S I G N

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Antithrombotic Therapy

A National Clinical Guideline

March 1999

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

The definitions of the types of evidence and the grading of recommendations used in this guideline originate from the US Agency for Health Care Policy and Research[1] and are set out in the following tables.

STATEMENTS OF EVIDENCE

Ia	Evidence obtained from meta-analysis of randomised controlled trials.
Ib	Evidence obtained from at least one randomised controlled trial.
IIa	Evidence obtained from at least one well-designed controlled study without randomisation.
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study.
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
IV	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

GRADES OF RECOMMENDATIONS

A **Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation.**
(Evidence levels Ia, Ib)

B **Requires the availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.**
(Evidence levels IIa, IIb, III)

C **Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality.**
(Evidence level IV)

GOOD PRACTICE POINTS

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

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Notes for users of the guideline

DEVELOPMENT OF LOCAL GUIDELINES

It is intended that this guideline will be adopted after local discussion involving clinical staff and management. The Area Clinical Audit Committee should be fully involved. Local arrangements may then be made for the derivation of specific local guidelines to implement the national guideline in individual hospitals, units and practices and for securing compliance with them. This may be done by a variety of means including patient-specific reminders, continuing education and training, and clinical audit.

SIGN consents to the copying of this guideline for the purpose of producing local guidelines for use in Scotland.

STATEMENT OF INTENT

This report is not intended to be construed or to serve as a standard of medical care. Standards of medical 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.

These parameters of practice should be considered guidelines only. Adherence to them will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the doctor in light of the clinical data presented by the patient and the diagnostic and treatment options available.

Significant departures from the national guideline as expressed in the local guideline should be fully documented and the reasons for the differences explained. Significant departures from the local guideline should be fully documented in the patient s case notes at the time the relevant decision is taken.

A background paper on the legal implications of guidelines is available from the SIGN secretariat.

REVIEW OF THE GUIDELINE

This guideline was issued in 1999 and will be reviewed in 2001 or sooner if new evidence becomes available. Any amendments in the interim period will be noted on the SIGN website. Comments are invited to assist the review process. All correspondence and requests for further information regarding the guideline should be addressed to:

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Abbreviations

AF	Atrial fibrillation
APTT	Activated partial thromboplastin time
CT	Computed tomography
DVT	Deep vein thrombosis
GI	Gastrointestinal
GP	General practitioner
INR	International normalised ratio of prothrombin time
IU	International unit
IV	Intravenous
IVC	Inferior vena cava
LMW	Low molecular weight
MI	Myocardial infarction
NNT	Number needed to treat
PE	Pulmonary embolism
SC	Subcutaneous
SD	Standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
TIA	Transient cerebral ischaemic attack

1 Introduction

1.1 BACKGROUND

Arterial, cardiac and venous thromboembolism are major causes of death and disability in developed countries, particularly Scotland. Each year, over 50,000 people in Scotland suffer coronary thrombosis (presenting as sudden cardiac death, acute myocardial infarction, or acute unstable angina) which frequently results in death or in disabling heart failure.[2] A further 17,000 people are hospitalised each year for stroke, which again is often fatal or disabling: about 85% of strokes are due to thromboembolism (from the heart, aorta, neck arteries or, rarely, leg veins) and about 15% are due to intracranial bleeding (including that associated with anticoagulant therapy).[3] About 500 amputations and 2,000 other operations are performed in Scotland annually for lower limb ischaemia, which is often due to thromboembolism from the heart, aorta or arteries to the lower limbs.[4] Finally, about 10,000 people in Scotland develop deep vein thrombosis of the lower limb (DVT) or its sequel, pulmonary embolism (PE) each year: PE occurs in about 1% of hospital admissions and is the most common preventable cause of death in hospitalised patients and pregnant or puerperal women.[5] DVT may also be followed by the post-thrombotic leg syndrome which includes chronic venous ulceration: another major consumer of health service costs.

1.2 CAUSES OF THROMBOSIS

Thrombosis usually occurs at sites of vessel or heart wall damage (e.g. rupture of an atherosclerotic plaque; diseased or replacement heart valves; mural thrombus following endocardial injury after myocardial infarction) and/or blood flow disturbance (e.g. atrial fibrillation, leg veins in immobile patients). The contributions of platelet-fibrin thrombi to arterial and venous occlusion and to clinical events have been established by morphological studies (pathological, angiographic and angioscopic); epidemiological studies of haemostatic variables (related to platelets, coagulation and fibrinolysis); and especially by large randomised controlled trials of antiplatelet, anticoagulant or thrombolytic therapies.[6]

1.3 ANTITHROMBOTIC THERAPY

Recent overviews of such controlled trials have suggested that antithrombotic prophylaxis in appropriate people at increased risk of thrombosis, and antithrombotic treatment in appropriate patients with acute thrombosis, not only reduces disability and mortality, but is also cost-effective.[6] Routine antithrombotic therapy in selected, high-risk patients therefore appears to offer a major, cost-effective health gain in Scotland.

1.4 ANTIPLATELET THERAPY

Antiplatelet therapy, usually with aspirin, is clearly effective (and also cost-effective) in reducing death in acute myocardial infarction or acute ischaemic stroke and in the prevention of serious vascular events when given as secondary prophylaxis to patients with clinical evidence of arterial disease (*see table 1*).[6-9] It is also effective in prevention of stroke in selected patients with heart valve disease, atrial fibrillation,[6, 10-12] and in primary prevention of myocardial infarction in men with multiple risk factors.[13, 14] Such patients are readily identified by general practitioners and by hospital doctors.

Table 1

ANTIPLATELET THERAPY: EFFECTS ON SECONDARY PROPHYLAXIS OF MYOCARDIAL INFARCTION, STROKE OR VASCULAR DEATH[7, 9]

Clinical Condition	**Risk of event in trials**		**Risk difference**	*mean trial duration (months)*	**NNT** *(duration)**
	Control	**Antiplatelet**			
Acute MI *(10 trials)*	14.3%	10.5%	3.8%	(1)	30 (1 month)
Unstable angina *(12 trials)*	13.5%	8.0%	5.5%	(18)	15 (1 year)
Prior MI *(12 trials)*	17.0%	13.5%	3.5%	(27)	65 (1 year)
Stable angina *(6 trials)*	15.9%	11.4%	4.5%	(33)	150 (1 year)
Peripheral arterial disease *(39 trials)*	7.5%	6.3%	1.2%	(12)	100 (1 year)
Prior TIA or ischaemic stroke *(22 trials)*	21.4%	17.9%	4.5%	(30)	69 (1 year)
Acute ischaemic stroke *(3 trials)*	9.3%	8.4%	0.9%	(0.75)	100 (3 weeks)

**NNT= number needed to treat over the duration indicated to prevent one vascular event*

Despite this clear evidence of efficacy, recent audit studies have shown that many such patients do not receive aspirin from their general practitioners or hospital doctors.[15, 16]

1.5 ANTICOAGULANT THERAPY

Anticoagulant therapy, usually with heparin injections short term and/or oral anticoagulants (usually warfarin) long term, is also clearly effective in prevention of serious vascular events when given as prophylaxis to high-risk patients, or as treatment of acute arterial or venous thrombosis.[5, 6, 10-12, 14, 17-22] *(See tables 2 and 3.)* However, full-dose anticoagulation is also a common cause of major internal bleeding, including intracranial, gastrointestinal or retroperitoneal haemorrhage, which can be fatal. Recent audit studies have shown that many high-risk patients do not receive anticoagulant prophylaxis or treatment; that there is wide variation in the doses of heparin and warfarin prescribed, the target effect and range, and in both inpatient and outpatient laboratory monitoring and patient monitoring; and that communication between clinicians, laboratories and patients can be improved.[16, 23-26]

It is therefore important to select patients most likely to benefit from anticoagulant therapy (i.e. those in whom the risk of major thromboembolic events exceeds the risk of major bleeding); and to minimise both thromboembolic and haemorrhagic morbidity and mortality during anticoagulant therapy. Approaches to the latter include: use (and clinical audit) of optimal target effect and range for unfractionated heparin and warfarin; patient and laboratory monitoring; patient education; and effective communication between patients, general practitioners, hospital doctors, anticoagulant clinics, haematology laboratories, and other relevant health care professionals (e.g. pharmacists, dentists). With the increasing use of heparin in hospitals, and the increasing use of long-term warfarin in outpatients (e.g. for primary or secondary prophylaxis in patients with atrial fibrillation), many people in Scotland are now iatrogenic haemophiliacs , for whom it is important that general practitioners, hospital services and health boards ensure that the considerable potential of anticoagulant prophylaxis to reduce thromboembolic mortality is not only assured by clinical audit of use and monitoring, but is also not outweighed by increased morbidity and mortality due to drug-induced bleeding.

1.6 THROMBOLYTIC THERAPY

As distinct from antithrombotic therapy with aspirin, heparin or warfarin, which prevents or reduces formation of platelet-fibrin thrombi, thrombolytic (fibrinolytic) agents lyse fibrin thrombi by activating endogenous plasminogen to plasmin, which dissolves fibrin. Short term thrombolytic therapy with streptokinase, anistreplase, or tissue plasminogen activator (alteplase) has been shown in a recent overview of large randomised controlled trials to significantly reduce mortality and morbidity (including stroke and heart failure) when given to selected patients with evolving acute myocardial infarction (MI).[27] A Scottish consensus statement on thrombolytic therapy in the early treatment of acute MI has been issued.[2] International guidelines and consensus statements on thrombolytic therapy, not only for acute myocardial infarction, but also for peripheral arterial and venous thromboembolism, have also been published.[28, 29] The benefits and risks of thrombolysis in acute ischaemic stroke are being evaluated in large, randomised controlled trials: at present the balance is unclear. The use of thrombolytic therapy will not be addressed in detail in the pilot edition of this guideline.

Table 2

INDICATIONS FOR PARENTERAL ANTICOAGULATION WITH HEPARINS

Low dose unfractionated heparin	*See section**
▪ Local prevention of clotting in peripheral arterial catheters	*10.1*
▪ DVT prophylaxis	
Routine 5000 IU 8-12 hourly or 7500 12 hourly by subcutaneous injection Monitoring of APTT nor routinely required [5]	*2.1*
Adjusted to maintain target APTT ratio (monitor) e.g. hip surgery, pregnancy [5]	*2.1*
Full dose unfractionated heparin (APTT should be monitored)	
▪ Treatment of acute deep vein thrombosis and/or pulmonary embolism; and maintenance of anticoagulation to prevent recurrence in selected patients	*2.3, 2.5*
▪ Prophylaxis of cardiac thromboembolism in selected patients	*3, 4*
▪ Severe unstable angina, selected patients with acute myocardial infarction	*5.1, 5.2*
▪ Coronary angioplasty or bypass surgery	*5.4*
▪ Acute critical limb ischaemia	*6.2*
▪ Peripheral angioplasty or bypass surgery	*6.3*
▪ Carotid endarterectomy	*7.3*
▪ Haemodialysis	*10.1*
Low dose low molecular weight heparin (monitoring of anti-Xa not routinely required)	
▪ DVT prophylaxis	*2.1*
Full dose low molecular weight heparin (monitoring of anti-Xa not routinely required)	
▪ Treatment of acute deep vein thrombosis and/or pulmonary embolism	*2.3*
▪ Severe unstable angina	*5.2*
▪ DVT prophylaxis in selected patients	*See SIGN guideline* [5]

* *For full discussion of the supporting evidence and grades of recommendations for these indications, see the sections noted*

1.7 PROPHYLAXIS OF VENOUS THROMBOEMBOLISM

A Scottish national guideline has been issued for identification of risk of venous thromboembolism and prophylaxis in patients at increased risk during hospitalisation, pregnancy or the puerperium[5] and is being revised in 1999. This use of anticoagulant therapy will therefore not be addressed in the present guideline.

1.8 AIM OF THE GUIDELINE

The aim of this national guideline is to assist individual health boards, general practitioners, hospital departments and hospitals to produce local guidelines for:

(i) identification of patients at increased risk for arterial thromboembolism, or who have acute thromboembolism

(ii) routine administration and monitoring of appropriate, effective antithrombotic prophylaxis and treatment in such patients

(iii) prevention and management of anticoagulant overdosage or bleeding during anticoagulant therapy.

1.9 CONTRAINDICATIONS AND OTHER EXCEPTIONS TO THE RECOMMENDATIONS

To avoid constant repetition, the words unless contraindicated have not been included in every recommendation on the use of drug therapy in this guideline, but all recommendations should be interpreted as carrying this caveat. The balance of risks (bleeding) and benefits of antithrombotic therapies should be carefully assessed in the individual patient.

Table 3

INDICATIONS FOR ORAL ANTICOAGULATION (USUALLY WITH WARFARIN)

Indication	**Target (desired range) of INR**	*See section**
Prophylaxis of central venous catheter thrombosis	Minidose warfarin (1 mg/day) with no routine INR monitoring	*10.2*
Prophylaxis of thrombosis during stage IV breast cancer chemotherapy	1.6 (1.3-1.9)	*10.2*
Primary prophylaxis of myocardial infarction in high risk men or women		*9.2*
Prophylaxis of venous thromboembolism in high risk patients	2.5 (2.0-3.0)	*2.1, 13.4*
Treatment of venous thromboembolism		*2.4*
Prophylaxis of cardiac thromboembolism		
▪ atrial fibrillation		*3*
▪ heart valve disease, heart failure, cardiomyopathy		*4.1-4.3*
▪ mechanical heart valves		*4.4*
first generation	3.5 (3.0-4.5)	
second generation	3.0 (2.5-3.5)	
▪ bioprosthetic heart valves (selected patients)	2.5 (2.0-3.0)	*4.5*
▪ acute myocardial infarction (selected patients)		*5.1*
Prophylaxis of recurrent myocardial infarction (selected patients)		*5.1*
Critical limb ischaemia		*6.2*
Prophylaxis of recurring venous, cardiac or arterial thromboembolism	2.5 (2.0-3.0) (± aspirin) or 3.5 (3.0-4.0) (± aspirin)	*2.7, 8*

* *For full discussion of the supporting evidence and grades of recommendations for these indications, see the sections noted*

2 Venous thromboembolism

2.1 SHORT TERM PROPHYLAXIS IN PATIENTS WITH TEMPORARY INCREASED RISK

This has been addressed in the SIGN guideline on Prophylaxis of Venous Thromboembolism,[5] which is currently being revised.

2.2 DIAGNOSIS OF ACUTE VENOUS THROMBOEMBOLISM

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

- *Predisposing factors:*

  Recent trauma, surgery, medical illness, or immobilisation from any other cause, especially in the presence of known thrombophilia, previous venous thromboembolism, pregnancy, puerperium, age over 40 years, obesity, varicose veins, oestrogen use, malignancy, heart failure, inflammatory bowel disease, or nephrotic syndrome.[5]

- *Suggestive symptoms or signs:*

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

  PE: breathlessness, faintness, collapse, chest pain, haemoptysis, tachycardia, tachypnoea, raised jugular venous pressure, focal signs in chest or on chest *x*-ray.

Clinical prediction guides may be useful in risk stratification.[30] *Evidence level III*

2.2.1 DIAGNOSTIC IMAGING

Less than 50% of patients with clinically-suspected DVT or PE have the diagnosis confirmed when routine diagnostic imaging is performed.[31, 32] *Evidence level III*

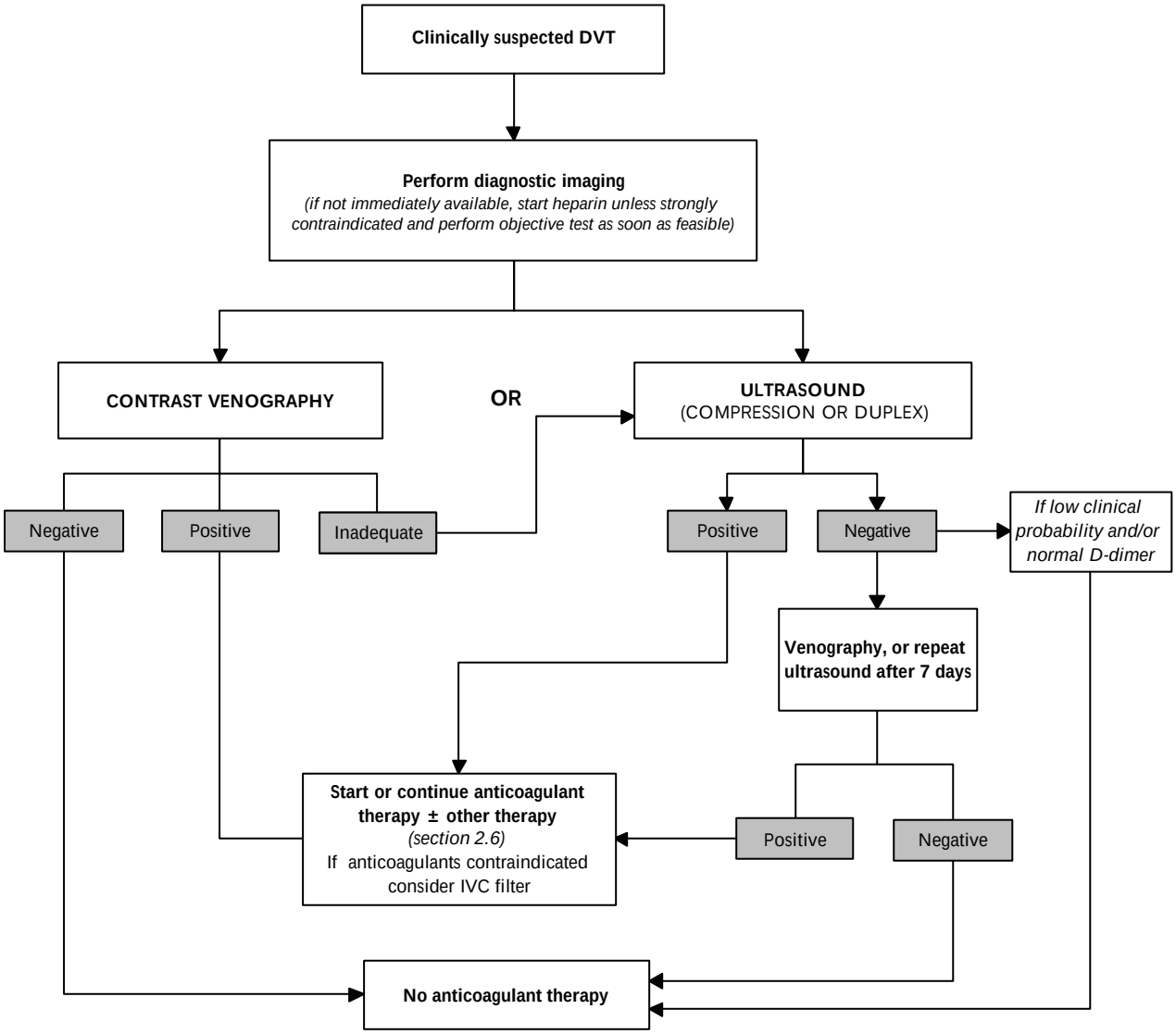
C **Diagnostic imaging should be performed expeditiously** (within 24 hours if possible) **in patients with suspected DVT** (venography, ultrasound) **or PE** (e.g. ventilation-perfusion lung scanning) **to minimise exposure to the risks of inappropriate continued full-dose anticoagulation in those patients in whom venous thromboembolism is not confirmed.**

