*. However, the risks are higher during the first year of use, approaching 30 per 100,000 women per year for users of third generation COC.[192] The risk is also much higher in women with thrombophilias.[192]

10.1.1 COMBINED ORAL CONTRACEPTIVES AND SURGERY

Whether or not to stop the combined oral contraceptive pill before major surgery is a controversial issue. The risk of postoperative VTE increases from 0.5% to 1% for pill users versus non-users.[193] This small absolute excess risk in COC users must be balanced against the risks of stopping the pill 4-6 weeks prior to surgery, including unwanted pregnancy, the effects of surgery and anaesthesia on a pregnancy, and the risks of a subsequent termination. These risks should be communicated to the patient and, if it is agreed to stop COC, adequate alternative contraception should be arranged until COC are restarted. The timing of restarting COC will involve individual assessment, e.g. postoperative complications or immobility. Each case should be judged according the patient's additional risk factors for VTE *(see Table 1)* and their contraceptive preferences. When considering perioperative prophylaxis in current (or recent) pill users, each case should be judged according to additional risk factors. In emergency surgery, routine VTE prophylaxis should be given as the risk of VTE is greater.

10.1.2 PROGESTOGEN-ONLY CONTRACEPTIVES

There is no evidence that low doses of progestogens used for contraception are associated with increased risk of VTE. They may be substituted for COC in women with previous VTE or who are at high risk of VTE.[61] There is no evidence that such preparations should be stopped prior to elective surgery.

However, there is evidence of an association of VTE risk with higher doses of progestogen used for other therapeutic indications (e.g. menstrual disorders), with a five to sixfold increase in the risk of VTE.[194,195]

10.2 HORMONE REPLACEMENT THERAPY AND RALOXIFENE

Recent studies have shown that, like COCs, oral oestrogen-containing hormone replacement therapy (HRT), and the selective oestrogen receptor modulator, raloxifene [196] also increase the risk of VTE threefold, especially in the first year of use. This translates to an absolute risk of 30 per 100,000 women per year for users of HRT compared to 10 per 100,000 women per year for non-users. The risk is increased by obesity and in the presence of thrombophilias[197,198] and is 10-fold higher in older women (mean age 67 years) with coronary heart disease.[199] It is not yet established if HRT is also a risk factor for postoperative VTE,[198] however most HRT users will merit routine prophylaxis (as age over 40 is an independent risk factor: *see Table 1)*.

In patients with a personal history of VTE, an RCT of oral HRT observed a high risk of recurrence, especially in patients with thrombophilias.[200,201] Such women who wish to continue HRT should be referred to a centre or specialist with expertise in thrombophilia; as should women with no personal history of VTE but where thrombophilia is identified through screening. Transdermal 1+

HRT may be preferred in such women because it has a lesser effect on haemostasis compared to oral HRT.[202]

C **Women starting COC, higher dose progestogens, oral HRT or raloxifene should be advised of the small absolute increased risk of VTE. They should have a personal and family history taken of VTE and of additional risk factors for thromboembolic disease** *(e.g. obesity: see Table 1).*

C **A personal history of VTE is a contraindication to the use of COC and oral HRT.**

C **A history of VTE in a first degree family member is a relative contraindication to use of COC, higher dose progestogens, oral HRT or raloxifene, irrespective of the results of thrombophilia screening.**

C **In current (or recent) COC, higher dose progestogen, HRT or raloxifene users who are undergoing surgery, it is recommended that medical practitioners:**

- **discuss the balance of risks and benefits with the patient when considering stopping these hormones prior to elective surgery**
- **arrange adequate alternative contraception if COC is to be discontinued**
- **consider specific antithrombotic prophylaxis according to overall risk factors** *(see Table 1)*
- **give VTE prophylaxis routinely in emergency surgery.**

11 Long distance travel

There are many published anecdotal reports which link VTE with prolonged travel, particularly air travel, but there are only three published case-control studies,[203-205] and some studies of consecutive patients which are small, prone to bias, and gave contrasting and imprecise results.[206-208]

The risk appears higher in patients with known risk factors[209,210] *(see Table 1)* and with flights over 3000 miles.[211]

Possible mechanisms include: immobility; cramped position; dehydration *(augmented by drinking alcohol and coffee)*; compression of popliteal vein by edge of seat; and seated posture, especially when sleeping.[206,207] The relative risk remains to be established in further case-control studies, and the absolute risk remains to be established in large, prospective studies.