2.2.2 DIAGNOSIS OF DVT

It is safe to withhold anticoagulation therapy in patients with clinically-suspected DVT in whom diagnostic imaging does not confirm the diagnosis.[30, 31, 33-36] Consequently, routine diagnostic imaging prevents inappropriate and potentially hazardous exposure of patients who do not have DVT to anticoagulant therapy.[37, 38] *Evidence level III*

Figure 1

POSSIBLE ALGORITHMS FOR INITIAL MANAGEMENT OF CLINICALLY SUSPECTED DVT



B **In all patients with clinically-suspected DVT, the diagnosis should be confirmed or excluded by diagnostic imaging, either:**

- **non-invasive testing by ultrasound (compression or Duplex scanning), followed by contrast venography if negative to detect calf DVT and non-occlusive proximal DVT; or**
- **contrast venography (which detects both calf and proximal DVT); or**
- **serial (repeat after seven days) non-invasive testing by ultrasound (compression or Duplex scanning) to detect proximal extension of calf DVT.**

It should be noted that the pre-test clinical probability of DVT strongly modifies both the positive predictive value and the negative predictive value of all diagnostic tests.[30, 39] Hence when the findings of ultrasound are at variance with a strong clinical impression, venography should be considered, especially when there is a high clinical probability of disease and a negative non-invasive test result.[30, 39] Conversely, there is some evidence that a single negative ultrasound test may be sufficient to exclude DVT in patients with a low clinical pre-test probability,[30] or a normal fibrin D-dimer test.[33]

Evidence level III

B **A single negative ultrasound may be sufficient to exclude DVT in patients with low clinical pre-test probability and/or a normal fibrin D-dimer assay.**

Figure 1 shows possible algorithms for initial management of clinically suspected DVT.

2.2.3 DIAGNOSIS OF PULMONARY EMBOLISM

It is safe to withhold anticoagulant therapy in patients with clinically-suspected PE in whom diagnostic imaging does not confirm the diagnosis of PE or DVT, and who have adequate cardiorespiratory reserve.[31, 32, 40] Consequently, routine objective testing prevents inappropriate and potentially hazardous exposure of patients who do not have PE or DVT to anticoagulant therapy.[37]

In up to 25% of cases, ventilation perfusion lung scans are diagnostic of PE and indicate anticoagulant therapy. In up to 25% of cases, lung scans are normal, and exclude PE. In the remaining 50% of cases, lung scans are non-diagnostic, and should be followed by venography or serial (repeat after seven days) non-invasive testing by ultrasound and/or by spiral CT angiography or pulmonary angiography (if available).[31, 32, 40-42]

Evidence level III

B **In all patients with clinically suspected PE, the diagnosis should be confirmed or excluded by an objective test.**

This is usually ventilation-perfusion lung scanning, supplemented by objective testing for DVT.[43] Pulmonary angiography,[43] spiral CT angiography,[41, 42] or echocardiography[41, 42] may also demonstrate PE.

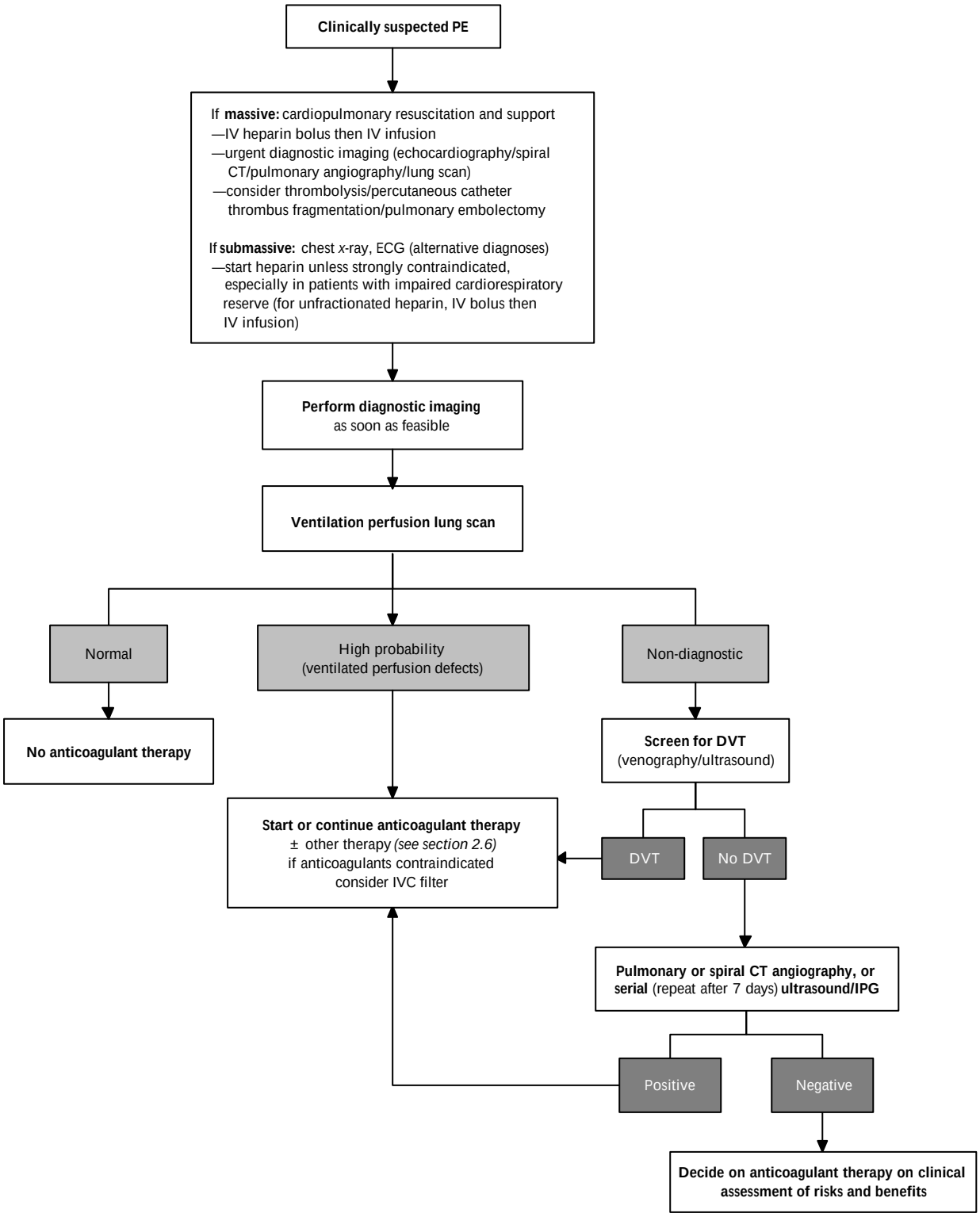
Evidence level III

Figure 2 shows one possible algorithm for initial management of clinically suspected PE.

The recent guideline from the British Thoracic Society[42] should also be consulted when developing local guidelines. The role of newer imaging techniques, as well as fibrin D-dimer assays,[44] in diagnosis merits further research.

Figure 2

POSSIBLE ALGORITHM FOR INITIAL MANAGEMENT OF CLINICALLY SUSPECTED PE



2.3 HEPARIN IN ACUTE TREATMENT OF DVT OR PE

One randomised controlled trial of intravenous heparin and oral anticoagulants versus no treatment in clinically suspected (but not objectively confirmed) PE[45] and one randomised controlled trial of intravenous heparin plus oral anticoagulants versus oral anticoagulants alone in objectively-confirmed proximal DVT[46] showed that heparin reduced the risk of further thromboembolism. Two large randomised controlled trials of heparin treatment of DVT observed that failure to reach the lower limit of the target therapeutic range of the APTT ratio (1.5-2.5) was associated with a 10-15-fold increase in relative risk of recurrent thromboembolic events.[32] Descriptive studies have indicated high risks of recurrent thromboembolism and death when heparin was not given to patients with suspected or proven DVT or PE, compared to low risks when heparin was given.[32, 47, 48]

Evidence level Ib supported by evidence levels II and III

Randomised trials have shown equivalent efficacy of low molecular weight heparins to unfractionated heparin.[20, 49-51]

Evidence level Ib

A **Outpatients with clinically suspected DVT or PE should be referred to hospital for diagnosis and consideration of initial anticoagulation with heparin, to reduce the risk of further venous thromboembolic events which are often fatal or disabling.**

A **In clinically-suspected DVT or PE, heparin should be commenced** (unless strongly contraindicated) **until the diagnosis is excluded by diagnostic imaging.**

2.3.1 INTRAVENOUS UNFRACTIONATED HEPARIN

This is commenced by an intravenous bolus dose (5,000 IU or 75 IU/kg body weight), followed by maintenance intravenous infusion (1,000-1,500 IU/hour). This is the traditional method of heparin treatment in acute DVT or PE, and remains the treatment of choice in massive PE because of its rapid effect, and because of clinical experience.[45, 47, 48, 52, 53]

Unfractionated heparin requires monitoring by the APTT. APTT ratios below 1.5 are associated with recurrent thromboembolism and ratios above 2.5 are associated with increased risk of bleeding.[31] Use of protocols for heparin dose adjustment according to APTT ratio results improves the achievement of therapeutic target ranges.[31, 52-54] Each laboratory should standardise its own target range for APTT ratio, which should correspond to an anti-Xa level of 0.35-0.70 u/ml or heparin level of 0.2-0.4 IU/ml by protamine titration.[54]

Evidence level Ib and II

B **Monitoring of the APTT ratio should be performed expeditiously in patients receiving unfractionated heparin, and heparin doses adjusted according to a local protocol, to achieve the therapeutic target range (usually 1.5-2.5) within 24 hours.**

C **The platelet count should be monitored to detect heparin-induced thrombocytopenia** (as stipulated by the Committee on Safety of Medicines).

2.3.2 SUBCUTANEOUS UNFRACTIONATED HEPARIN

A meta-analysis of randomised controlled trials has shown that 12-hourly subcutaneous unfractionated heparin is as effective in prevention of recurrent thromboembolism in patients with acute DVT, and is at least as safe, as intravenous unfractionated heparin.[55] There are no published trials of subcutaneous unfractionated heparin in acute PE.

Evidence level Ia

A **Subcutaneous unfractionated heparin is an effective alternative to intravenous unfractionated heparin for the initial treatment of DVT.**

Subcutaneous administration may be advantageous in patients with poor venous access (e.g. intravenous drug users); facilitates mobilisation; and may allow outpatient treatment of some patients with DVT. A conventional intravenous bolus (5,000 IU or 75 IU/kg body weight) should be given, and monitoring of the APTT ratio and dose adjustment performed as for IV heparin, to achieve a therapeutic target range and hence minimise risks of recurrent thromboembolism and of bleeding. Use of a weight-based algorithm allows rapid achievement of effective and safe anticoagulation.[56] The platelet count should be monitored, to detect heparin-induced thrombocytopenia.

2.3.3 LOW MOLECULAR WEIGHT HEPARINS

A meta-analysis of randomised controlled trials of unfractionated heparin versus low molecular weight (LMW) heparins in treatment of DVT suggests that the latter are similarly effective in reducing extension of DVT and the risk of thromboembolic recurrence; possibly carry a lesser risk of major bleeding; and may be associated with lower mortality.[20] Dalteparin, enoxaparin and tinzaparin are licensed for this purpose in the UK. Two trials have also shown equivalence in treatment of PE.[50, 51] Tinzaparin and enoxaparin are licensed for this purpose in the UK.

Evidence level Ia

A **Low molecular weight heparins are effective alternative treatment to unfractionated heparin for DVT and PE.**

LMW heparins also have the logistic advantages of efficacy as once-daily subcutaneous injections (facilitating outpatient treatment of DVT in some patients);[21, 22] and of no requirement for routine daily monitoring of coagulation tests due to their more predictable effect, which is advantageous in patients with poor venous access (e.g. intravenous drug users). However, monitoring of the platelet count is suggested, as for unfractionated heparin, because the incidence of heparin-induced thrombocytopenia appears to be similar.[20]

2.3.4 BASELINE BLOOD SAMPLES WHEN INITIATING ANTICOAGULANT THERAPY FOR DVT OR PE

☑ A baseline citrated sample for coagulation screen, and thrombophilia screen if indicated *(see table 4)*; and a baseline blood count including platelet count should be sent to the haematology laboratory prior to starting heparin (which can lower antithrombin levels and platelet count) or oral anticoagulants (which can lower protein C and S levels).

☑ Blood samples should also be sent for baseline urea, electrolytes and liver function tests, to exclude renal or hepatic impairment which are cautions for anticoagulant therapy.

2.4 ORAL ANTICOAGULANTS IN ACUTE AND MAINTENANCE TREATMENT OF DVT OR PE

One randomised controlled trial of intravenous heparin and oral anticoagulants versus no treatment in clinically suspected PE;[45] one randomised controlled trial of oral anticoagulants versus no anticoagulants for three months in symptomatic calf DVT;[57] and three randomised controlled trials of high-intensity oral anticoagulants versus low-dose heparin, adjusted-dose heparin, or lower-intensity oral anticoagulants in proximal vein thrombosis[58-60] showed that oral anticoagulants reduce the risk of further thromboembolism. Descriptive studies have reported a high risk of recurrent thromboembolism and death when oral anticoagulants were not given, compared to low risks when oral anticoagulants were given.[48, 61]

Evidence level Ib supported by evidence level III

A **Following initial heparinisation in patients with DVT or PE, maintenance of anticoagulation with oral anticoagulants is recommended in non-pregnant patients.**

☑ In intravenous drug users, the advisability of any continued anticoagulant therapy following hospital discharge should be critically assessed, given the poor compliance with medical care, the bleeding risks of femoral vein and artery self-injection under therapeutic anticoagulation, and the lack of venous access for monitoring of oral anticoagulants and for treatments of oral anticoagulant-induced bleeding.

2.4.1 TARGET INR

Randomised controlled trials[58-60, 62-64] indicate the use of a target INR of 2.5, range 2.0-3.0. This is supported by retrospective descriptive studies which have shown a higher risk of recurrence (in patients without cancer) when INR values are below 1.9,[65] or lower risk of bleeding at INR 2.0-3.0.[32, 66, 67]

Evidence level Ib supported by evidence level III

A **The optimal target INR during oral anticoagulant therapy for a first episode of venous thromboembolism is 2.5, range 2.0-3.0.**

2.4.2 HEPARIN COVER OF INITIAL ORAL ANTICOAGULANT THERAPY

Evidence from animal studies, pharmacodynamic studies, and clinical reports collectively suggest that heparin is required during the first few days of oral anticoagulant therapy for acute thrombosis, to prevent thrombosis due to a prothrombotic imbalance (earlier reduction in protein C, protein S and factor VII than in factors II, IX and X). Such thrombosis may include microvascular thrombosis causing coumarin-induced skin necrosis, especially in patients with deficiencies of proteins C or S.[32]

C **When oral anticoagulant therapy is initiated for treatment of acute DVT or PE it should be overlapped with heparin therapy for 4-6 days and until the INR is > 2.0 on two consecutive days.**

2.4.3 TIMING OF ANTICOAGULANT THERAPY

Early institution of oral anticoagulants is as effective and safe as delaying their institution for several days.[62-64]

A **Early institution of oral anticoagulants is recommended in most patients.** *Evidence level Ib*

Particularly when intravenous unfractionated heparin is used, this reduction in the duration of heparin allows earlier mobilisation, earlier discharge from hospital, less infusion-related phlebitis, lower treatment costs, and lower incidence of heparin-induced thrombocytopenia.[64] It has been suggested (but not proven) that patients with massive iliofemoral DVT may benefit from a longer duration of heparin therapy.[32]

2.4.4 DURATION OF ORAL ANTICOAGULANT THERAPY

Six randomised trials have compared shorter durations (4-6 weeks) to longer durations (3-6 months); however differences and defects in their study designs make their interpretation difficult[32, 66] and at present a minimum of three months duration of treatment is recommended.[31, 32, 48, 57-66] *Evidence level Ib supported by evidence level III*

A retrospective analysis of one randomised trial has suggested that four weeks therapy might be as effective as three months therapy in patients with transient risk factors (e.g. surgery).[68] However, further trials in this area are needed.[66]

A **The routine recommended duration of oral anticoagulant therapy following a first episode of DVT or PE is for at least three months.**

C **At three months, patients should be assessed for continuing risk factors** (e.g. idiopathic, premature or familial presentation; thrombophilias (*see table 4*); malignancy; chronic infection; inflammatory bowel disease; nephrotic syndrome; thromboembolic pulmonary hypertension).[66, 69]

C **The presence of continuing risk factors suggests consideration of anticoagulation long term, or until such risk factors resolve.**

☑ The relative risks of recurrence and of bleeding should be balanced in the individual patient.