Small RCTs have observed reductions in the incidence of asymptomatic DVT by GECS.[212,214] Stockings used in hospital are designed for use in recumbent patients and are not suitable for use in flight.[213] Patients should be provided with the correct type and size of stocking, and should be instructed how to wear them correctly. Stockings also reduce leg oedema after long flights. They may precipitate superficial thrombophlebitis in people with varicose veins.[214]

One small RCT observed reduction in the incidence of asymptomatic DVT by a single dose of LMWH heparin 2-4 hours before flight, but not by aspirin *(400 mg daily for three days, starting 12 hours before flight)*.

D **To minimise the risk of thrombosis when travelling long distances** *(e.g. over four hours)*, **especially by air, all travellers should be advised to:**

- **ensure good hydration**
- **restrict alcohol and coffee intake**
- **regularly carry out simple leg exercises and take occasional walks during travel.**

D **In patients at high risk of thrombosis** *(e.g. previous DVT or PE; known thrombophilia; recent major trauma, surgery or immobilising medical illness, pregnancy)*, **the following prophylactic methods should be considered:**

- **GECS**
- **a single dose of aspirin (150 mg) before travel (± GECS)**
- **a single injection of a LMWH before travel in prophylactic dose** *(see section 3)* **(± GECS)**
- **patients already receiving warfarin should continue to take it (± GECS).** INR should be checked one week before long distance travel and the dose adjusted to within the target therapeutic range.

D **The risks of bleeding should be considered** *(e.g. increased risk of major bleed with aspirin or heparins, which is difficult to treat on a long haul flight)*, **and the balance of risks and benefits should be discussed with the individual patient.**

At present, the balance of risk and benefit is difficult to estimate because the absolute risks of symptomatic VTE with long distance travel, and the absolute risks of bleeding with single-dose aspirin or heparin, are undefined. Further research is required to define these risks.

The UK Royal College of Obstetricians and Gynaecologists has published advice on prophylaxis of VTE for pregnant women travelling by air (www.rcog.org.uk).

12 Development of the guideline

12.1 INTRODUCTION

SIGN is a collaborative network of clinicians, other health care professionals, and patient organisations, funded by the Clinical Resource and Audit Group (CRAG) of the Scottish Executive Health Department. SIGN guidelines are developed by multidisciplinary groups 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.**

12.2 THE GUIDELINE DEVELOPMENT GROUP

Professor Gordon Lowe (Chairman)	*Professor of Vascular Medicine, University of Glasgow & Chairman of SIGN*
Mr Michael Aitchison	*Consultant Urologist, Gartnavel General Hospital, Glasgow*
Mrs Moira Balmer	*Chief Officer, Borders Local Health Council*
Professor Jill Belch	*Professor of Vascular Medicine, Ninewells Hospital, Dundee*
Mr Ivan Brenkel	*Consultant Orthopaedic Surgeon, Queen Margaret Hospital, Dunfermline*
Professor Ian Greer	*Professor of Obstetrics & Gynaecology, University of Glasgow*
Mr Robin Harbour	*Quality and Information Director, SIGN*
Dr John Irving	*Consultant Physician, St John's Hospital at Howden, Livingston*
Ms Brenda Jackson	*Quality Coordinator, Glasgow Royal Infirmary*
Mr Nizam Mamode	*Consultant Transplant Surgeon, Guy's Hospital, London*
Dr Safia Qureshi	*Programme Director, SIGN*
Mr Lech Rymaszewski	*Consultant Orthopaedic Surgeon, Glasgow Royal Infirmary*
Professor Peter Sandercock	*Professor of Medical Neurology, University of Edinburgh*
Ms Lorna Thomson	*Senior Pharmacist, Royal Infirmary of Edinburgh*
Dr Isobel Walker	*Consultant Haematologist, Glasgow Royal Infirmary*
Professor Tony Wildsmith	*Professor of Anaesthesia, Ninewells Hospital, Dundee*

The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. Declarations of interests were made by all members of the guideline development group. Further details are available from the SIGN Executive. A General Practitioner and a General Surgeon were originally part of the guideline development group, but did not attend any meetings. Guideline development and literature review expertise, support, and facilitation were provided by the SIGN Executive.

12.3 SYSTEMATIC LITERATURE REVIEW

The evidence base for this guideline was developed through a systematic review of the literature using an explicit search strategy devised by the SIGN Information Officer in collaboration with members of the guideline development group. Searches covered a number of key Internet sites as well as the CINAHL, Cochrane Library, Embase, Healthstar, and Medline databases. Systematic searches covered the period up until June 1998. Details of the main search strategy and supplementary searches carried out by a member of the guideline development group, are available on the website. The evidence base was updated during the development of the guideline. During this period, SIGN methodology was being reviewed and improved, resulting in the methodology now set out in SIGN 50. The timing of this review means that this guideline was not developed using current methodolgy and does not meet current standards in terms of documentation of the evidence base and considered judgement process.

12.4 CONSULTATION AND PEER REVIEW

12.4.1 NATIONAL OPEN MEETING

A national open meeting is the main consultative phase of SIGN guideline development, at which the guideline development group presents their draft recommendations for the first time. The national open meeting for this guideline was held on 13th December 1999. 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.

12.4.2 SPECIALIST REVIEW

The guideline is reviewed in draft form by a panel of independent expert referees, who are asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. SIGN is very grateful to all of these experts for their contribution to this guideline. The following experts have been invited to comment on this draft:

Dr Trevor Baglin	*Consultant Haematologist, Addenbrooke's Hospital, Cambridge*
Dr Grant Baxter	*Consultant Radiologist, Western Infirmary, Glasgow*
Dr James Beattie	*General Practitioner, Inverurie*
Dr Chris Burton	*General Practitioner, Sanquhar Health Centre*
Dr Ola Dahl	*Senior Researcher & Consultant, Ulleval University Hospital, Norway*
Mr Stan Dobrzanski	*Clinical Pharmacist, Bradford Royal Infirmary*
Professor Gerald Fowkes	*Professor of Epidemiology, University of Edinburgh*
Professor Keith Fox	*Professor of Cardiology, Royal Infirmary of Edinburgh*
Miss Tracey Gillies	*Surgical Registrar, Royal Infirmary of Edinburgh*
Professor Michael Greaves	*Professor of Haematology, University of Aberdeen*
Mr Colin Howie	*Consultant Orthopaedic Surgeon, Royal Infirmary of Edinburgh*
Professor Christopher Ludlam	*Professor of Haematology and Coagulation Medicine Royal Infirmary of Edinburgh*
Dr Simon Maxwell	*Clinical Pharmacologist, Western General Hospital, Edinburgh*
Dr Allan Merry	*General Practitioner, Ardrossan*
Dr Cathy Nelson-Piercy	*Consultant Obstetric Physician, Guy's and St Thomas's Hospitals, London*
Professor Colin Prentice	*Emeritus Professor of Medicine, University of Leeds*
Dr John Reid	*Consultant Radiologist, Borders General Hospital, Melrose*
Professor Vaughan Ruckley	*Emeritus Professor of Vascular Surgery, University of Edinburgh*
Dr Richard Soutar	*Consultant Haematologist, Western Infirmary, Glasgow*
Professor Graham Turpie	*HGH/MacMaster Hospitals, Hamilton, Ontario, Canada*
Ms Anne Walker	*Programme Director, Effective Professional Practice Programme, Aberdeen*

12.4.3 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 peer 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 is as follows:

Dr Doreen Campbell	*Scottish Executive Department of Health*
Professor Ian Campbell	*Royal College of Physicians Edinburgh*
Mrs Patricia Dawson	*Royal College of Nursing*
Dr John Gillies	*Royal College of General Practitioners*
Mr Douglas Harper	*Royal College of Surgeons of Edinburgh*
Dr Cameron Howie	*Royal College of Anaesthetists*
Dr Chris Kelnar	*Vice Chairman of SIGN*
Ms Juliet Miller	*Editor*
Dr Gillian Penney	*Royal College of Obstetricians & Gynaecologists*