2.5 HEPARINS IN MAINTENANCE TREATMENT OF DVT OR PE

Adjusted-dose subcutaneous heparin (target APTT ratio 2.0, range 1.5-2.5)[59] or subcutaneous low molecular weight heparin[22] are effective alternatives to oral anticoagulation, e.g. in pregnancy.[70] *Evidence level Ib supported by evidence level IV*

A **Adjusted-dose subcutaneous heparin may be considered as an alternative therapy for patients in whom oral anticoagulants are either contraindicated** (e.g. pregnancy), **inconvenient** (e.g. distance from monitoring facilities) **or ineffective** (e.g. in some cancer patients).

It should be noted that heparin therapy for more than four months carries a high risk of osteopenia and bone fractures. LMW heparins may reduce this risk.[22]

2.6 OTHER ANTITHROMBOTIC THERAPIES IN TREATMENT OF DVT OR PE

2.6.1 MASSIVE PE

C **In patients with massive PE, cardiorespiratory resuscitation and support, urgent intravenous heparinisation, and urgent confirmation of the diagnosis by echocardiography, spiral CT, pulmonary angiography, or lung scanning are appropriate.**

C **Thrombolytic therapy, percutaneous catheter thrombus fragmentation, or pulmonary embolectomy may each be considered, according to local facilities and expertise.**[28, 31, 32, 42, 66]

(See also figure 2.)

2.6.2 MASSIVE DVT

C **In patients with massive DVT, leg elevation to reduce oedema, urgent intravenous heparinisation, and urgent confirmation of the diagnosis by venography or ultrasound are appropriate.**

C **Thrombolytic therapy or venous thrombectomy may be considered in patients with threatened venous gangrene.** [28, 31, 32, 66]

2.6.3 ACUTE NON-MASSIVE DVT

C **In acute non-massive DVT, leg oedema can be reduced initially by leg elevation, and recurrent oedema minimised by mobilisation with a graduated elastic compression stocking and intermittent leg elevation.**

2.6.4 INFERIOR VENA CAVA (IVC) FILTER INSERTION

C **If therapeutic anticoagulation is contraindicated (e.g. due to high bleeding risk), inferior vena cava (IVC) filter insertion (e.g. with a Greenfield caval filter) should be considered.**[32]

A recent randomised trial suggests that an initial protective effect may be balanced by a later increased risk of recurrent DVT.[71] Temporary filters may reduce this risk, and are under evaluation.

Evidence level Ib

Temporary filters may reduce this risk, and are under evaluation.

2.6.5 GRADUATED ELASTIC COMPRESSION STOCKINGS

A randomised controlled trial has shown a reduction in the incidence of severe post-thrombotic leg syndrome from 23% to 11% over two years.[72]

Evidence level Ib

A **Graduated elastic compression stockings should be worn on the affected leg following proximal DVT for at least two years to reduce the incidence of severe post-thrombotic leg syndrome.**

2.7 RECURRENT VENOUS THROMBOEMBOLISM

☑ Clinically suspected recurrent venous thromboembolism during oral anticoagulant therapy should be fully investigated, including obtaining objective evidence of recurrence; intensity of oral anticoagulant effect at the time of recurrence (an INR below 2.0 is an indication for heparin therapy, followed by warfarin until target INR is reached); presence of continuing risk factors, especially malignancy and thrombophilias[69] *(see section 2.10)*; and hereditary warfarin resistance.[66]

Prophylactic options in documented recurrence despite an oral anticoagulant effect within the therapeutic range include:[32, 66]

- higher-intensity warfarin (target INR 3.5, range 3.0-4.0); or
- subcutaneous APTT-monitored unfractionated heparin, or subcutaneous unmonitored LMW heparin *(see sections 2.3.2 and 2.3.3)*; or
- insertion of an IVC filter (*see section 2.6.4*).

2.8 SECONDARY PROPHYLAXIS OF DVT

☑ All patients with DVT, and their general practitioners, should be advised of the increased risk of recurrence in future high risk situations (trauma, surgery, medical illness, immobilisation, pregnancy, puerperium) and of the need for prophylaxis.[5]

2.9 VENOUS THROMBOEMBOLISM IN PREGNANCY

The management of pregnancy-related venous thromboembolism has been fully discussed in a recent national guideline.[70]

2.10 IDENTIFICATION AND MANAGEMENT OF PATIENTS WITH CHRONIC INCREASED RISK (THROMBOPHILIAS)

C **Screening for congenital or acquired thrombophilias** (deficiencies of antithrombin, protein C or protein S; activated protein C resistance which is usually due to the coagulation factor V Leiden mutation; the prothrombin 20210A mutation; lupus anti-coagulants which are usually antiphospholipid antibodies) **is recommended in the groups of patients listed in table 4.**[73]

C **Patients with such thrombophilias should be referred to consultant haematologists or centres with expertise in management of thrombophilia, which includes:**

genetic counselling

general education and advice on the additive risks of obesity and oestrogen-containing oral contraceptives or hormone replacement therapy

prophylaxis: either short term anticoagulant prophylaxis during periods of increased risk of DVT or PE (pregnancy, puerperium, trauma, surgery, or medical illness) or in selected patients long term anticoagulation with warfarin.[5, 73]

Table 4

INDICATIONS FOR SCREENING FOR THROMBOPHILIAS

- Venous thromboembolism before the age of 45 years
- Recurrent venous thromboembolism or thrombophlebitis
- Venous thrombosis in an unusual site (e.g. mesenteric, cerebral)
- Unexplained neonatal thrombosis
- Skin necrosis, particularly if on coumarins
- Arterial thrombosis before the age of 40 years (antiphospholipid syndrome)
- Relatives of patients with thrombophilic abnormality
- Patients with clear family history of venous thrombosis
- Unexplained prolonged activated partial thromboplastin time (APTT) (lupus anticoagulants)
- Selected patients with recurrent fetal loss, idiopathic thrombocytopenic purpura, or systemic lupus erythematosus (antiphospholipid syndrome)

(Modified from the British Committee for Standards in Haematology guideline on the investigation and management of thrombophilia.[73])

Further randomised trials are required to establish optimum management of thrombophilias.

Recent retrospective or modelling studies suggest that in patients found to have only factor V Leiden (whose prevalence is about 2.5% in the Scottish population[74]) after a first episode of DVT, long term anticoagulation with warfarin may carry a higher relative risk of major bleeding compared to prevention of recurrent DVT.[75, 76]

Evidence level III

3 Atrial fibrillation: Prophylaxis of systemic embolism

3.1 ATRIAL FIBRILLATION AND SYSTEMIC THROMBOEMBOLISM

Most people in Scotland with atrial fibrillation (AF) do not have valvular heart disease (non-valvular atrial fibrillation). The prevalence of non-valvular AF increases with age, from about 0.5% at age 50-59 to about 9% at age 80-89. Compared to persons in sinus rhythm, persons with AF have a five-fold mean increase in risk of stroke, largely due to an increased risk of atrial thrombosis which may embolise to the brain (and less frequently to the limbs or other internal organs), although associated arterial disease (e.g. carotid stenosis) may also increase the risk of stroke due to arterial thromboembolism. Stroke mortality is also higher in patients with AF, compared to patients in sinus rhythm.[77, 78]

The risk of stroke in non-valvular AF appears to be similar in men and in women, and in persons with continuous AF and in paroxysmal AF.[10] The role of echocardiography in risk stratification in non-valvular AF remains unclear. Impaired left ventricular function or mitral valve calcification are risk predictors.[79] A consensus statement recommends that echocardiography (to determine whether or not valvular disease and left ventricular systolic dysfunction are present) is part of optimal assessment of AF.[79]

3.2 EFFICACY OF WARFARIN AND ASPIRIN AS ANTITHROMBOTIC PROPHYLAXIS

A prospective pooled analysis[10] of five randomised controlled trials of **warfarin** in prophylaxis of systemic embolism (usually in patients with no history of previous embolism, i.e. primary prophylaxis), showed relative risk reductions for stroke of 68% (95% CI 50-79%) and for death of 33% (95% CI 9-51%).

Evidence level Ia

The efficacy of warfarin was probably underestimated, because most strokes in patients in the warfarin groups occurred when patients were not taking warfarin.[10, 82] While the five trials used various target ranges of INR (between 1.5 and 4.5) the minimum risk of stroke appeared to occur in the INR range 2.0-3.0.[10, 82] The annual risk of intracranial haemorrhage increased from 0.1% in controls to 0.3% in warfarin groups, (i.e. an excess of two intracranial bleeds per year per thousand patients treated) and was associated with an INR greater than 3.0 and with uncontrolled hypertension (there was also a non-significant association with increasing age).[10, 82] (It should be noted that patients in these trials were selected to exclude those at increased risk of bleeding.) Lower intensity warfarin (INR 1.5-2.5) plus aspirin was less effective than standard intensity warfarin in high risk patients in the SPAF-3 study.[80]

Evidence level Ia and Ib

Contraindications to warfarin include increased risk of bleeding due to co-existing medical conditions, and any tendency to falls or other exposure to trauma. Another consideration is the likelihood of poor concordance (compliance), which will be influenced not only be the patient s ability to manage medication but also by local facilities for control of the INR. Special care must be taken with other drugs that interact with warfarin, including amiodarone. Patient preference is important.[79]

Aspirin has been evaluated as *primary prophylaxis* of systemic embolism in AF in two randomised controlled trials compared against no antithrombotic treatment [7, 10-12, 18] and in one randomised controlled trial compared to warfarin.[81] On-treatment analysis showed that aspirin was less effective than warfarin (20% risk reduction vs. 68%);[11, 12, 18] however aspirin is simpler, less hazardous and less costly than warfarin.

Evidence level Ib

Aspirin was significantly less effective than warfarin as *secondary prophylaxis* in patients with previous stroke or TIA .[10, 17]

Warfarin and aspirin should only be given together in special circumstances[79] *(see sections 4.4 and 8)*.

The absolute risk of stroke in persons with non-valvular AF (and hence the absolute benefits of aspirin or warfarin prophylaxis) varies greatly with the presence or absence of **risk factors for thromboembolism**.[10, 82]

Evidence level III

Meta-analyses of randomised controlled trials in primary prophylaxis[6, 7, 10-12, 18, 19, 82] and one randomised controlled trial in secondary prophylaxis[17] have shown that lower risk patients (annual stroke rate under 3%) require no antithrombotic prophylaxis, unless there are other indications for aspirin. In higher risk patients (annual stroke rate over 3%), warfarin (at a target INR of 2.5, range 2.0-3.0) is effective in prophylaxis of stroke, and significantly more effective than aspirin; however, it also carries a higher risk of bleeding.

Evidence level Ia and Ib

B **In all patients with atrial fibrillation, risk factors for systemic thromboembolism should be assessed routinely.**

A **Lower risk patients** (annual stroke rate under 3%, as defined in section 3.4 below) **should be given no antithrombotic prophylaxis , unless aspirin (75-300 mg/day) is given for other indications.**

A **Higher risk patients** (annual stroke rate over 3%, as defined in section 3.3 below) **should be considered for warfarin at a target INR of 2.5 (range 2.0-3.0). The balance of risks and benefits of warfarin should be assessed and discussed with the patient, and reassessed annually in individual higher risk patients: aspirin may be a safer alternative to warfarin in some of these patients.**

A **Anticoagulant therapy after an acute cerebral ischaemic event should be delayed until most of the deficit has resolved or, in the case of more severe strokes, more than two weeks has elapsed.**[79] *(See section 7.1.)*

Having undertaken risk assessment, there are a variety of methods which may be used to stratify patients.[79, 83] The following is one approach.

3.3 HIGHER RISK GROUPS

3.3.1 **People with non-valvular AF and previous ischaemic stroke or TIA** had a high annual risk of stroke in a meta-analysis of randomised trials of warfarin: 11.7% in controls and 5.1% in warfarin groups.[10] These results are similar to those in a randomised trial of secondary prophylaxis with warfarin in patients with a previous stroke or TIA: 12% in controls and 4% in warfarin groups.[17] In contrast, the relative risk reduction with aspirin was only 19%,[11] which is similar to that seen for secondary prevention of stroke in patients in sinus rhythm.[7] Detailed sensitivity analyses have suggested that these estimates may be overoptimistic when applied in routine clinical practice.[79, 83]

Evidence level Ia and Ib

A **Warfarin** (target INR 2.5, range 2.0-3.0) **should be considered for antithrombotic prophylaxis in patients with non-valvular atrial fibrillation and a history of previous ischaemic stroke or TIA.**

A **If warfarin is declined, or contraindicated by increased risk of bleeding, aspirin** (75-300 mg/day) **should be considered, but is less effective than warfarin.**

3.3.2 **People with non-valvular AF who are aged over 65 and also have at least one other risk factor for stroke** (history of hypertension, diabetes, heart failure, or left ventricular dysfunction) also have a high annual risk of stroke (5-8%) which is significantly reduced by warfarin.[10, 12, 82] Such patients should also be considered for warfarin, which reduces this risk below 5%. Warfarin is also cost-effective in these patients.[12] However, the incidence of intracranial haemorrhage also increases with age and blood pressure. Warfarin sensitivity also increases with age and in heart failure. Poor compliance, difficulty in attending clinics for monitoring, warfarin interactions with multiple diseases and drugs, and tendency to falls with head injury may each increase the risk of intracranial haemorrhage, especially in older patients (age over 75 years). Aspirin (75-300 mg/day) is a less effective, but safer, alternative antithrombotic drug in this group.[11]

Evidence level Ia

People with non-valvular AF who are aged over 65 years without other risk factors, or who are aged under 65 and have at least one other risk factor for stroke (history of hypertension, diabetes, heart failure, or left ventricular dysfunction) also have a significant increased annual risk of stroke (3-5%) which is significantly reduced by warfarin. Such patients should also be considered for warfarin.[10, 12, 82] Warfarin is cost-effective in such patients.[12] Aspirin is again a less effective alternative antithrombotic drug in this group.[11]

A **Warfarin** (target INR 2.5, range 2.0-3.0) **should be considered for antithrombotic prophylaxis in patients with non-valvular atrial fibrillation and other risk factors for stroke (age over 65 years, history of hypertension, diabetes, heart failure, or left ventricular dysfunction). In patients over 75 years, the relative balance of risks and benefits of warfarin should be carefully assessed.**

A **Warfarin** (target INR 2.5, range 2.0-3.0) **should also be considered for antithrombotic prophylaxis in patients with non-valvular atrial fibrillation who are aged under 65 and have a history of hypertension, diabetes, heart failure, or left ventricular dysfunction.**

A **If warfarin is declined, or contraindicated by increased risk of bleeding, aspirin** (75-300 mg/day) **should be considered but is less effective than warfarin.**

3.3.3 Observational studies suggest an increased risk of systemic embolism in patients with AF associated with **heart valve disease or prosthesis** *(see section 4.3)*, **thyrotoxicosis, intracardiac thrombus, or non-cerebral thromboembolism.**[84-86]

Evidence level III

C **Warfarin prophylaxis should be considered in patients with atrial fibrillation and heart valve disease or prosthesis, thyrotoxicosis, intracardiac thrombus, or non-cerebral thromboembolism.**

3.3.4 The annual risk of major bleeding (up to 2% in randomised trials[10, 81]) should be considered when deciding the level of risk which merits use of warfarin.

☑ To minimise the risk of intracranial bleeding from prophylactic warfarin in patients with AF, hypertension should be adequately controlled, compliance assessed, and the risks and benefits of warfarin reviewed annually, especially in patients aged over 75 years.

3.4 LOWER RISK GROUPS

People with non-valvular AF who are aged under 65 and have none of the above risk factors for stroke, have a low annual risk of stroke (about 1%) which is not significantly reduced by either warfarin or aspirin.[10-12] Warfarin is not indicated (and is not cost-effective) in such patients.[12] Aspirin may be considered if there are other indications, e.g. ischaemic heart disease or peripheral arterial disease.

The annual risk of stroke for patients with atrial fibrillation and number needed to treat with warfarin instead of aspirin for one year to prevent one stroke are summarised in table 5.

3.5 CARDIOVERSION

Restoration of sinus rhythm may avoid the need for long term warfarin. Cardioversion, however, carries a moderate risk of systemic thromboembolism in patients who have been in AF for more than two days.[79, 82, 86, 87]

Evidence level III and IV

A consensus statement[79] recommends that:

C **Cardioversion of AF should be considered in selected patients.**

C **Patients with very recent onset AF require immediate assessment and treatment with heparin.**

C **If it is certain that AF has been present for two days or less, cardioversion should be attempted electrically or pharmacologically. Warfarin therapy is not required in these patients if cardioversion is successful.**

B **If AF has been present for more than two days, warfarin should be given to reduce the risk of thromboembolism* for three weeks before cardioversion and continued for at least four weeks after cardioversion.**

* *The SIGN guideline development group recommend a target INR of 2.5, range 2.0-3.0.*

With the latter strategy, the risk of thromboembolism early after the procedure is reduced from 5-7% to 1-2%. Whether warfarin should be given beyond four weeks is uncertain, but this treatment may be considered in patients with a continuing high risk of recurrence of AF (large left atrium, poor left ventricular function, hypertension) or previously symptomatic AF.[79]

Table 5

ANNUAL RISK OF STROKE ON NO TREATMENT, ASPIRIN, OR WARFARIN IN HIGH, MODERATE AND LOW RISK PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION

Risk group	***Untreated***	***Aspirin***	***Warfarin***	***NNT****
Very high Previous ischaemic stroke or TIA	12%	10%	5%	13
High Age over 65 and one other risk factor: – hypertension – diabetes mellitus – heart failure – LV dysfunction	5-8%	4-6%	2-3%	22-47
Moderate – Age over 65, no other risk factors – Age under 65, other risk factors	3-5%	2-4%	1-2%	47-83
Low Age under 65, no other risk factors	1.2%	1%	c. 0.5%	200

* Number needed to treat with warfarin *instead of aspirin* for one year to prevent one stroke

(Adapted from the Royal College of Physicians of Edinburgh Atrial Fibrillation Consensus Statement[79])

4 Other cardiac causes of systemic embolism

In patients in sinus rhythm, systemic emboli may arise from mural thrombi in the left atrium or left ventricle, from prosthetic valves, or from infected valves in bacterial endocarditis. High, moderate and low risk groups may be defined *(see table 6)*. Echocardiography is helpful in defining risk, particularly in the diagnosis of dilated cardiomyopathy, valve abnormalities, intracardiac thrombus, and left atrial enlargement. As for non-valvular AF, prophylaxis is usually with warfarin for higher-risk patients, and with aspirin or no treatment for lower-risk patients. Intravenous heparin may be indicated in acute thrombosis *(see section 6.2)*, or if warfarin has to be stopped, e.g. for elective surgery *(see section 13.4)*. In high-risk patients, anticoagulants should be discontinued only if justified by emergencies. Anticoagulants should generally be avoided in patients with active bacterial endocarditis.