12.5 REVIEW AND UPDATING

This guideline was issued in 2002 and will be considered for review in 2006, or sooner if new evidence becomes available. Any updates to the guideline in the interim period will be noted on the SIGN website: **www.sign.ac.uk.**

13 Implementation, audit & key messages for patients

13.1 LOCAL IMPLEMENTATION

Implementation of national clinical guidelines is the responsibility of each NHS Trust and is an essential part of clinical governance. It is acknowledged that every Trust cannot implement every guideline immediately on publication, but mechanisms should be in place to ensure that the care provided is reviewed against the guideline recommendations and the reasons for any differences assessed and, where appropriate, addressed. These discussions should involve both clinical staff and management. Local arrangements may then be made to implement the national guideline in individual hospitals, units and practices, and to monitor compliance. This may be done by a variety of means including patient-specific reminders, continuing education and training, and clinical audit.

Following publication of the original guideline in 1995, most acute hospital trusts in Scotland appear to have established local guidelines for prophylaxis of VTE.[26-29] The revised guideline includes several major changes to the recommendations of the pilot guideline (*summarised in section 1).*

It is recommended that hospitals in Scotland should:

- ensure that local guidelines are in place for relevant surgical, medical and family planning patients
- update existing local guidelines in accordance with the revised national guideline
- perform clinical audit at appropriate intervals.

13.2 KEY POINTS FOR AUDIT

- presence of a local guideline,[26] updated in accordance with the present national guideline
- audit of compliance with local guideline.[29]

13.3 RESOURCE IMPLICATIONS

A recent national audit of VTE prophylaxis in NHS hospitals across Scotland showed a high level of compliance with the local guideline.[29] It is therefore unlikely that there are major new resource implications overall in implementing the current revised national guideline.

The major new recommendation with cost implications is that general medical patients be prescribed heparin prophylaxis (*section 8.3.1*): LMWHs are noted to carry a lower risk of bleeding than UFH.

On the other hand, for patients undergoing major orthopaedic surgery prophylaxis with mechanical methods or aspirin is recommended at a similar level of evidence to heparins *(section 5),* at potentially lower cost.

The current revised national guideline notes that for prophylaxis in surgical patients there is no evidence to prefer LMWH to UFH for efficacy or safety (*section 3*). However, LMWH is safer for prophylaxis in general medical patients (*section 8.3.1*) and in pregnancy (*section 9*). LMWH is increasingly used for outpatient treatment of established DVT[6] and for treatment of unstable angina, in which situations it is more effective than UFH. Acute trusts in Scotland may therefore wish to consider their overall purchasing strategy for heparins when developing their local guidelines for prophylaxis of VTE *(current guideline),* treatment of VTE *(SIGN guideline 36)*[6] and treatment of unstable angina. While LMWHs are more expensive than UFH according to the British National Formulary[94], there may be cost savings due to bulk purchase contracts, and staff time *(LMWHs require fewer injections than UFH)*.

13.4 KEY MESSAGES FOR PATIENTS ADMITTED TO HOSPITAL

This example patient information leaflet is provided for possible use, or adaptation, when discussing treatment options with patients.

There is an increased risk of blood clots in the veins of the leg (deep vein thrombosis or DVT) in patients who are less mobile after admission to hospital. Patients in this group include those with major injuries (e.g. fractures),major surgery, or major medical illness. About one in twenty of these patients gets either a swollen leg due to a DVT, or shortness of breath or chest pain due to the clot travelling from the legs through the bloodstream to the lungs (a pulmonary embolism or PE). About six per one thousand of such patients dies from a large blood clot in the lungs. Patients at highest risk include older patients, those who are overweight, those with a history of blood clots in the legs or lungs, and those with cancer.