The evidence for thrombotic risk and for efficacy of antithrombotic therapy in patients with cardiac sources of systemic embolism has recently been reviewed in detail in consensus statements[84-86] and is summarised here.

4.1 RHEUMATIC MITRAL VALVE DISEASE

Well-conducted observational studies, extrapolation of randomised controlled studies in non rheumatic AF,[82] and the recommendations of expert bodies[84-86] indicate that warfarin prophylaxis is indicated in patients with rheumatic mitral valve disease (especially mitral stenosis), who have a high risk of systemic embolism. This risk increases in the presence of previous systemic embolism; atrial fibrillation; heart failure; or the presence of atrial thrombi, increased atrial size or possibly spontaneous echo contrast at echocardiography.

Evidence level II, III and IV

C **Long-term warfarin prophylaxis** (target INR 2.5, range 2.0-3.0) **is recommended in patients with rheumatic mitral valve disease.**

B **Long-term warfarin prophylaxis** (target INR 2.5, range 2.0-3.0) **is recommended in patients with rheumatic mitral stenosis with atrial fibrillation.**

4.2 MITRAL VALVE PROLAPSE, MITRAL ANNULAR CALCIFICATION, AND ISOLATED AORTIC VALVE DISEASE

These patient groups appear to have a low risk of systemic embolism in the absence of previous systemic embolism or atrial fibrillation. Extrapolation of studies in non rheumatic AF and the recommendations of expert bodies[84-86] indicate that warfarin prophylaxis is only indicated in the presence of previous systemic embolism or atrial fibrillation.

C **Long-term warfarin prophylaxis** (target INR 2.5, range 2.0-3.0) **is recommended for patients with mitral valve prolapse, mitral annular calcification, or isolated aortic valve disease only in the presence of previous systemic embolism or atrial fibrillation.**

Table 6

RISK OF SYSTEMIC EMBOLISM IN CARDIAC CONDITIONS OTHER THAN ATRIAL FIBRILLATION

High risk
Rheumatic heart valve disease (especially mitral stenosis)
Prosthetic heart valves ▪ mechanical ▪ bioprosthetic, if: — atrial fibrillation — previous systemic embolism — left atrial thrombus at surgery — mitral, for first three months
Left ventricular mural thrombus ▪ acute myocardial infarction (especially anterior Q wave) ▪ left ventricular aneurysm
Moderate risk
Dilated cardiomyopathy
Non-rheumatic heart valve disease with atrial fibrillation
Congestive cardiac failure
Low risk
Uncomplicated acute myocardial infarction, other than large anterior Q-wave infarctions
Minor valve abnormalities in sinus rhythm
Hypertropic cardiomyopathy

The risk of embolism increases in the presence of atrial fibrillation or previous history of embolism

4.3 CARDIOMYOPATHIES AND CARDIAC FAILURE

Studies indicate that dilated cardiomyopathy and cardiac failure carry a risk of embolism of 2.0-2.4% per annum in the absence of previous systemic embolism or atrial fibrillation.[88]

Hypertrophic cardiomyopathy carries a low embolic risk.

The benefits and risks of warfarin, aspirin or no antithrombotic therapy in cardiac failure with sinus rhythm are not well-established, and are currently being assessed in the Warfarin/Aspirin/Heart Failure (WASH) study. *(See the SIGN guideline on Diagnosis and Treatment of Heart Failure due to Left Ventricular Systolic Dysfunction.[89])*

C **Long-term warfarin prophylaxis (target INR 2.5, range 2.0-3.0) is recommended for patients with dilated cardiomyopathy or cardiac failure only in the presence of previous systemic embolism or atrial fibrillation.**

4.4 MECHANICAL HEART VALVES

Well-conducted observational studies show that patients with mechanical heart valves have a high risk of embolism which is reduced by long term oral anticoagulation.[10, 11, 85, 86]

Evidence level II, III and IV

B **Patients with mechanical heart valves should receive long-term prophylaxis with warfarin.**

C **A target INR of 3.5, range 3.0-4.5, has traditionally been recommended for patients with mechanical heart valves and is appropriate for first generation valves** (e.g. Starr-Edwards, Bjork Shiley standard).

B **More recent studies support a reduction in target INR to 3.0, range 2.5-3.5, for patients with second generation mechanical heart valves** (e.g. St. Jude, Medtronic, Monostrut).[85, 86]

The addition of aspirin (100 mg/day) reduced vascular mortality in one study,[90] but increased the risk of bleeding. Dipyridamole is also effective, without increased risk of bleeding.[85, 86]

Evidence level Ib

A **Addition of aspirin or dipyridamole should be considered in patients who suffer systemic embolism despite adequate-intensity warfarin.**[85]

4.5 BIOPROSTHETIC HEART VALVES

Patients with bioprosthetic heart valves have a high risk of embolism if they have atrial fibrillation, a history of systemic embolism, evidence of left atrial thrombus at surgery, persistent left atrial enlargement, or persistent heart failure.[85, 86]

C **Patients with bioprosthetic heart valves who have additional thrombotic risk factors should receive long term prophylaxis with warfarin** (INR 2.5, range 2.0-3.0).

The addition of aspirin (100 mg/day) reduced vascular mortality in one study, but increased the risk of bleeding.[90]

Evidence level Ib

A **Selected patients may receive aspirin as additional therapy.**

A C **Other patients with mitral bioprosthetic valves should receive:**
warfarin for 3-6 months (target INR 2.5, range 2.0-3.0)
followed by long-term aspirin (300 mg/day).

C **In other patients with isolated aortic or tricuspid bioprosthetic valves, warfarin is recommended for three months only, in the absence of atrial fibrillation or a history of systemic embolism.**

4.6 RECONSTRUCTIVE VALVE PROCEDURES

The recommendations of the European Consensus Statement should be consulted.[86]

4.7 PREGNANCY IN PATIENTS WITH HEART VALVE DISEASE OR PROSTHESES

Guidance is available from expert consensus statements.[6, 70, 84-86]

5 Ischaemic heart disease

5.1 MYOCARDIAL INFARCTION

5.1.1 ASPIRIN AND OTHER ANTIPLATELETS

Ten randomised trials and meta-analyses[7, 9] have shown that antiplatelet treatment (aspirin) for one month in patients with acute myocardial infarction results in a 3.8% absolute risk difference of myocardial infarction, stroke or vascular death over one month (*see table 1*). Most of the evidence comes from one large trial using 150 mg/day, which showed an additive benefit to thrombolysis with streptokinase for mortality, and maintenance of benefit for four years.[91]

Evidence level Ia and Ib

Routine use of aspirin is supported by many expert groups.[2, 6, 7, 9, 92] Sequential clinical audit has shown a significant improvement in the percentage of GPs who carry aspirin so that therapy can be initiated at diagnosis.[15]

Evidence level III and IV

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

☑ All general practitioners should carry aspirin so that treatment can be initiated at diagnosis.

A **In patients already taking aspirin, it should be continued at a dose of 150-300 mg/day.**

☑ To achieve rapid inhibition of platelet function, the aspirin tablets should not be enteric-coated, and should be swallowed as soon as possible.

Meta-analyses of 12 randomised controlled trials[7, 9] have demonstrated that aspirin is effective as secondary prophylaxis of cardiovascular events following acute myocardial infarction.[9, 92] Antiplatelet treatment for one year results in a 3.5% absolute risk difference for myocardial infarction, stroke or vascular death (*see table 1*).

Evidence level Ia

Clopidogrel appears to be as effective as aspirin for prophylaxis of cardiovascular events following myocardial infarction.[93] Dipyridamole plus aspirin shows similar efficacy to aspirin alone.[7]

Evidence level Ib

A **It is strongly recommended that aspirin** (75-300 mg) **be continued long term in survivors of myocardial infarction.**

A **Clopidogrel** (75 mg/day) **is an effective alternative in patients with contraindications to aspirin, or who are intolerant of aspirin.**

Randomised controlled trials have shown that warfarin is also effective in secondary prophylaxis of cardiovascular events after myocardial infarction.[94-99] but is more complicated to manage and has a higher risk of bleeding than antiplatelet agents. Conjoint use of warfarin and aspirin increases the risk of bleeding.[14, 92] Aspirin should therefore be discontinued in warfarinised patients.

Evidence level Ib

A **Aspirin may be continued in heparinised patients with acute myocardial infarction** *(see below),* **but should be discontinued in patients receiving warfarin for ischaemic heart disease.**

5.1.2 THROMBOLYTICS

Meta-analyses of randomised controlled trials have shown that thrombolysis in selected patients reduced mortality in acute myocardial infarction.[27, 100]

Evidence level Ia

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

A **Thrombolysis should be used concurrently with aspirin, which has an additive effect.**[91]

Scottish,[2] UK,[28] and North American[100] guidelines have been published.

5.1.3 ANTICOAGULANTS

A meta-analysis of randomised trials[101] has shown that routine intravenous or subcutaneous heparin reduces mortality in suspected acute myocardial infarction by about 25% in the absence of aspirin; and by about 6% in the presence of aspirin, at the cost of increased bleeding (about 3% increase in major bleeds). Many trials also predated the routine use of thrombolytics, which also reduces the additional benefit of heparin.[95, 101]

Evidence level Ia and Ib

A **Heparin should not be used routinely in addition to aspirin in acute myocardial infarction, but reserved for patients at increased thromboembolic risk.**

Trials of low molecular weight heparins in acute myocardial infarction are in progress.

Intravenous heparin is commonly given during and following thrombolysis with alteplase to reduce the risk of early coronary rethrombosis.[28, 100, 102] The usual dose of heparin is an intravenous bolus infusion (5,000 IU) when commencing alteplase, continuing for 48 hours at an initial rate of 1,000 IU/h, titrated to maintain a target APTT ratio of 1.5-2.0. Use of a nomogram for dose adjustment may improve the achievement of target APTT ratios.[102] However, the risks and benefits of adding heparin to thrombolytic therapy should be carefully considered,[101] especially the risk of haemorrhagic stroke.

A **Patients with acute, established myocardial infarction 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.**

Based on meta-analysis of randomised trials,[101] and on additional long-term trials in atrial fibrillation [5, 10-12, 17, 19]

(see section 3)

The duration and intensity of anticoagulation will depend on the clinical course, and will also be influenced by echocardiographic findings.

Meta-analyses of randomised controlled studies have shown a reduction in deep vein thrombosis in acute myocardial infarction by low-dose subcutaneous heparin.[92, 101]

Evidence level Ia

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

C **In patients in whom the bleeding risks of low-dose heparin are judged to outweigh the benefits, graduated elastic compression stockings or intermittent pneumatic compression should be considered for prophylaxis of venous thromboembolism.**

Recommendation based on extrapolation of data from trials in other hospital patient groups.[5]

Randomised controlled trials have shown that warfarin is similarly effective to aspirin in secondary prophylaxis of cardiovascular events.[92, 94-99]

Evidence level Ib

A **For long term prophylaxis of arterial events following myocardial infarction, antiplatelet agents** (usually aspirin) **are usually preferred to warfarin because of their lower complexity, bleeding risk, and cost.**

A **Long term warfarin** (target INR 2.5, range 2.0-3.0) **should be considered instead of aspirin in patients with persistent atrial fibrillation and heart failure or left ventricular dysfunction** (see section 3).

5.2 UNSTABLE ANGINA

Meta-analyses of 12 randomised controlled studies have shown that antiplatelet agents, usually aspirin (75-1300 mg/day) reduce the risk of myocardial infarction, stroke or vascular death (absolute risk difference 5.5% over 18 months) [7, 9, 92] (*see table 1*).

Evidence level Ia

A **It is strongly recommended that all patients with clinically suspected unstable angina should receive aspirin** (150-300 mg/day) **as soon as possible.**

A **This should be continued long term as prophylaxis of cardiovascular events** (75-300 mg/day).

A meta-analysis of six randomised controlled trials has shown that full-dose intravenous heparin, in addition to aspirin, further reduces the risk of myocardial infarction or death.[103]

Evidence level Ia

A **It is strongly recommended that all patients who are hospitalised with severe unstable angina should receive in addition to aspirin full-dose heparin** (target APTT ratio 2.0, range 1.5-2.5), **which should be maintained for 3-4 days, or until resolution of unstable angina.**

A **Alternatively, LMW heparin** (enoxaparin or dalteparin) **can be given.**[104-106]

Recent trials indicate that platelet glycoprotein IIb/IIIa inhibitors (e.g. abciximab) are also effective.[107-109]

Evidence level Ib

A meta-analysis of randomised trials has shown an *increased* rate of death and myocardial infarction for thrombolytic therapy in unstable angina.[110] Hence, this is not routinely recommended.

Evidence level Ia

5.3 STABLE ANGINA

Six randomised controlled studies and meta-analyses have shown that aspirin reduces the risk of cardiovascular events (absolute risk difference 4.5% over 33 months)[7, 9, 92] *(see table 1).*

Evidence level Ia and Ib

A **Patients with stable angina should receive aspirin** (75-300 mg/day) **long term as prophylaxis of cardiovascular events.**

5.4 CORONARY ANGIOPLASTY, STENTS AND BYPASS GRAFTS

Meta-analyses of randomised controlled studies have shown improved maintenance of graft or arterial patency and reduction in cardiovascular events following aspirin therapy.[7-9, 111, 112]

Evidence level Ia

Aspirin use prior to **bypass grafting** does not appear to increase antithrombotic efficacy, and increases perioperative bleeding,[8] hence it may be discontinued one week prior to surgery. It can be commenced postoperatively (150-300 mg/day by nasogastric tube).

Evidence level Ia

A **Aspirin** (300 mg/day) **should be given as antithrombotic prophylaxis, starting at least two hours prior to angioplasty, or six hours following bypass grafting** (unless contraindicated by bleeding) **and continued long term** (75-300 mg/day).

It is standard practice to give full dose intravenous heparin prior to **coronary angioplasty**, and to continue this for up to 24 hours in the presence of unstable angina, complex lesions, multivessel angioplasty, or a technically suboptimal result.[111] Continued heparin therapy in unstable angina is supported by randomised studies (*see section 5.3)*. Following placement of coronary artery stents, antiplatelet therapy with aspirin ± ticlopidine (which is not presently licensed for this indication in the UK) appears significantly superior to aspirin combined with warfarin.[113] Platelet glycoprotein IIb/IIIa receptor antagonists (e.g. abciximab) may be appropriate in high risk coronary angioplasty, particularly when complicated by thrombus formation[108,109] *(see the SIGN guideline on Coronary Revascularisation in the Management of Stable Angina Pectoris*[114]*)*.

Evidence level Ia

It is also standard practice to heparinise systemically during **cardiac bypass surgery**.

6 Peripheral arterial disease

6.1 INTERMITTENT CLAUDICATION

A meta-analysis of randomised trials of antiplatelet therapy has shown a reduction in the risk of cardiovascular events in patients with peripheral arterial disease, usually intermittent claudication (absolute risk difference 1.2% over one year)[7] *(see table 1)*. Reduction in progression of atherosclerosis has been shown in randomised controlled angiographic studies.[8] A reduction in the risk of peripheral arterial surgery in patients receiving aspirin therapy was a retrospective observation of a randomised study.[115, 116] A large randomised controlled trial including patients with peripheral arterial disease has shown increased efficacy and similar safety of clopidogrel versus aspirin.[93]

Evidence level Ia and Ib

A **Patients with intermittent claudication should receive aspirin** (75-300 mg/day) **long term as prophylaxis of cardiovascular events.**

(See SIGN guideline on Drug Therapy for Peripheral Vascular Disease.[117])

A **Clopidogrel** (75 mg/day) **is an effective alternative in patients with contraindications to aspirin, or who are intolerant of aspirin.**

The role of long term oral anticoagulants is uncertain: further trials are in progress.[118]

6.2 CRITICAL LIMB ISCHAEMIA AND AMPUTATION

Hospitalised patients who are immobilised with chronic critical limb ischaemia, including those who have undergone amputation, are at high risk of thromboembolism. Extrapolation of results from other patient groups[5] and the opinion of a consensus group[119] suggests that such patients should receive anticoagulant prophylaxis for venous thromboembolism.

Evidence level III and IV

C **Hospitalised patients with chronic critical limb ischaemia should receive prophylaxis for venous thromboembolism with either subcutaneous low dose standard heparin** (5,000 IU 8 hourly) ***or*** **adjusted-dose warfarin** (target therapeutic range of INR 2.0-3.0).[5]

C **In patients with acute critical ischaemia, full-dose intravenous heparin** (target APTT ratio 2.0, range 1.5-2.5) **is standard practice.**[116]

6.2.1 PERIPHERAL ARTERIAL EMBOLISM AND ATRIAL FIBRILLATION

A **In patients with peripheral arterial embolism and atrial fibrillation or other cardiac source of embolism, long-term prophylaxis with warfarin** (target INR 2.5, range 2.0-3.0) **is recommended.** *(See sections 3 and 4.)*

6.2.2 LOCAL THROMBOLYTIC THERAPY

In selected patients with acute critical limb ischaemia, overviews of the results of randomised trials suggest that thrombolysis may be an alternative to surgery.[28, 29, 116, 119, 120]

Evidence level Ib

A **In patients with acute critical limb ischaemia, local thrombolytic therapy should be considered.**

6.3 PERIPHERAL ANGIOPLASTY AND BYPASS GRAFTS

C **It is standard practice to give intravenous heparin during peripheral angioplasty, and to heparinise systemically during bypass graft surgery.**[116]

Meta-analyses of randomised controlled trials of postoperative antiplatelet agents, including aspirin, have shown improved synthetic graft patency. The evidence for benefit from antiplatelet agents when native graft material is used is not available. Antiplatelet agents, including aspirin, have been shown to improve arterial patency in patients with peripheral arterial disease, as well as reducing cardiovascular events.[7-9, 116]

Evidence level Ia

A **Aspirin** (300 mg/day) **should be given as antithrombotic prophylaxis of cardiovascular events, starting 6 hours following angioplasty or bypass grafting and continued long-term** (75-300 mg/day).

A **Clopidogrel** (75 mg/day) **is an effective alternative treatment for long term prophylaxis in patients with contraindications to aspirin, or who are intolerant of aspirin.**

There is insufficient evidence to support routine long-term anticoagulation in patients with infra-inguinal grafts or angioplasty.[116, 118]

7 Cerebrovascular disease

7.1 ACUTE STROKE

7.1.1 INVESTIGATION

C The SIGN guideline on Management of Patients with Stroke, Part I: Assessment, investigation, immediate management and secondary prevention recommends that **all patients with acute stroke should undergo CT brain scanning as soon as possible** preferably within 48 hours and no later than seven days.[124] A local protocol for more urgent scans (e.g. patients receiving anticoagulant or recent thrombolytic therapy) should be available.

This recommendation is based on the following considerations:

- Specific treatment of intracranial haemorrhage (e.g. neurosurgery, cessation/ reversal of antithrombotic therapies) may be indicated if rapidly diagnosed.
- There is conclusive evidence for the efficacy of antiplatelet or anticoagulant therapies in the secondary prevention of acute stroke, but they should be avoided in cases of haemorrhagic stroke.[7, 17, 125, 126]
- Clinical scoring systems have been found to be unreliable in distinguishing ischaemic and haemorrhagic stroke.[127]

7.1.2 ACUTE PROPHYLAXIS OF FURTHER VASCULAR EVENTS

Since publication of Part I of the SIGN guideline on Management of Patients with Stroke,[124] a meta-analysis of three randomised trials of early treatment of acute ischaemic stroke with aspirin (160-300 mg/day) has shown modest, but definite (2P = 0.001) net reduction in early death or non-fatal stroke: nine (SD 3) per 1,000.[126] This represents a balance between prevention of 11 (SD 3) per 1,000 ischaemic strokes or death and an increase in haemorrhagic strokes of two (SD 1) per 1,000. Application of these results to Scotland (about 10,000 acute strokes/year) would avoid about 90 early deaths, strokes or myocardial infarctions per year. Furthermore, early aspirin treatment in acute ischaemic stroke is likely to lead to more patients being sent home on long-term aspirin, further reducing morbidity and mortality *(see section 7.2)*.[126] Early aspirin also reduced the risks of myocardial infarction and pulmonary embolism in patients with acute ischaemic stroke.[126]

Evidence level Ia

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

About one third of patients with acute stroke cannot swallow safely, and are at risk of aspiration. In such patients, aspirin may be given as a 300 mg suppository per rectum until swallowing recovers or a nasogastric or percutaneous gastrostomy tube is placed.

The International Stroke Trial[125] has shown that unfractionated heparin (either low dose or intermediate dose) did not improve clinical outcome in acute stroke, and increased the risk of intracranial haemorrhage, with a dose-dependent relationship.

Evidence level Ib

A **Routine use of unfractionated or low molecular weight heparin (even at low doses) in acute stroke is not recommended.**

C **In patients at increased risk of venous thromboembolism, additional prophylaxis with graduated elastic compression stockings should be considered in all immobile patients following acute stroke.**

C **Early institution or maintenance of anticoagulant therapy** (with heparin or warfarin) **in acute ischaemic stroke should be reserved for patients with a high risk of either venous thromboembolism** (e.g. previous venous thromboembolism, thrombophilias) **or recurrent thromboembolic stroke** (e.g. rheumatic valve disease or mechanical heart valves, especially in the presence of atrial fibrillation) **in whom these risks are judged to outweigh the increased risk of intracranial bleeding.**[128]

Based on extrapolation from RCTs in other patient groups[5]

C **Urgent CT brain scans are indicated in such patients, to exclude intracranial bleeding and predictors of haemorrhagic transformation such as major cerebral infarction. Careful control of both hypertension and the intensity of anticoagulants in such patients is also recommended to reduce the risk of intracranial bleeding.**

7.2 SECONDARY PREVENTION AFTER ACUTE ISCHAEMIC STROKE OR TRANSIENT CEREBRAL ISCHAEMIC ATTACK (TIA)

7.2.1 ASSESSMENT

C The SIGN Guideline on Management of Patients with Stroke, Part I: Assessment, investigation, immediate management and secondary prevention,[124] recommends that **local admissions policies should be agreed, as well as local protocols for referral to a fast-track assessment clinic for those with minor strokes or TIAs not requiring hospital admission, for identification and modification of risk factors and rapid administration of secondary prevention including antithrombotic treatments.**

7.2.2 ASPIRIN

Meta-analyses of 22 randomised controlled trials have shown that antiplatelet drugs (usually aspirin) reduce the long term risk of cardiovascular events in patients with prior TIA or ischaemic stroke (absolute risk difference 4.5% over 30 months, *see table 1*).[7, 9] Medium dose aspirin therapy (75-300 mg/day) is the most widely tested; higher doses are associated with increased risk of adverse events.[7]

Evidence level Ia

A **Antiplatelet therapy normally aspirin (75-300 mg/day) should be prescribed as early as possible for secondary prevention of stroke and other vascular events in patients who have sustained an ischaemic stroke (or TIA). In acute ischaemic stroke, the starting dose should be 150-300 mg/day.**

7.2.3 DIPYRIDAMOLE

One large randomised placebo-controlled trial in patients with ischaemic stroke has shown that dipyridamole in a sustained release preparation appears as effective as low dose aspirin (50 mg/day) in prevention of cardiovascular events, and that an additive effect is achieved in combination with this dose of aspirin for prevention of recurrent stroke.[129, 130] Previous, smaller randomised trials of aspirin vs. dipyridamole and aspirin have not shown additive effects,[7] and updated meta-analyses are awaited.

Evidence level Ib

A **Dipyridamole** (200 mg twice daily in a sustained release preparation) **should be considered for prevention of cardiovascular events following ischaemic stroke:**

C
- **as an alternative to aspirin in patients with contraindications to aspirin, or who are intolerant of aspirin; and**
- **in addition to aspirin, especially in patients with recurrent stroke or TIA despite aspirin.**

7.2.4 CLOPIDOGREL

Clopidogrel (75 mg/day) appears to be as effective as moderate dose aspirin (300 mg/day) for prophylaxis of cardiovascular events following ischaemic stroke.[93]

Evidence level Ib

A **Clopidogrel** (75 mg/day) **should be considered as an alternative to aspirin in suitable patients with contraindications to aspirin, or who are intolerant of aspirin, for prevention of cardiovascular events following ischaemic stroke.**

7.2.5 WARFARIN

A **In patients with atrial fibrillation, warfarin** (target INR 2.5, range 2.0-3.0) **should be used in preference to antiplatelet therapy to reduce the risk of a further ischaemic stroke because of its greater efficacy.**[17]

(See section 3)

C **Warfarin should also be considered as secondary prophylaxis after cardioembolic stroke from valvular heart disease or recent myocardial infarction.**[124]

(See sections 3 and 4)

The balance of risk and benefit for warfarin (target INR 2.5, range 2.0-3.0) in secondary prevention in patients with TIA or ischaemic stroke who do not have atrial fibrillation or other cardiac source of embolism is not known reliably, and so is not recommended at present.[131] A randomised trial of higher intensity warfarin (target INR 3.7, range 3.0-4.5) vs. aspirin was terminated early because of excessive intracranial bleeding.[132]

7.3 CAROTID ENDARTERECTOMY

C The SIGN Guideline on Management of Patients with Stroke, Part II: Management of carotid stenosis and carotid endarterectomy,[133] recommends that **patients should continue on antiplatelet drugs throughout the perioperative period and should be heparinised during the procedure.**

8 Recurrent arterial thrombosis or embolism

☑ Patients with recurrent arterial thrombosis or embolism should be carefully evaluated for:

- compliance with antithrombotic prophylaxis
- modifiable risk factors (smoking, blood pressure, lipids)
- cardiac sources of peripheral embolism (echocardiography)
- thrombophilias (see table 4) in patients under 40 years[73]
- arteritis (e.g. collagen disorders, syphilis)
- malignant disease.

* **In patients with recurrent arterial thromboembolism despite aspirin or other antiplatelet agents, especially those with cardiac sources of embolism or thrombophilias, prophylactic warfarin** (target INR 2.5, range 2.0-3.0) **should be considered, balanced against the increased risk of bleeding.**

* *This is a grade A recommendation for patients with atrial fibrillation or myocardial infarction (see section 3); grade C for patients with peripheral arterial thrombosis (see section 6.1).*

C **In patients with recurrent arterial thrombosis or embolism despite warfarin at target INR of 2.5, range 2.0-3.0, either the addition of aspirin** (75 mg/day), **high-intensity warfarin** (target INR 3.5, range 3.0-4.0), **or (if there is further recurrence) high-intensity warfarin plus aspirin** (75 mg/day) **may be considered.**

Based on level III evidence[19]

C **The increased risk of bleeding with such regimens should be considered.**

There is evidence from retrospective studies that in patients with lupus anticoagulants, a target INR of 3.5, range 3.0-4.0, is more effective in prevention of recurrent thrombosis than warfarin at INR range 2.0-3.0.[134]

9 Primary prophylaxis of myocardial infarction in high risk patients

9.1 ASPIRIN

Two primary prevention trials and one trial in hypertension using aspirin have shown significant reductions in the risk of non-fatal myocardial infarction in high risk men: the US Physicians Health Study;[13] the Thrombosis Prevention Trial[14] in UK general practice; and the Hypertension Optimal Treatment (HOT) trial.[135] These trials have not been powerful enough to show an effect on mortality. In the UK trial, aspirin (75 mg/day) was associated with a relative reduction in myocardial infarction of 20% (annual NNT about 400), which should be balanced against a small increased risk of bleeding.[136] This increased risk of bleeding was higher in the HOT study.[135] This balance of benefit over risk increases with the absolute risk of myocardial infarction, which can be estimated from, for example, the Joint British Guidelines[137] *(see the SIGN guideline on Lipids and the Primary Prevention of Coronary Heart Disease*[138]*)*. Because aspirin is much cheaper than lipid-reducing drugs, its use should be considered in pharmacological primary prevention of myocardial infarction in those at increased risk,[136] e.g. 2% per year.[137]

Evidence level Ib

The relative reduction in vascular events in diabetics in a pooled analysis of eight trials was similar (annual NNT 360) but was not statistically significant.[8]

A **Aspirin** (75 mg/day) **should be considered for primary prophylaxis of myocardial infarction in men at high risk,** (e.g. 2% per year) **balanced against the increased risks of bleeding.**

C **Aspirin** (75 mg/day) **should also be considered for primary prophylaxis of myocardial infarction in women at high risk,** (e.g. 2% per year) **balanced against the increased risks of bleeding.**

Based on level III evidence and extrapolation of level Ib evidence in men

9.2 WARFARIN

The Thrombosis Prevention Trial[14] also assessed the effect of low-dose warfarin (INR 1.3-1.9, mean 1.47) with and without aspirin (75 mg/day) in prevention of ischaemic heart disease (IHD). Low-dose warfarin (without aspirin) was associated with a similar reduction in non-fatal myocardial infarction, and a similar increase in risk of bleeding, as low-dose aspirin.

Evidence level Ib

Because of the added workload (need for INR monitoring) compared to aspirin, aspirin is preferred for primary prophylaxis, as for secondary prophylaxis.

Low-dose warfarin combined with aspirin was associated with a greater reduction in myocardial infarction (fatal and non-fatal) than either agent alone (relative risk reduction 34%).[14] However, combined treatment was also associated with significantly greater risk of bleeding, including haemorrhagic stroke.

Evidence level Ib

For this reason, as well as the need for INR monitoring, aspirin is again preferred for routine primary prophylaxis. Further research is required to establish whether subgroups derive greater benefit from warfarin.

A **Low-dose warfarin** (target INR 1.6, range 1.3-1.9) **is effective in primary prophylaxis of IHD in high risk men. However, the need for INR monitoring and the risk of bleeding, especially when combined with aspirin, render it less attractive than aspirin for routine antithrombotic primary prophylaxis.**

10 Other indications for anticoagulant therapy

10.1 HEPARIN

Systemic heparin (unfractionated or LMW) is used routinely to prevent clotting of blood *in vivo* during haemodialysis.[139]

Local low-dose heparin is used routinely to prevent clotting of peripheral venous or arterial catheters. A meta-analysis of randomised trials found that intermittent heparin flushes had no benefit over normal saline flushes. Heparin infusion prolonged patency of arterial catheters, but further studies are required to establish its benefit for venous catheters.[140]

Evidence level Ia

10.2 WARFARIN

Low-dose warfarin has been shown in two studies to be effective in prophylaxis of thrombosis in central venous catheters,[141] and in prophylaxis of thrombosis during chemotherapy in stage IV breast cancer[142] (*see table 3*).

Evidence level Ib

A **Minidose warfarin** (1 mg/day, no INR monitoring) **is recommended for prophylaxis of thrombosis in 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.**

11 Antiplatelet agents

11.1 ASPIRIN

11.1.1 DOSAGE

Aspirin is the antiplatelet agent of choice: it is of comparable efficacy to other currently available antiplatelet agents in prevention of cardiac or arterial thromboembolic events[7, 8, 9] and is widely available and inexpensive. The standard dose preparations available in the UK are 75 mg and 300 mg. Standard, dispersable, and enteric-coated preparations are available. For patients with clinically-suspected acute myocardial infarction or unstable angina, or CT-confirmed non-haemorrhagic acute stroke, who are not already taking regular aspirin, it is recommended that 150-300 mg of non-enteric-coated aspirin should be swallowed as soon as possible, to achieve rapid inhibition of platelet function. Doses of 30-1200 mg/day have been used in randomised controlled trials of aspirin as an antithrombotic agent in most other indications. The evidence suggests that, for most indications, 75-300 mg/day is as effective as higher doses, and appears less likely to cause gastric irritation, bleeding or constipation.[7, 143] 75 mg/day is sufficient to suppress platelet aggregation in most persons after several days.[143]

Evidence level Ib

11.1.2 ADVERSE EFFECTS

Adverse effects of aspirin include allergy (e.g. bronchospasm); gastric irritation, ulceration and bleeding; constipation; renal failure;[144] and bleeding at other sites (bruising, subconjunctival, and intracranial). The risk of haemorrhagic stroke is about 1 in 2500 patient-years.[145]

The risk of gastrointestinal symptoms and bleeding is dose-dependent, but is still increased even at low doses.[146, 147] There is no evidence that use of enteric-coated or buffered preparations reduces the risk of major gastrointestinal bleeding.[148] A review of all trials listed in the antiplatelet trialists collaboration showed a pooled odds ratio of 2 for gastrointestinal bleeding or major bleeding, and a pooled odds ratio of 1.5 for gastrointestinal symptoms leading to withdrawal of treatment.[147] In secondary prophylaxis of vascular disease, these risks are considerably outweighed by the benefits,[8] and aspirin is likely to be cost-saving or cost-neutral.[8] In primary prophylaxis of vascular disease, the benefit:risk ratio is lower, as discussed in section 9. With low-dose aspirin, the absolute risk of major gastrointestinal bleeding was about 1 in 500 man-years in the Thrombosis Prevention Trial.[14, 149]

In patients with acute major haemorrhage (e.g. gastrointestinal, intracranial, retroperitoneal) aspirin should be discontinued; and consideration given to reversal of the platelet function defect by platelet transfusion, with due regard to its complications which include viral transmission.[150] As noted in section 5.4, aspirin may be stopped one week prior to bypass grafting.

In patients who experience gastric intolerance to aspirin, options are to reduce the dose of aspirin to the minimum effective dose (75 mg); to change to dispersable or enteric-coated preparations; to add concomitant gastro-protective drugs such as antacids, misoprostol, proton pump inhibitors, or H_2-receptor antagonists;[143, 151] or to change to another antithrombotic agent: clopidogrel, dipyridamole or warfarin if appropriate.

11.1.3 CONTRAINDICATIONS

Contraindications to aspirin include: known allergy; age under 12 years (risk of Reye s syndrome); active peptic ulceration; history of recent gastrointestinal bleeding; history of recent intracranial bleeding; and bleeding disorders including haemophilia, von Willebrand s disease, thrombocytopenia and severe liver disease.

11.1.4 CAUTIONS

Cautions with aspirin include asthma; uncontrolled hypertension (risk of intracranial bleeding); and previous peptic ulceration (risk of gastrointestinal bleeding: proton pump inhibitors or H_2-receptor antagonists may be considered for prophylaxis). As noted above, combination therapy with aspirin and oral anticoagulants increases the risk of bleeding[14, 92, 143] and should be avoided, except in situations of high thrombotic risk where the antithrombotic benefits of combination therapy are perceived to outweigh the risk of bleeding; e.g. prosthetic heart valves *(see section 4.4)* and recurrent arterial thromboembolism *(see section 8)*.