This hospital has a local guideline for reducing these risks:

- we encourage our patients to mobilise as early as possible, and to perform regular leg exercises when confined to bed or chair
- we encourage our patients to drink plenty of fluids (some patients may require their fluids to be given in other ways)
- some patients are offered elastic stockings to wear on both legs, which increase blood flow in the legs and reduce the risk of clots. It is important that stockings are the correct size and checked every day for correct fit. Some patients find them tight or uncomfortable to wear
- some patients are offered low-dose aspirin, which thins the blood and reduces the risk of clots in the leg and lungs. (Some patients may already be taking low-dose aspirin to reduce the risk of heart attacks or strokes). Low-dose aspirin increases the risk of bleeding, including bleeding from the stomach and bleeding into surgical wounds, and may not be suitable for some patients
- some patients are offered low-dose heparin, which also thins the blood and reduces the risk of clots in the leg and lungs. Low-dose heparin increases the risk of bleeding including bleeding into surgical wounds, and may not be suitable for some patients
- while low-dose aspirin and low-dose heparin increase the risk of bleeding, it is important to remember that they reduce the risk of death from a large blood clot in the lungs in high risk patients (from six patients per thousand to 2 patients per thousand)

If you have any questions about the risk of blood clots in the legs and lungs while in hospital, or about the preventative measures which we advise for you, please ask your doctor or nurse.

14 Glossary

APTT	Activated partial thromboplastin time
CI	Confidence interval
COC	Combined oral contraceptive
DVT	Deep vein thrombosis
GECS	Graduated elastic compression stockings
HRT	Hormone replacement therapy
INR	International Normalised Ratio of the prothrombin time
IPC	Intermittent pneumatic compression
IU	International units
LMWH	Low molecular weight heparin
MI	Myocardial infarction
NNT	Number needed to treat
OR	Odds ratio
PE	Pulmonary embolism
PEP	Pulmonary Embolism Prevention
PLS	Post-thrombotic leg syndrome
RCT	Randomised controlled trial
TURP	Transurethral resection of the prostate
UFH	Unfractionated heparin
VTE	Venous thromboembolism

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MEDICAL PATIENTS

ACUTE MYOCARDIAL INFARCTION

A
- **All patients with clinically suspected evolving acute MI should be**
  - **given aspirin, if not already receiving it** *(initially 150-300mg)*
  - **considered for thrombolytic therapy**

A
- **Heparins should not be used routinely in addition to aspirin but reserved for patients at increased thromboembolic risk** *(and for certain patients undergoing thrombolysis)*

B
- **Compression stockings may be considered in patients who are at increased risk of VTE,** especially when heparin prophylaxis is contraindicated.

ACUTE STROKE

C
- **Compression stockings** *(high risk patients)*

A
- **Early treatment with aspirin** *(initially 150-300 mg/day starting as soon as intracranial haemorrhage is excluded)*

A
- **Subcutaneous low dose UFH or LMWH** *(patients at high risk of VTE & low risk of haemorrhagic complications)*

GENERAL MEDICAL PATIENTS

A
- **Subcutaneous low dose UFH or LMWH** *(immobilised patients, especially those with heart failure, respiratory failure, infections, intensive care, diabetic coma, cancer, IBD, nephrotic syndrome, leg paralysis e.g. Guillain-Barre Syndrome)*

C
- when these agents are contraindicated substitute with:
  - **GECS**

CANCER PATIENTS

A
- **Subcutaneous UFH, LMWH** *OR* **GECS when immobilised in acute medical or surgical wards**
- **Minidose warfarin** *(1mg/day in patients with central venous catheters)*
- **Low-dose warfarin** *(during chemotherapy in stage IV breast cancer)*

PREGNANCY, DELIVERY & THE PUERPERIUM

Pregnant women:

C
- **should be regularly assessed for VTE risk factors**

D
- **with a personal or family history of VTE should be offered screening for thrombophilias**

C
- **with VTE events during previous pregnancy or COC use, previous idiopathic VTE, or certain thrombophilias should start antenatal prophylaxis as soon as possible**

High Risk Pregnancy

C
- **Subcutaneous LMWH –** check platelet count before and one week after introducing
- **Aspirin in women with antiphospholipid syndrome**
- **GECS may be added or substituted**
- **Warfarin and other coumarins should be avoided if possible during pregnancy and at least between 6-12 weeks gestation.**

N.B. Refer pregnant women on long term anticoagulants or with a heritable thrombophilic defect to an experienced unit.