11.1.5 RECURRENCE

In patients who experience recurrent thrombosis despite low-dose aspirin prophylaxis, options are to increase the dose (up to 1200 mg/day); add dipyridamole or substitute another antiplatelet agent (*see below*); or consider oral anticoagulants if appropriate (*see section 13*).

11.2 DIPYRIDAMOLE

Dipyridamole is currently licensed in the UK as an adjunct to oral anticoagulation for prophylaxis of thromboembolism associated with prosthetic heart valves (*see section 4.4*) and as an alternative (or in addition) to aspirin in secondary prevention of ischaemic stroke *(see section 7.2)*. In the large European Stroke Prevention Study (ESPS-2) which gives evidence for the latter indication,[129] dipyridamole (200 mg twice daily in a sustained release preparation) was not associated with increased bleeding compared to placebo, but was associated with initial headache. Dipyridamole is contraindicated in uncontrolled angina, which it may exacerbate.

11.3 CLOPIDOGREL

Clopidogrel is licensed in the UK as an alternative to aspirin for secondary prevention of myocardial infarction and stroke in patients with previous myocardial infarction (*see section 5.1)*, ischaemic stroke *(see section 7.2)* or peripheral arterial disease *(see section 6.1)*. Compared to aspirin, clopidogrel was associated with a lower risk of gastrointestinal bleeding, but a higher risk of skin rashes.[93] Ticlopidine, a related drug which is not presently licensed for this indication in the UK, has similar efficacy to clopidogrel but increased risk of adverse effects including neutropenia.[143]

12 Heparins

12.1 UNFRACTIONATED HEPARIN

Unfractionated heparin is a naturally-occurring glycosaminoglycan (porcine or bovine) with a molecular weight range of 5,000-35,000 daltons (mean 12-14,000). It inactivates activated clotting factors (thrombin, factor Xa) by potentiating the effect of the endogenous coagulation inhibitor, antithrombin; and thereby prolongs the activated partial thromboplastin time (APTT) when given in therapeutic doses. Heparin is given parenterally, either by intravenous (IV) injection which has an immediate effect and short plasma half-life (30 minutes 2 hours); or by subcutaneous injection which has a delayed (2 hours) but more prolonged (10 hours) effect. There is a 10-fold intersubject variability in response to a given dose of heparin; hence with full-dose heparin therapy its coagulation effect (APTT ratio) must be monitored at least daily and the dose adjusted to achieve the target therapeutic range, within which the risks of bleeding and thrombosis are each minimised.[152]

12.1.1 INITIATION, DOSAGE AND MONITORING

Indications for heparin are summarised in table 2. Heparin is usually given in hospital and replaced by warfarin for outpatient anticoagulation; however subcutaneous heparin therapy is increasingly used in some outpatients (e.g. pregnancy).

☑ After clinical assessment has demonstrated an indication for heparin treatment *(see table 2)*, the patient s medical and drug history should be assessed for cautions and contraindications *(see table 7)*.

☑ A baseline blood count including platelet count, coagulation screen, urea, electrolytes and liver function tests should be obtained prior to starting full-dose heparin therapy. This may show contraindications or risk factors for bleeding, such as anaemia, thrombocytopenia, renal failure, or coagulopathy (e.g. due to severe liver disease). A baseline platelet count is useful for the subsequent diagnosis of heparin-induced thrombocytopenia. In venous thromboembolism, a baseline sample may help in diagnosis of antithrombin deficiency prior to reduction in antithrombin by heparin therapy.

Low dose unfractionated heparin (5,000 IU 8-12 hourly or 7,500 IU 12-hourly subcutaneously), given as routine prophylaxis of venous thromboembolism, does not require monitoring of the APTT ratio; nor does low dose infusion for prevention of clotting in peripheral arterial catheters.

A **In patients given full-dose unfractionated heparin therapy, routine monitoring of the APTT ratio (at least daily) and adjustment of heparin doses according to a local protocol, to achieve the target therapeutic range of anticoagulant effect** (APTT ratio) **is strongly recommended.**

Table 7

CONTRAINDICATIONS TO AND CAUTIONS WITH FULL-DOSE ANTICOAGULANT DRUGS

Note: These depend on individual circumstances and are seldom absolute.

- **Uncorrected major bleeding**
- **Uncorrected major bleeding disorder**
  e.g. thrombocytopenia, haemophilias, liver failure, renal failure
- **Uncontrolled severe hypertension**
  e.g. systolic > 200 mm Hg or diastolic > 120 mm Hg
- **Potential bleeding lesions**
  e.g. active peptic ulcer, oesophageal varices
  aneurysm, proliferative retinopathy
  recent organ biopsy
  recent trauma or surgery to head, orbit, spine
  recent stroke
  confirmed intracranial or intraspinal bleed
- **Heparin**
  history of heparin-induced thrombocytopenia or thrombosis
- **Warfarin**
  pregnancy (usually)
  homozygous protein C deficiency (risk of skin necrosis)
  history of warfarin-related skin necrosis
  uncooperative/unreliable patients (long-term therapy)

This recommendation is based on five trials in acute deep vein thrombosis or acute myocardial infarction which showed that that failure to reach the lower limit of the target range of the APTT ratio (usually 1.5-2.5) was associated with substantial increases in relative risks of recurrent thrombotic events;[32, 152] on evidence from randomised controlled trials that use of protocols for heparin dose adjustment according to APTT ratio results improves the achievement of therapeutic target ranges,[32, 53, 56] and on a large reported clinical experience that the risk of bleeding increases with APTT ratios above the upper limit of the target therapeutic range.[152, 153]

Evidence level Ib

C **Each laboratory should standardise its own target range for APTT ratio.**[32, 54]

Clinically-important **heparin-induced thrombocytopenia** is immune-mediated and usually occurs between six and 10 days (up to 20 days) after initiation of heparin therapy; it may be complicated by thrombosis.

C **The platelet count should be monitored in all patients receiving heparin for five days or more, to detect heparin-induced thrombocytopenia, as recommended by the Committee on Safety of Medicines.**[154]

C **If thrombocytopenia is detected, heparin should be stopped immediately, and alternative anticoagulation considered, e.g. with recombinant hirudin; the heparinoid, danaparoid** (unlicensed indication in UK); **or the defibrinating agent, ancrod** (unlicensed indication in UK). **Warfarin may be considered once the platelet count has recovered.**[152]

Osteoporosis and fractures have followed prolonged heparin use, e.g. in pregnancy.[152]

Evidence level III

C **Monitoring of bone density may be considered in patients at high risk of osteoporosis.**

Full-dose unfractionated heparin is usually initiated with an initial intravenous loading dose over five minutes (5000 IU in an average-sized adult; or 75 IU/kg body weight in children, small adults and large adults). For most indications for full-dose heparin, an intravenous infusion is then given (1400 IU/hour in an average-sized adult; 15-25 IU/kg body weight/hour in children, small adults and large adults). A lower initial infusion rate (1000 IU/hour) is usually given if heparin is given following thrombolytic therapy, which produces an anticoagulant effect *(see section 5.1)*. The APTT ratio should be measured about six hours after the initial bolus injection, and the infusion rate adjusted using a local schedule. After each change of heparin dose, the APTT ratio should be measured after 6-10 hours, when a steady state will have been reached. When the target therapeutic range has been achieved, the APTT ratio should be measured at least daily.[152]

As noted in section 2.3, 12-hourly subcutaneous injection of unfractionated heparin is as effective and as safe as intravenous heparin in treatment of deep vein thrombosis.[55, 56] Treatment should be initiated with a conventional intravenous bolus, and monitoring of the APTT ratio (4-6 hours after injection, preferably at the same time each day) and dose adjustment performed. It should be noted that there have been no reported trials of subcutaneous unfractionated heparin in patients with pulmonary embolism.

12.1.2 REVERSAL OF UNFRACTIONATED HEPARIN

☑ As the half-life of unfractionated heparin is short, it is usually sufficient to stop heparin if there is mild bleeding. If severe bleeding occurs, protamine sulphate should be given.[154]

12.2 LOW MOLECULAR WEIGHT HEPARINS

Several low molecular weight (LMW) heparins have recently been licensed in the UK as alternatives to unfractionated heparin for the prophylaxis of DVT and PE *(see section 2.1)* and treatment of DVT and PE *(see section 2.3)* or unstable angina *(see section 5.2)*.[49] Their lower molecular weight gives the advantage of greater bioavailability after subcutaneous injection compared to standard, unfractionated heparin: hence they are effective antithrombotic agents when given once or twice daily (as compared to twice or thrice daily) and do not require routine daily monitoring of coagulation tests. LMW heparins have little effect on the APTT, hence if monitoring of their anticoagulant effect is required, plasma anti-Xa levels should be used.[49, 152]

12.2.1 MONITORING OF LMW HEPARINS

Monitoring of plasma anti-Xa levels should be performed if there are complications such as haemorrhage, extension of thrombosis, or accidental overdose; and in patients with renal failure.[155] Monitoring of the platelet count is recommended to detect heparin-induced thrombocytopenia.[20]

Long term LMW heparin therapy may carry a lower risk of bone fractures than unfractionated heparin in older patients,[22] but monitoring of bone density may be considered in high risk patients.

12.2.2 REVERSAL OF LMW HEPARINS

The manufacturer s data sheet should be consulted.

13 Oral anticoagulants

13.1 INTRODUCTION

Warfarin is the oral anticoagulant of choice. Nicoumalone and phenindione are licensed in the UK but are potentially more toxic than warfarin and are seldom used. All currently-available oral anticoagulants act by antagonising the effect of vitamin K, resulting in reduced hepatic production of active coagulation factors II, VII, IX and X, and hence in prolongation of the prothrombin time and INR. This usually takes 48-72 hours to develop fully. Hence in acute thromboembolism anticoagulation should be commenced with heparin, which should be continued until the INR has been within the desired range of the target for at least two consecutive days. Heparin is not required when oral anticoagulants are started electively for prophylaxis of thromboembolism, except in certain thrombophilias.[19, 73]

Indications for oral anticoagulants are summarised in table 3, together with a summary of the target INR[134] and its optimal range as defined in observational studies or randomised trials. It should be noted that audits have indicated that only about 30% of INRs are within the target range at any one time.[134]

The average daily dose of warfarin to achieve an INR within the desired range of the target (usually 2.0-3.0) is 5 mg, but with wide variation (range 1-15 mg). Warfarin sensitivity varies widely between individuals, and within the same person, due to variables such as age, diet, diseases and drugs.[19]

☑ A well-stabilised patient may need an INR check only every 4-8 weeks; however, any change in clinical state or in medication should prompt more frequent checks. The doctor monitoring anticoagulant treatment should be aware of the indication for treatment, target therapeutic range, and the planned duration of therapy.

13.2 INITIATION, DOSAGE AND MONITORING OF ORAL ANTICOAGULANTS

☑ After clinical assessment has demonstrated an indication for oral anticoagulant treatment *(see table 3)*, the patient s medical history, drug history, and compliance should be assessed for cautions and contraindications *(see table 8)*. Many drugs interfere with both the pharmacology and bleeding risks of oral anticoagulants, most by enhancing, but some by suppressing the anticoagulant effect *(see table 9)*. The drug regimen should be simplified if possible. Potentially interacting drugs should be exchanged for non-interacting ones (e.g. cimetidine should be replaced by an alternative H_2 receptor antagonist such as ranitidine); and aspirin stopped unless combination therapy is indicated *(see section 4)*. In patients with peptic ulcer, *H. pylori* eradication therapy should be considered (see the SIGN guideline on *H.pylori* eradication in dyspeptic disease[156]).

☑ The indication for oral anticoagulants, the appropriate target therapeutic range of the INR, and the proposed duration of treatment should be recorded in the case records, and notified in writing to the anticoagulant clinic if monitoring is to be performed there. Details of other medications and relevant medical conditions should also be notified in writing to the anticoagulant clinic.

Table 8

CHECKLIST OF DRUG INTERACTIONS WITH WARFARIN

Note: This list is not exhaustive: if in doubt consult the British National Formulary

AVOID	
Aspirin	Except where combination specifically indicated e.g. mechanical valve prosthesis, recurrent thrombosis
Analgesics	Co-proxamol Ketorolac (postoperative)
Antifungals	Miconazole
Diabetes	Glucagon
Non steroidal anti-inflammatory drugs	Azapropazone Phenylbutazone
Others	Enteral feeds containing vitamin K
ADJUST DOSE	
Ulcer healing	Cimetidine Omeprazole
Antiarrhythmics	Amiodarone Propafenone
Lipid lowering	Fibrates
Antiepileptics	Carbamazepine Phenobarbitone Phenytoin Primidone
Dependency	Disulfiram
Antibiotics/antifungals	Aztreonam Cephamandole Chloramphenicol Ciprofloxacin Co-trimoxazole Erythromycin Griseofulvin Metronidazole Ofloxacin Rifampicin Sulphonamides

ADJUST DOSE	
Thyroid	Carbimazole Thiouracils Thyroxine
Nonsteroidal anti-inflammatory drugs	Diflunisal
Gout	Allpurinol Sulphinpyrazone
Others	Aminoglutethimide Barbiturates Cyclosporin Mercaptopurine Oral contraceptive steroids
MONITOR INR	
GI motility	Cisapride
Antiarrhythmics	Quinidine
Lipid lowering	Cholestyramine Statins
Antidepressants	Serotonin uptake antagonists
Antibiotics/antifungals	Consult BNF if not listed under adjust dose
Diabetes	Tolbutamide
Non steroidal anti-inflammatory drugs	If not listed under avoid or adjust dose
Others	Anabolic steroids Corticosteroids Hormone antagonists Ifosfamide Influenza vaccine Rawachol Sucralfate

Table 9

ONE SCHEDULE FOR INPATIENT DOSAGE AND MONITORING OF FULL-DOSE WARFARIN THERAPY IN PATIENTS WITH ACTIVE THROMBOSIS[53]

Day	**INR** *(9-11am)*	**Warfarin dose** (mg) *(given at 5-7pm)*
1st	<1.4	10
2nd	<1.8	10
	1.8	1
	>1.8	0.5
3rd	<2.0	10
	2.0-2.1	5
	2.2-2.3	4.5
	2.4-2.5	4
	2.6-2.7	3.5
	2.8-2.9	3
	3.0-3.1	2.5
	3.2-3.3	2
	3.4	1.5
	3.5	1
	3.6-4.0	0.5
	>4.0	0
4th		*predicted maintenance dose*
	<1.4	>8
	1.4	8
	1.5	7.5
	1.6-1.7	7
	1.8	6.5
	1.9	6
	2.0-2.1	5.5
	2.2-2.3	5
	2.4-2.6	4.5
	2.7-3.0	4
	3.1-3.5	3.5
	3.6-4.0	3
	4.1-4.5	miss out next day s dose then give 2 mg
	>4.5	miss out next two days doses then give 1mg

APTT ratio should be within or below therapeutic range (1.5-2.5). If APTT ratio is above this range the heparin effect on INR should be neutralised by adding protamine (0.4 mg/ml plasma) to the sample in the haematology laboratory.

☑ A baseline blood sample for blood count (including platelet count), coagulation screen, urea, and liver function tests should be obtained prior to starting oral anticoagulants. This may show contra-indications or risk factors for bleeding, such as anaemia, thrombocytopenia, renal failure, or a prolonged prothrombin time due to auto-anticoagulation , e.g. due to severe liver disease. In venous thromboembolism, a baseline thrombophilia screen may help in diagnosis of protein C or S deficiency prior to reduction of plasma levels of these proteins by oral anticoagulant therapy.

☑ On starting oral anticoagulants, the INR should be charted in the case records along with daily dosage. A Department of Health oral anticoagulant booklet (issued by The Stationery Office and available from hospital and community pharmacists) should be fully completed, and patients (or relatives/carers) taken systematically through the educational dos and don ts in the booklet prior to anticoagulant therapy, and periodically thereafter.

☑ The daily dose of warfarin should be taken at a fixed time.

In hospitalised patients with active thromboembolism, the generally accepted starting regimen for treatment of acute thromboembolism is 5-10 mg/day warfarin on days one and two; thereafter dosing is determined according to the daily INR[53] *(see table 9)*. The initial dosing regimen should be lower (5 mg) when there is increased sensitivity to warfarin (e.g. age over 65 years, low body weight, parenteral feeding, drug therapy which increases warfarin sensitivity e.g. some antibiotics, heart failure, liver failure, prolonged baseline prothrombin time). In patients taking both heparin and warfarin at the start of treatment, the INR can be used for dosing warfarin without stopping heparin, provided that the APTT ratio is within or below the therapeutic range for heparin *(see table 9)*.

☑ Hospitalised patients with acute thromboembolism should not be discharged from hospital INR monitoring until stability within the appropriate target therapeutic range is achieved. Prior to hospital discharge, the hospital should communicate with the general practitioner (or other medical practitioner assuming patient care) to advise the recommended INR target range and the duration of therapy; and agree and ensure arrangements for continued patient and INR monitoring. Prior to discharge, patients should be given written information on the date and place of the next monitoring visit.

In outpatients without acute thromboembolism who are started on long term prophylactic oral anticoagulants (e.g. for atrial fibrillation) a less intensive starting regimen is appropriate.[149, 157, 158]

☑ Long term monitoring of oral anticoagulant therapy may be performed either by hospital departments (e.g. anticoagulant clinics managed by haematology departments) or by the patient s general practitioner; local arrangements vary. In either case:

- monitoring should be performed or supervised by knowledgeable and experienced staff; and quality control of clinical performance monitored
- cumulative records of INR and warfarin dose should be maintained
- a reliable patient recall and review system should be kept.

A review of comparative trials of anticoagulant clinic care versus routine medical care reported a trend for lower rates of major bleeding and thromboembolic events with anticoagulant clinic care;[159] however, further comparative studies are required.

Computer programs for management of oral anticoagulant dose may be superior to management by experienced medical staff.[160, 161]

Patient self-management of oral anticoagulation also requires further study.[162]

☑ While near patient testing of the INR by several devices is commercially available, their accuracy and quality control should be professionally validated prior to use, and ongoing quality control arranged with a local haematology laboratory. Professional guidelines state that INR measurement be performed (or quality controlled) by a haematology department.[163] Such a department should be accredited by Clinical Pathology Accreditation Ltd; and should make appropriate arrangements for the transfer of patients blood samples to the laboratory for prompt processing.

☑ Written reports should be sent to the requesting clinician through the hospital internal delivery systems, or by first class post to other hospitals or general practitioners. All INR results outwith the range 2.0-4.5 should be communicated to the requesting clinician on the same day, as should any other requests marked as urgent . Such a department should also provide a 24-hour consultative medical service to respond to clinical queries about anticoagulation.

☑ Each clinical unit (e.g. ward, outpatient clinic, GP surgery) must have formal arrangements for processing reports to ensure the result reaches the requesting doctor timeously, and to ensure that the result is entered on the patient s clinical record (and in the outpatient s anticoagulant booklet). There should be a reliable system for promptly informing patients of the results of their INRs and any change in oral anticoagulant dose.

13.3 REVERSAL OF ORAL ANTICOAGULANT THERAPY IN PATIENTS WITH BLEEDING OR HIGH INR

C **The most common cause of fatal or disabling bleeding in patients receiving anticoagulant therapy is intracranial or intraspinal bleeding.[164-168] Any such patients who have head injury, headache (recent, severe), confusion, impaired consciousness, or focal neurological symptoms and signs should have urgent CT scanning to detect such bleeding, followed by appropriate referral.**

The necessity for therapeutic intervention and the urgency for reversal of oral anticoagulant therapy will depend upon the reason why the patient is anticoagulated, the desired therapeutic range of the INR, the presence of either known local pathology (e.g. peptic ulcer) or systemic disorders (e.g. renal failure), and the severity and site of haemorrhage. The risk of haemorrhage rises with increasing INR, and the risk of thrombosis rises with decreasing INR.[164-168] If the patient has become over anticoagulated it is important to ascertain the reason for this. Recent guidelines have been published.[134, 154, 169]

☑ In the patient with active bleeding, as well as measuring the INR, it is important to perform a full coagulation screen (APTT, fibrinogen and platelet count) and a full blood count to ensure that the patient does not have any other abnormality predisposing to bleeding, e.g. thrombocytopenia. Blood urea and liver function tests should be checked to assess the hepatic and renal status.

☑ Immediate management should be directed towards arresting bleeding, even although in doing so it may temporarily increase the risk of thrombosis in individuals with continuing long term risk, e.g. in the presence of a prosthetic heart valve.

Reversal of anticoagulation can be achieved by stopping warfarin, administering vitamin K_1, or giving blood products containing the vitamin K dependent clotting factors, i.e. factor IX complex concentrate (containing factors II, IX and X) and factor VII concentrate, or fresh frozen plasma. The advantages and disadvantages of each of these options are set out in table 10.

A suggested scheme for treating patients is set out in table 11. After corrective therapy has been initiated the INR should be monitored at appropriate time intervals: for those given vitamin K_1 after 4-6 hours; and after factor IX complex concentrate immediately, again after 4-6 hours, and then daily.[170, 171]

In patients with a high INR but no bleeding, stopping anticoagulant therapy alone will only result in a gradual reduction over several days in the INR. In the presence of a very high INR (over 8.0) or other risk factors for bleeding, a small dose of **vitamin K_1** (0.5 mg intravenously or 5 mg orally) can be given.[170, 172, 173] Such a dose will restore the INR to the usual therapeutic range and not make the patient resistant to further anticoagulation with oral anticoagulants.

Evidence level III

B **In patients with a high INR** (>8.0) **or other risk factors for bleeding, vitamin K_1** (0.5 mg intravenously or 5 mg orally) **should be considered.**

B **In patients with non-severe bleeding and a high INR, warfarin should be stopped for 1-2 days and vitamin K_1** (0.5-2 mg intravenously or 5-10 mg orally) **should be considered.**

For individuals with more severe haemorrhage a larger dose of vitamin K_1 can be used, but this may render the patient relatively resistant to re-anticoagulation. Vitamin K_1 should be infused slowly, because large doses given rapidly may result in facial flushing, chest tightness, cyanosis and hypotension. It should not be given intramuscularly because of the risk of haematoma formation. The bioavailability of vitamin K_1 after oral administration is very variable; if permanent reversal of anticoagulation is required a dose of 10 mg is appropriate.[134] Vitamin K_1 has a short plasma half of 1-2 hours and a biological effect that only lasts for a few hours and therefore repeated infusions are desirable.[175] Major haemorrhage associated with a high INR, in patients who need continued long term anticoagulation, can be managed by intravenous vitamin K_1 along with an infusion of factor IX complex concentrate.[171, 174] **Factor IX complex concentrate** also contains factors II and X (but not factor VII). It is therefore effective therapy for rapid reversal of the anticoagulant effect of warfarin but carries a risk of thrombosis.[171, 174] It should only be used when there is severe haemorrhage and not merely to correct a high INR which can be more appropriately accomplished by a small dose of vitamin K_1. **Factor VII concentrate** should also be given if available.

Evidence level III

Table 10

OPTIONS FOR REVERSAL OF ORAL ANTICOAGULANT THERAPY

Method	Advantages	Disadvantages
Stop warfarin	Simple	May take several days for INR to normalise particularly with liver disease
Vitamin K_1 *Dosage:* 0.5-5 mg IV 5-10 mg orally (depending on urgency)	Safe if given slowly	 2-6 hours to take effect 12-24 hours to take effect
Factor IX complex concentrate (Factor II, IX, X) *Dosage:* 50 IU/kg body weight	Acts immediately Small volume Can be given quickly	Exposes patient to pooled blood product which rarely may transmit hepatitis B (but safe from hepatitis C and HIV) Effect is temporary (8-24 hours) and should be combined with Vitamin K_1 Risk of thromboembolism
Factor VII concentrate *Dosage:* 50 IU/kg body weight	Should be given with factor IX complex	As for factor IX complex concentrate
Fresh frozen plasma *Dosage:* 1 litre for adult	Acts immediately	Large intravenous volume load Allergic reactions Not as efficacious as factor IX complex concentrate Difficult to give repeat infusions because of large volume Virally inactivated plasma is preferred

Table 11

STRATEGIES FOR REVERSAL OF ORAL ANTICOAGULANT THERAPY

A	**Life threatening bleeding** *(e.g. intracranial or major gastrointestinal bleed)*
1	Stop warfarin
2	Intravenous vitamin K_1 (5 mg, repeated if necessary)
3	Intravenous factor IX concentrate (50 IU/kg body weight) *and* factor VII concentrate (50 IU/kg body weight) (if available) or fresh frozen plasma (15 ml/kg body weight - approximately 1 litre for adult)
B	**Less severe bleeding** (e.g. haematuria, epistaxis)
1	Stop warfarin for 1-2 days
2	Give vitamin K_1 0.5-2 mg intravenously or 5-10 mg orally
C	**High INR but no bleeding**
1	Stop warfarin, monitor INR, restart warfarin when INR <5.0
2	Consider giving vitamin K_1 0.5 mg intravenously or 5 mg orally if: ▪ INR >8.0 ▪ other risk factors for bleeding

B **In patients with life threatening haemorrhage, factor IX complex concentrate should be given at a dose of 50 IU/kg body weight: such therapy is more efficacious than fresh frozen plasma.**[174, 176] **If factor VII concentrate is available it should be given at a simlar dose.**[134] **In addition, intravenous vitamin K_1 should be given** (5 mg, repeated as necessary).

The potential of coagulation factor concentrates (or fresh frozen plasma) to transmit most clinically important viral infections should be considered; this is reduced by a viral inactivation step during manufacture.

☑ Consideration should also always be given to ascertain whether there may be an underlying structural lesion predisposing to bleeding, particularly if bleeding is present when the INR is within the therapeutic range.

☑ For all individuals who become over anticoagulated it is essential (if the clinical decision is to continue oral anticoagulants) that they are well tutored in their use. In particular, they should be re-educated as to know what medicines to avoid (especially aspirin), what to do if they bleed, and when and where to get their INR checked; and be taken through their Department of Health anticoagulant booklet which they should carry with them. It is particularly important that the patients are well educated when initially starting on warfarin because the most common time for bleeding is during the first month of therapy.

13.4 MANAGEMENT OF ORAL ANTICOAGULANT THERAPY BEFORE AND AFTER SURGERY AND INVASIVE PROCEDURES

When patients receiving oral anticoagulant drugs require surgery (including dental extractions), or other invasive procedures, their increased risk of excessive bleeding during and after surgery should be considered.

C **Possible measures to reduce this risk include:**

- **urgent reversal of oral anticoagulant therapy**
- **elective discontinuation of the oral anticoagulant, or dose reduction, to achieve a lower INR**
- **substitution of heparin.**

Urgent reversal of oral anticoagulant therapy *(see section 13.3)* may be required in the event of need for urgent surgery with high risk of bleeding (e.g. neurosurgery, ocular surgery) or need for urgent invasive procedures (e.g. liver or renal biopsy, transhepatic percutaneous shunting, lumbar puncture, myelograpy, epidural or spinal anaesthesia). The latter procedures carry an increased risk of spinal haemorrhage and paraplegia, and should not be performed until anticoagulation has been reversed. The need for lumbar puncture or myelography should be discussed with a neurologist or neurosurgeon before anticoagulant therapy is reversed, because reversal carries a risk of thromboembolism and because alternative investigations (e.g. MRI scanning) may be preferable.

Elective discontinuation of the oral anticoagulant, or dose reduction, to achieve a lower INR under which elective surgery can be performed, with an acceptable risk of bleeding. The individual s risk of bleeding will vary both with the type of surgery, and with the presence of other risk factors for bleeding.

With the exceptions of neurosurgery, ocular surgery, and surgery performed under epidural or spinal anaesthesia (which require total reversal of the INR to <1.3), most surgery can be safely performed when the INR falls to 1.5.[177, 178] For the majority of patients with an initial INR within the usual target therapeutic range (2.0-3.0), it takes 4-5 days after discontinuation of warfarin therapy for the INR to fall to 1.5 or less; elderly patients and those with INR greater than 3.0 may require a longer discontinuation time.[177, 178] If total reversal of warfarin (INR under 1.3) is required, 6-7 days of discontinuation may be required. After warfarin therapy is restarted, it takes about three days on average for the INR to increase above 2.0.[178]

Substitution of heparin (which can be rapidly reversed in the event of bleeding) during the period of lower INR, to reduce the risk of thromboembolism. Surgery increases the risk of venous thromboembolism: both heparin and oral anticoagulants are effective in prophylaxis.[5] While a perioperative INR between 1.5 and 2.0 may have some prophylactic effect,[178] patients at increased risk of venous thromboembolism should be considered for additional antithrombotic prophylaxis while the perioperative INR is less than 2.0.[178] Options include intravenous unfractionated heparin (monitored by the APTT); low molecular weight heparin; mechanical methods (graduated elastic compression stockings or intermittent pneumatic compression); or insertion of an inferior vena caval filter in very high risk patients (e.g. surgery within two weeks of proximal DVT or PE).[178]

There is also an increased risk of arterial and cardiac thromboembolism during the period of lower INR when oral anticoagulants are discontinued or reduced to reduce the risk of perioperative bleeding.[177, 178] Options include intravenous unfractionated heparin (monitored by the APTT) in high risk patients (e.g. surgery within four weeks of arterial or cardiac thromboembolism); or subcutaneous low-dose unfractionated heparin or low molecular weight heparin.[178]

☑ It is recommended that surgeons, dentists and physicians intending to perform surgery or invasive procedures in patients receiving anticoagulant therapy seek advice concerning management of such therapy from a haematologist, prior to performing such procedures. Management will vary according to the perceived relative risks of bleeding and thromboembolism in the individual patient.

13.5 DRUG INTERACTIONS

Oral anticoagulants have many interactions with commonly prescribed drugs. A checklist is given in table 8.

13.6 THE ROLE OF THE PHARMACIST OR NURSE SPECIALIST IN ANTICOAGULATION CLINICS

Pharmacists can play an important role in improving anticoagulant control (both in hospital and in primary care) by drug history taking, titration of dosage according to INR, patient counselling and dispensing of continuing supplies, and in making arrangements for future clinical appointments.[179, 180] Advantages from pharmacist-run anticoagulant clinics include continuity of care, maintenance of accurate patient records, reduced workload for doctors, identification of drug interactions, and identification and minimisation of adverse effects.[181, 182] Guidance on how to establish such a clinic has been published.[179-182] There is also increasing involvement of nurse specialists in anticoagulation clinics.

14 Implementation of the guideline

Antithrombotic therapy with antiplatelet or anticoagulant drugs is indicated in a wide range of disorders which carry an increased risk of venous, cardiac or arterial thromboembolism. The recommendations in this guideline should therefore be considered when developing several local guidelines:

- Management of venous thromboembolism *(section 2)*
- Management of atrial fibrillation *(section 3)*
- Management of other cardiac causes of systemic embolism *(section 4)*
- Management of ischaemic heart disease *(section 5)*, peripheral arterial disease *(section 6)*, and cerebrovascular disease *(section 7)*
- Management of oral anticoagulant therapy *(section 13)*.

Development of these local guidelines will require coordinated action by health boards, NHS trusts, general practitioners, relevant hospital medical staff (cardiovascular physicians and surgeons, haematologists, radiologists, anaesthetists), pharmacists, nurses, and the Area Clinical Audit Committee.

Local guidelines should be discussed with and circulated to all relevant staff, and displayed in appropriate areas (primary care clinics, accident and emergency departments, relevant hospital clinics and wards, haematology departments, and pharmacies).

14.1 PATIENT-SPECIFIC REMINDERS AT TIME OF CONSULTATION OR ADMISSION

These may include proformas in case records; and display of tables and flow diagrams in the above areas. Figures 1-2 and tables 1-11 may be useful in development of such reminders.

14.2 CONTINUING EDUCATION

Continuing education of relevant staff in primary and secondary care (medical, nursing, pharmacy) is desirable in this rapidly-changing area.

14.3 AUDIT

There is considerable scope for audit of antithrombotic therapy, in both primary care and hospital settings *(see section 15)*. Pharmacists are well-placed to perform such audit activities.

14.4 INPATIENT ANTICOAGULATION

Published studies indicate that performance is often suboptimal, but can be improved by the availability of summary practice points.[183, 184] The development and introduction of guidelines for anticoagulation using heparin *(see Annex 1)* and warfarin *(see Annex 2)* offer opportunities to audit practice before and after development of local guidelines.

14.5 OUTPATIENT ANTICOAGULATION

Again there is evidence of suboptimal performance at hospital anticoagulant clinics.[24] Probable reasons include inadequate record keeping and historical reliance on junior doctors who lack experience and/or knowledge of the patient. Supervised training should be part of postgraduate training. Computerisation[160] and involvement of experienced medical staff and/or pharmacists[179-182] may improve performance. In primary care, where the patient is likely to be better known to the supervising physician, experience again varies, and studies show a high percentage of patients with INR values outside the target range.[159] Again, the input of a pharmacist may improve performance. Annex 3 outlines an audit protocol for management of oral anticoagulation.[184]

14.6 PROVISION OF ANTITHROMBOTIC PROPHYLAXIS TO PATIENTS WHO MAY BENEFIT

Several recent audit studies have shown that many patients who may benefit from antiplatelet (aspirin) prophylaxis do not receive it;[15, 16] and more importantly that patients who may derive a greater benefit from oral anticoagulant (warfarin) prophylaxis, e.g. those with atrial fibrillation, do not receive it.[25, 26, 185, 186] Audits in both primary care and hospital practice are therefore required to monitor practice.

15 Recommendations for audit and research

15.1 AUDIT OF ANTICOAGULATION

15.1.1 AUDIT OF ANTICOAGULATION IN INPATIENT CARE

Key points for audit of heparin treatment in hospital are noted at Annex 1.[183] Key points for audit of warfarin initiation are noted at Annex 2.[183] Because many patients start warfarin during the initial exposure to heparin, many of the Practice and Audit Points are the same. The objective is to examine anticoagulation in patients in whom heparin or warfarin is introduced in hospital, before and after the introduction of the local guideline for anticoagulation. The method is a retrospective review of the case notes of a sample of recent patients treated with heparin or warfarin in the wards, utilising the identification of essential practice points and audit of their documentation.[184]

The initial audit provides an indication of baseline local standards for initiation of anticoagulation. An identical audit carried out several months after the introduction of the local guideline for anticoagulation allows an assessment of changes in standards. This exercise should also enable identification of reasons for any failure to meet the guideline standards and methods to improve awareness of the guideline.

Potential factors which may reduce impact of the guideline include:

- inaccessibility
- methods of reporting and filing of results
- failure of computer networks
- methods of documentation

Potential methods to improve awareness of the guideline include:

- display on ward notice boards
- reminder each time APTT ratio or INR ordered (laboratory)
- reminder each time heparin or warfarin prescribed (pharmacy)
- incorporation in ward information booklets
- dissemination to all junior doctors
- presentation in brief note form
- incorporation into hospital computer system.

A further audit after consideration of such factors completes the final audit loop.

15.1.2 AUDIT OF ANTICOAGULATION IN GENERAL PRACTICE OR HOSPITAL OUTPATIENT CLINIC

Key points for audit are noted at Annex 3. The objective is to examine oral anticoagulant management in patients attending either their general practitioner or a hospital outpatient clinic. The method is a retrospective analysis of a sample of case records of current attenders at the clinic utilising the identification of essential practice points and audit of their documentation.[184]

The initial audit provides an indication of current local standards for long term oral anticoagulation e.g. the recording of essential information; the appropriateness of therapeutic ranges for individual patients; the documentation of critical events and the identification of their causes; and the percentage of patients within their appropriate INR therapeutic range. An identical audit several months after the introduction of a local guideline allows an assessment of changes in standards. This exercise should also enable identification of reasons for any failure to meet the standards in the local guideline.