Delivery

C
- **At the onset of labour stop the administration of LMWH** in women who have requested epidural anaesthesia
- **LMWH can be administered or readministered 3 hours** after atraumatic epidural or spinal anaesthesia or removal of epidural catheter

Puerperium

C
- **All women with a past or family history of VTE, thrombophilia or other risk factors should receive postpartum prophylaxis**
- **UFH** *OR* **LMWH should be introduced (or reintroduced) 3-6 hours after delivery**
- **Anticoagulation should continue at least 6 weeks postpartum in patients with previous VTE or thrombophilias.**
- **Warfarin** can be introduced 24-48 hours after delivery, with **heparin** continuing until INR > 2.0 for 2 consecutive days. Some women may wish to continue LWMH.
- **In other patients continue until discharge; review need for prophylaxis after 5 days.**
- There is **no contraindication to breast feeding** when the mother is being treated with **heparins, warfarin or other coumarins.**

HORMONE USE IN WOMEN

Oral Contraception and Hormone Therapies

C
- Women starting **COC, higher dose progestogens, oral HRT or raloxifene** should be advised of the **small absolute increased risk of VTE**
- **A personal history of VTE is a contraindication to use of COC, oral HRT and raloxifene**
- In current or recent users of COC, higher dose progestogens, oral HRT or raloxifene, who are undergoing surgery, medical practitioners should:
  - **discuss the balance of risks and benefits of stopping these hormones prior to elective surgery**
  - **arrange adequate alternative contraception if COC is to be discontinued**
  - **consider specific antithrombotic prophylaxis according to overall risk factor profile**
  - **give VTE prophylaxis routinely in emergency surgery**

LONG DISTANCE TRAVEL

D
- **To minimise the risk of thrombosis when travelling long distances** *(e.g. over 4 hours)*, **especially by air, all travellers should be advised to:**
  - **ensure good hydration**
  - **restrict alcohol and coffee intake**
  - **regularly carry out simple leg exercises and take occasional walks during travel**

D
- **In patients at high risk of thrombosis** *(e.g. previous VTE, known thrombophilia, recent major trauma, surgery OR immobilising medical illness, pregnancy)*, **the following prophylactic methods should be considered:**
  - **GECS**
  - **a single dose of aspirin** (150mg) **before travel (± GECS)**
  - **a single injection of a LMWH 2-4 hours before travel in prophylactic dose (± GECS)**
  - **patients already receiving warfarin should continue to take it (± GECS)**

D
- **The risks of bleeding should be considered** *(e.g. increased risk of major bleed with aspirin or heparins)* and **the balance of risk and benefits should be discussed** with the individual patient.

HOSPITAL PATIENTS

D **Assess all patients admitted to hospital for:**
- **major trauma** *(e.g. immobilising fracture)*
- **major surgery** *(e.g. duration >30mins)*
- **acute major medical illness** *(e.g. likely to involve >3 days bed rest)*

INDIVIDUAL RISK FACTORS

D **Assessment of individual risk factors should include:**
- *age*
- *obesity*
- *varicose veins*
- *previous VTE*
- *thrombophilia*
- *cancer*
- *heart failure*
- *recent MI or stroke*
- *oestrogen therapy*
- *high dose progestogen*
- *tamoxifen*
- *raloxifene*
- *pregnancy*
- *puerperium*
- *immobility*
- *inflammatory bowel disease*
- *nephrotic syndrome*

EFFECTIVE PROPHYLAXIS

A
- **Subcutaneous low dose UFH** *(5000IU 8-12 hourly or 7500IU 12 hourly for 5 days or until discharge) OR* **LMWH** *(dosage from manufacturer's recommendations)*
- **Aspirin 150mg/day started preoperatively & continued for 35 days**
- **Graduated elastic compression stockings** (GECS) **(± pharmacological prophylaxis or IPC)**
- **Intermittent pneumatic compression** (IPC)
- **mechanical footpumps**

See guideline for cautions and contraindications

PRECAUTIONS PRIOR TO INSTITUTING SPINAL AND EPIDURAL BLOCKS

D
- **Aspirin** – proceed normally, remembering interactions
- **UFH** – proceed normally & exercise caution *OR* administer 4-6 hours before block *OR* delay first dose until after block or after surgery
- **LMWH** – administer 10-12 hours before block

SURGICAL PATIENTS

GENERAL & GYNAECOLOGICAL SURGERY

A
- **Subcutaneous low dose UFH or LMWH**
- **GECS can be *combined* with UFH or LMWH in patients at high risk due to the presence of multiple risk factors**

When heparins are contraindicated substitute with:
- **GECS** *OR*
- **IPC followed by above-knee GECS** *OR*
- **Aspirin** *(150 mg/day; oral, rectal or NG tube) OR*
- **Intravenous dextran 40 or 70** *(an alternative for high risk patients) OR*

C
- **Warfarin** *(e.g. in those already receiving; target INR 2.0-2.5)*

ORTHOPAEDIC SURGERY & TRAUMA

Total Hip or Knee Replacement

A
- **Mechanical prophylaxis** *(GECS ± IPC or foot pumps)*
- **Aspirin** *(150 mg orally, started before surgery and continued for 35 days)*
- **Subcutaneous low dose UFH or LMWH** *(for 7-15 days, extended to 4-5 weeks in very high risk patients)*
- **Warfarin** *(e.g. in those already receiving; target INR 2.0-3.0)*

Hip Fracture Surgery

C **Early surgery** *(within 24 hours)* **where possible**

A
- **Mechanical prophylaxis** *(IPC or foot pumps)*
- **All patients should receive aspirin** *(150 mg orally, started on admission and continued for 35 days)* **± mechanical prophylaxis**
- **Subcutaneous low dose UFH** *OR* **LMWH** *(only in patients at high risk due to multiple risk factors, or contraindications to mechanical prophylaxis and/or aspirin)*

Other Trauma

A
- **LMWH for patients with spinal cord injury, major lower limb fractures or multiple trauma**
- **Mechanical prophylaxis in patients with contraindications to LMWH**

C **Aspirin in patients in whom LMWH is contraindicated and mechanical prophylaxis is not feasible**

UROLOGICAL SURGERY

A **In major or open procedures:**
- **Subcutaneous low dose UFH or LMWH**

when heparins are contraindicated substitute with:

B
- **GECS ± IPC**

B **In patients undergoing TURP who are at high risk of VTE due to multiple risk factors, consider prophylaxis with UFH, LMWH** *OR* **GECS ± IPC.**

NEUROSURGERY

A
- **GECS ± IPC**
- **LMWH can also be considered but there is an increased risk of haemorrhage**

CARDIOTHORACIC SURGERY

A
- **Subcutaneous low dose UFH or LMWH**

B
- **IPC + low dose heparin** *(cardiac surgery)*

A
- **Aspirin should be discontinued prior to elective cardiac bypass surgery** because of the risks of bleeding **& resumed** *(75-300mg/day)* **via nasogastric tube 6 hours following bypass grafting** and continued long term.

PERIPHERAL VASCULAR SURGERY

C
- **GECS** *(patients undergoing varicose vein surgery with no additional risk factors)*
- **Subcutaneous low dose UFH or LMWH** *(patients with critical limb ischaemia, or undergoing major peripheral vascular surgery or varicose vein surgery in the presence of additional risk factors)*

A
- **Aspirin should be given or resumed** *(75-300mg/day via nasogastric tube)* **6 hours following bypass grafting** and continued long term.

GLOSSARY

COC	combined oral contraceptives
DVT	deep vein thrombosis
GECS	graduated elastic compression stockings
HRT	hormone replacement therapy
IPC	intermittent pneumatic compression
LMWH	low molecular weight heparin
PE	pulmonary embolism
TURP	transurethral resection of the prostate
UFH	unfractionated heparin
VTE	venous thromboembolism