15.2 RECOMMENDATIONS FOR RESEARCH

- Management studies of risk stratification in clinically-suspected DVT or PE using combinations of clinical variables and non-invasive laboratory variables (e.g. fibrin D-dimer).
- Management studies of out-patient treatment of DVT.
- Studies of optimal duration of warfarin in patients with DVT or PE.
- Management studies of risk stratification and selective oral anticoagulant prophylaxis in atrial fibrillation using combinations of clinical variables and laboratory variables (e.g. echocardiography, fibrin D-dimer).
- Management studies of risk stratification and selective oral anticoagulant prophylaxis in patients with arterial disease using combinations of clinical variables and laboratory variables (e.g. fibrinogen, fibrin D-dimer).
- Management studies of risk stratification and selective antiplatelet or oral anticoagulant prophylaxis in patients at increased risk of arterial thrombosis using combinations of clinical variables and laboratory variables (e.g. ankle-brachial pressure index, fibrinogen, fibrin D-dimer).
- Management studies of control of oral anticoagulant therapy in primary and secondary care, e.g. pharmacist, nurse specialist, patient and computer-led management.
- Studies of new anticoagulant drugs requiring less monitoring than warfarin.

Annex 1

KEY POINTS FOR AUDIT OF HEPARIN TREATMENT IN HOSPITAL[183]

PRACTICE POINT	AUDIT POINT
▪ Objective test for diagnosis e.g. of venous thromboembolism	▪ Appropriate investigation results documented e.g. ultrasound scanning and/or venography for deep venous thrombosis; chest x-ray and ventilation/ perfusion scanning for pulmonary embolism.
▪ Minimal delay in anticoagulation for venous thromboembolism.	▪ Time from provisional diagnosis to initiation of heparin
▪ Baseline investigations before full-dose heparin.	▪ Results of coagulation screen; blood count including platelet count; urea and electrolyte; liver function tests.
▪ Risk factors for full-dose anticoagulation.	▪ Age, past history; drug history recorded.
▪ Method of introduction of full-dose unfractionated heparin (bolus followed by intravenous infusion or subcutaneous injection).	▪ Initial intravenous heparin bolus prescribed; continuous intravenous heparin infusion or subcutaneous injection prescribed.
▪ Monitoring of unfractionated heparin anticoagulation (within 4-6 hours of introduction, then daily).	▪ First measurement of activated partial thromboplastin time (APTT) ratio four to six hours after introduction; APTT ratio documented on each day of heparin; APTT ratio within the therapeutic range for each day of heparin treatment.

Annex 2

KEY POINTS FOR AUDIT OF WARFARIN INITIATION IN HOSPITAL[183]

PRACTICE POINT	AUDIT POINT
▪ Objective test for diagnosis e.g. of venous thromboembolism	▪ Appropriate investigation results documented e.g. ultrasound scanning and/or venography for deep venous thrombosis; chest *x*-ray and ventilation/ perfusion scanning for pulmonary embolism
▪ Baseline investigations	▪ Results of coagulation screen; blood count including platelet count; urea and electrolytes; liver function tests
▪ Risk factors for anticoagulation	▪ Age, past history, drug history recorded
▪ Start warfarin on day one of heparin administration (or confirmation of diagnosis).	▪ First dose of warfarin on first day of heparin (or confirmation of diagnosis)
▪ Overlap heparin and warfarin by 72 hours	▪ Both heparin and warfarin prescribed concurrently for three days
▪ Use algorithm to predict warfarin dose	▪ Agreement of initial warfarin dose with that predicted from algorithm
▪ Stop heparin when International Normalised Ratio (INR) within therapeutic range for two days	▪ INR within target range for two days on day heparin stopped
▪ Measure INR daily and at discharge	▪ INR documented on each day of treatment; INR within target range on day of discharge; INR on day of discharge; time to achieve INR in target range
▪ Anticoagulant management plan	▪ Planned duration of anticoagulant treatment documented; target INR and range specified
▪ Book appointment at anticoagulation clinic	▪ Clinic appointment documented
▪ Arrange interim INR if more than four days to clinic appointment	▪ Arrangement for interim INR documented

Annex 3

KEY POINTS FOR AUDIT OF ANTICOAGULANT MANAGEMENT

PRACTICE POINT	AUDIT POINT
▪ Indication for anticoagulation	▪ Appropriate indication(s) for anticoagulation documented
▪ Screening investigations	▪ Results of full blood count including platelet count; urea and electrolytes; liver function tests; at entry
▪ Risk factors for anticoagulation	▪ Age; past history; drug history; complete list of concomitant diagnoses and current drugs documented at each visit
▪ Anticoagulation management plan	▪ Planned duration of anticoagulation treatment document; target INR range specified
▪ Anticoagulant drug and dose	▪ Anticoagulant drug and dose documented at each visit; dose adjustments communicated to patient
▪ Other appropriate therapy	▪ Additional use of aspirin where indicated e.g. mechanical prosthetic valves
▪ Follow-up	▪ INR recorded at each visit; percentage of INRs within target range at each visit
▪ Anticoagulant control	▪ Date of next clinic visit documented
▪ Patient held record	▪ Fully completed; information on dos and dont s ; updated at each visit

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SIGN

Antithrombotic Therapy

Quick Reference Guide

ISCHAEMIC HEART DISEASE

A All patients with **suspected acute myocardial infarction** or **unstable angina** not already taking aspirin should be given aspirin (150-300 mg) as soon as possible *(unless contraindicated)*

☑ General practitioners should carry aspirin so that treatment can be initiated at diagnosis

A Patients with **acute myocardial infarction** should also be considered for thrombolysis as quickly as possible after the onset of symptoms

A Patients who are **hospitalised with severe unstable angina** should also be considered for full dose heparin or low molecular weight heparin

A All patients with **previous myocardial infarction, angina,** or **previous coronary artery surgery** or **angioplasty** should *(unless contraindicated)* be considered for antiplatelet prophylaxis, usually with aspirin (75-300 mg/day)

A In patients with contraindications to aspirin, clopidogrel (75 mg/day) should be considered for prophylaxis

CEREBROVASCULAR DISEASE

C Patients with **acute stroke** should have an early CT scan *(preferably within 48 hours and no later than seven days)*

A Patients shown to have ischaemic stroke should receive aspirin as soon as the diagnosis is confirmed (150-300 mg) *(unless contraindicated)*

A Anticoagulant therapy should be reserved for acute ischaemic stroke patients with a high risk of either venous thromboembolism or recurrent thromboembolic stroke

C Patients with **TIA** should be investigated promptly

A Patients with **ischaemic stroke** or **TIA** should *(unless contraindicated)* receive secondary prevention with one of:

- aspirin (75-300 mg/day)
- dipyridamole (200 mg twice daily) for patients intolerant of aspirin and (in combination with aspirin) for those with recurrent events despite aspirin
- clopidogrel (75 mg/day) for patients intolerant of aspirin
- warfarin in suitable patients with atrial fibrillation or other suspected cause of cardioembolic stroke

C Following **carotid endarterectomy**, patients should *(unless contraindicated)* receive aspirin (75-300 mg/day)

PERIPHERAL ARTERIAL DISEASE

A Patients with **intermittent claudication** or a history of **peripheral angioplasty** or **arterial grafts** should receive aspirin *(unless contraindicated)* or clopidogrel (75 mg/day)

Key:	☑	good practice point
A B C		grade of recommendation

SIGN Publication Number 36

ATRIAL FIBRILLATION

(For other cardiac causes of systemic embolism, see full guideline)

B Risk factors for **systemic thromboembolism** should be assessed routinely in all patients with atrial fibrillation

Risk factors for thromboembolism in AF are:

- *previous ischaemic stroke or TIA*
- *age over 65 years*
- *hypertension*
- *diabetes mellitus*
- *cardiac failure*
- *echocardiography showing LV dysfunction or mitral valve calcification*

Warfarin (target INR 2.5, range 2.0-3.0) reduces stroke risk by 68%

Aspirin (75-300 mg/day) reduces stroke risk by 20%

A **Patients with AF but without additional risk factors** require no antithrombotic prophylaxis unless there are other indications for aspirin. **Patients with one or more risk factors** should be considered for warfarin therapy in preference to aspirin

C Warfarin prophylaxis should also be considered in patients with **atrial fibrillation and heart valve disease or prostheses, thyrotoxicosis, intracardiac thrombus, or non-cerebral thromboembolism**

B The decision to use warfarin or not should be based on discussion of the **balance of risk and benefit** with each individual, including assessment of compliance

☑ To minimise the risk of intracranial bleeding in patients on warfarin, hypertension should be controlled, compliance assessed and the risks and benefits of warfarin reviewed annually, especially in those aged over 75 years

C **Cardioversion to restore sinus rhythm** should be considered in selected patients, because it may avoid the need for long term warfarin. *For recommended anticoagulant cover for cardioversion, see full guideline.*

ANNUAL RISK OF STROKE ON NO TREATMENT, ASPIRIN, OR WARFARIN IN HIGH, MODERATE AND LOW RISK PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION

Risk group	untreated	aspirin	warfarin	NNT*
Very high:				
—*previous ischaemic stroke or TIA*	12%	10%	5%	18
High:				
—*age over 65 and one other risk factor* *(hypertension, diabetes mellitus, heart failure, LV dysfunction)*	5-8%	4-6%	2-3%	42
Moderate:				
—*age over 65, no other risk factors* —*age under 65, other risk factors*	3-5%	2-4%	1-2%	71
Low:				
—*age under 65, no other risk factors*	1.2%	1%	c. 0.5%	142

* Number needed to treat with warfarin *instead of aspirin* for one year to prevent one stroke

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Derived from the national clinical guideline recommended for use in Scotland by the Scottish Intercollegiate Guidelines Network (SIGN) Royal College of Physicians,
9 Queen Street, Edinburgh EH2 1JQ

SIGN Guidelines are also available on the SIGN website: www.show.scot.nhs.uk/sign/home.htm

This guideline was issued in March 1999 and will be reviewed in 2001

VENOUS THROMBOEMBOLISM (DEEP VEIN THROMBOSIS AND/OR PULMONARY EMBOLISM)

DIAGNOSIS OF ACUTE VENOUS THROMBOEMBOLISM

C **Diagnostic imaging should be performed expeditiously** (within 24 hours if possible) in patients with suspected DVT (venography, ultrasound) or PE (e.g. ventilation-perfusion lung scanning) to minimise exposure to the risks of inappropriate continued full-dose anticoagulation in those patients in whom venous thromboembolism is not confirmed

B **In all patients with clinically-suspected DVT, the diagnosis should be confirmed or excluded by diagnostic imaging**, either:

— non-invasive testing by ultrasound (compression or Duplex scanning) followed by contrast venography if negative to detect calf DVT and non-occlusive proximal DVT; *or*

— contrast venography (detects both calf and proximal DVT); *or*

— serial (repeat after seven days) non-invasive testing by ultrasound to detect proximal extension of calf DVT

B **A single negative ultrasound** may be sufficient to exclude DVT in patients with low clinical pre-test probability and/or a normal fibrin D-dimer assay

HEPARIN IN ACUTE TREATMENT OF DVT OR PE

A **Outpatients with clinically suspected DVT or PE should be referred to hospital** for diagnosis and consideration of initial anticoagulation with heparin

A **In clinically-suspected DVT or PE, heparin should be commenced** (unless strongly contraindicated) **until the diagnosis is excluded by objective testing**

B **Monitoring of the APTT ratio** should be performed expeditiously in patients receiving unfractionated heparin, and heparin doses adjusted according to a local protocol to achieve the therapeutic target range (usually 1.5-2.5) within 24 hours

A **Subcutaneous unfractionated heparin** is an effective alternative to intravenous unfractionated heparin for the initial treatment of DVT. **Low molecular weight heparins** are effective alternative treatment to unfractionated heparin for DVT or PE

ORAL ANTICOAGULANTS IN ACUTE AND MAINTENANCE TREATMENT OF DVT OR PE

C If therapeutic anticoagulation is contraindicated, **inferior vena cava (IVC) filter insertion** should be considered

A Following initial heparinisation in patients with DVT or PE, **maintenance of anticoagulation with oral anticoagulants** is recommended in non-pregnant patients. **Adjusted-dose subcutaneous heparin** may be considered as an alternative therapy for patients in whom oral anticoagulants are contraindicated, inconvenient, or ineffective

☑ In intravenous drug users, the advisability of any continued anticoagulant therapy following hospital discharge should be assessed critically

A **Early institution** of oral anticoagulants is recommended in most patients

A The **optimal target INR** during oral anticoagulant therapy for a first episode of venous thromboembolism is 2.5, range 2.0-3.0

C When oral anticoagulant therapy is initiated for treatment of acute DVT or PE, it should be **overlapped with heparin therapy** for 4-6 days until the INR is >2.0 on two consecutive days

A The routine recommended duration of oral anticoagulant therapy following a first episode of DVT or PE is **at least three months**

C **At three months, patients should be assessed for continuing risk factors** (e.g. idiopathic, premature or familial presentation; thrombophilias; malignancy; chronic infection; inflammatory bowel disease; nephrotic syndrome; thromboembolic pulmonary hypertension)

C **The presence of continuing risk factors suggests consideration of anticoagulation long term**, or until risk ractors resolve

C **Patients with thrombophilias** should be referred to consultant haematologists or to centres with expertise in management of these patients

OTHER ANTITHROMBOTIC THERAPIES IN TREATMENT OF DVT OR PE

A **Graduated elastic compression stockings** should be worn on the affected leg following proximal DVT for at least two years to reduce the incidence of severe post-thrombotic leg syndrome

DOSAGE, MONITORING, REVERSAL, AND CONTRAINDICATIONS TO ANTITHROMBOTIC DRUGS

WARFARIN

A **Dose: usually 1-15 mg/day to maintain target INR**
(range usually 2.0-3.0; patients with certain mechanical heart valves or recurrent thromboembolic events require higher target ranges)

☑ Monitoring of INR should be performed at 4-8 week intervals when stable, but more frequently when change in clinical state or medication

☑ Patients and/or relatives or carers should be educated on advice in the DoH oral anticoagulant booklet

☑ Clinicians providing anticoagulant care must have explicit systems for handling results promptly; making informed decisions on further treatment and testing; and communicating results to patients accurately

☑ Surgeons, dentists and physicians intending to perform surgery or invasive procedures in patients receiving anticoagulant therapy should seek advice concerning management of such therapy from a haematologist

C Possible means to **reduce the risk of excessive bleeding** during and after surgery or other invasive procedures include:
— urgent reversal of oral anticoagulant therapy
— elective discontinuation of oral anticoagulant, or dose reduction, to achieve a lower INR
— substitution of heparin

B **In patients with a high INR** (>8.0) **or other risk factors for bleeding, vitamin K_1** (0.5 mg IV or 5 mg orally) should be considered

B **In patients with non-severe bleeding and a high INR,** warfarin should be stopped for 1-2 days and **vitamin K_1** given (0.5-2 mg IV or 5-10 mg orally)

B **In patients with life threatening haemorrhage:**
— **factor IX complex concentrate** should be given at a dose of 50 IU/kg body weight: such therapy is more efficacious than fresh frozen plasma
— if **factor VII concentrate** is available it should be given at a similar dose
— in addition, intravenous **vitamin K_1 should be given** (5 mg, repeated as necessary)

C The most common cause of fatal or disabling bleeding in patients receiving anticoagulant therapy is **intracranial** or **intraspinal bleeding**. Any such patients who have head injury, headache (recent, severe), confusion, impaired consciousness, or focal neurological symptoms and signs should have **urgent CT scanning** to detect such bleeding, followed by appropriate reversal of anticoagulant therapy

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ASPIRIN

A **Dose: 75-300 mg/day is as effective as higher doses**
Although 75 mg/day suppresses platelet aggregation in most patients after several days, earlier effects are achieved with 150-300 mg in acute myocardial infarction or acute ischaemic stroke

The risk of major GI bleeding is 1:500 patient-years and is dose dependent above 300 mg/day

C **Gastric intolerance** can be reduced by using the minimum effective dose (75 mg), using dispersible or enteric-coated preparations, or co-prescribing antacids, misoprostol, proton pump inhibitors or H_2-receptor antagonists

A **Concomitant use of warfarin should be avoided**, except in certain patients with prosthetic heart valves or recurrent thromboembolism with one or other drug alone

FULL DOSE UNFRACTIONATED HEPARIN

A **Monitor APTT ratio to achieve target range** (usually 1.5-2.5)

C **Monitor platelet count after five days therapy**; stop heparin if thombocytopenia detected

CONTRAINDICATIONS TO AND CAUTIONS WITH FULL-DOSE ANTICOAGULANT DRUGS

(Note: these depend on individual circumstances and are seldom absolute)

- **Uncorrected major bleeding**
- **Uncorrected major bleeding disorder**
  — e.g. thrombocytopenia, haemophilias, liver failure, renal failure
- **Uncontrolled severe hypertension**
  — *e.g. systolic >200 mm Hg or diastolic >120 mm Hg*
- **Potential bleeding lesions**
  — *e.g. active peptic ulcer, oesophageal varices*
  aneurysm, proliferative retinopathy
  recent organ biopsy
  recent trauma or surgery to head, orbit, spine
  recent stroke
  confirmed intracranial or intraspinal bleed
- **Heparin**
  history of heparin-induced thrombocytopenia or thrombosis
- **Warfarin**
  pregnancy (usually)
  homozygous protein C deficiency (risk of skin necrosis)
  history of warfarin-related skin necrosis
  uncooperative/unreliable patients (long term therapy)