Healthcare Improvement Scotland

SIGN
Scottish Intercollegiate Guidelines Network

SIGN 129 • Antithrombotics: indications and management

A national clinical guideline

August 2012

Evidence

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

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

GRADES OF RECOMMENDATION	
Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.	
A	At least one meta-analysis, systematic review, or RCT rated as 1^{++}, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1^{+}, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2^{++}, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1^{++} or 1^{+}
C	A body of evidence including studies rated as 2^{+}, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2^{++}
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2^{+}
GOOD PRACTICE POINTS	
	Recommended best practice based on the clinical experience of the guideline development group

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First published August 2012

ISBN 978 1 905813 91 9

Citation text
Scottish Intercollegiate Guidelines Network
(SIGN). Antithrombotics: indications and management.
Edinburgh: SIGN; 2012. (SIGN publication no. 129). [August 2012].
Available from URL: http://www.sign.ac.uk

Contents

1 Introduction

1.1 THE NEED FOR A GUIDELINE

Antithrombotics are among the most extensively prescribed drugs. For example, in relation to aspirin there were more than 500,000 person years of exposure in Scotland in 2002.[1] In a survey of 55 primary care practices in Scotland the prevalence of atrial fibrillation was 9.4/1,000 in men and 7.9/1,000 in women; 42% of these patients were receiving warfarin and 44% aspirin.[2]

Although of proven benefit in a range of indications, antithrombotics are associated with adverse effects, principally abnormal bleeding. In many cases, patients who may gain most from antithrombotic treatment are also those at highest risk of bleeding, such as the elderly with comorbidities. The use of combinations of antithrombotics, with inevitable additional bleeding risk, is expanding, for example after percutaneous coronary artery interventions. To maximise benefit over risks, the selection of patients for treatment with antithrombotics and their management should be evidence based.

Developments since the publication of SIGN 36: Antithrombotic Therapy in 1999 include the introduction to clinical practice of novel antithrombotics (for example orally active inhibitors of thrombin and activated factor X), changes to models of care (including patient self testing and self dosing for warfarin) and exploration of new indications for antithrombotics (for example recurrent miscarriage).

This guideline complements, and should be used alongside, a range of current SIGN guidelines:

- SIGN 89: Diagnosis and management of peripheral arterial disease,[3]
- SIGN 93: Acute coronary syndromes,[4]
- SIGN 94: Cardiac arrhythmias in coronary heart disease,[5]
- SIGN 95: Management of chronic heart failure,[6]
- SIGN 96: Management of stable angina,[7]
- SIGN 97: Risk estimation and the prevention of cardiovascular disease,[8]
- SIGN 108 Management of patients with stroke or TIA: assessment, investigation, immediate management and secondary prevention,[9]
- SIGN 111: Management of hip fracture in older people,[10]
- SIGN 118: Management of patients with stroke: rehabilitation, prevention and management of complications and discharge planning,[11] and
- SIGN 122: Prevention and management of venous thromboembolism.[12]

1.2 REMIT OF THE GUIDELINE

1.2.1 OVERALL OBJECTIVES

This guideline provides recommendations based on current evidence for best practice in the management of adult patients on antithrombotic therapy. It includes antiplatelet therapy, parenteral and oral anticoagulant therapy and thrombolytic therapy for prophylaxis and treatment in a range of clinical conditions such as atrial fibrillation, peripheral arterial disease and cerebrovascular disease. Antithrombotic therapy during pregnancy and for patients with intravascular devices is also covered. The use of antithrombotic therapy in the management of established ischaemic heart disease is not included here, but is covered in SIGN's suite of cardiovascular guidelines (SIGN 93-97).[4-8]

1.2.2 TARGET USERS OF THE GUIDELINE

This guideline will be of particular interest to healthcare professionals in a wide range of specialties including general practitioners, surgeons, nurses, physicians, pharmacists and dentists. It may also be of interest to patients and their carers, members of the voluntary sector and those involved in the development of research strategies in pharmacotherapy.

1.2.3 SUMMARY OF UPDATES TO THE GUIDELINE BY SECTION

Where no new evidence was identified to support an update, text and recommendations are reproduced from SIGN 36. The original supporting evidence was not re-appraised by the current guideline development group. The key questions used to develop this guideline are displayed in Annex 1.

2	Key recommendations	New
3	Antiplatelet agents	Completely revised
4	Parenteral anticoagulation	Minor update
5	Oral anticoagulation with vitamin K antagonists	Updated
6	Other antithrombotic drugs	New
7	Atrial fibrillation: prophylaxis of systemic embolism	Completely revised
8	Other cardiac causes of systemic embolism	Updated
9	Primary prophylaxis of vascular disease	Updated
10	Peripheral arterial disease	Completely revised
11	Cerebrovascular disease	Completely revised
12	Myeloproliferative disorders	New
13	Other indications for anticoagulant therapy	Completely revised
14	Intravascular devices	New
15	Pregnancy	New
16	Models of care	New
17	Provision of information	New

1.3 STATEMENT OF INTENT

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

1.3.1 PRESCRIBING OF LICENSED MEDICINES OUTWITH THEIR MARKETING AUTHORISATION

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

Generally the unlicensed use of medicines becomes necessary if the clinical need cannot be met by licensed medicines; such use should be supported by appropriate evidence and experience.[13]

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

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

Prescribing medicines outside the recommendations of their marketing authorisation alters (and probably increases) the prescribers' professional responsibility and potential liability. The prescriber should be able to justify and feel competent in using such medicines.[13]

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

Prior to prescribing, the licensing status of a medication should be checked in the current version of the British National Formulary (BNF).[13] The summary of product characteristics should also be consulted in the electronic medicines compendium (www.medicines.org.uk).

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

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

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

SMC advice relevant to this guideline is summarised in section 18.3.

2 Key recommendations

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

2.1 ANTIPLATELET AGENTS

A **To minimise the risk of bleeding, the lowest recommended dose of aspirin should be used for the clinical indication.**

2.2 ATRIAL FIBRILLATION: PROPHYLAXIS OF SYSTEMIC EMBOLISM

D **In all patients with AF, risk factors for systemic thromboembolism should be assessed routinely using $CHADS_2$ or CHA_2DS_2-VASc score.**

B **Patients with AF who are clearly low risk,** (age<65 and lone AF) **do not require antithrombotic therapy. This applies to male patients with CHA_2DS_2-VASc score=0 and female patients with CHA_2DS_2-VASc score=1 in whom the single point is allocated due to female sex.**

A **All patients with AF who have a $CHADS_2$ or CHA_2DS_2-VASc score of ≥1** (one or more clinically relevant risk factors) **should be considered for warfarin at a target INR of 2.5** (range 2.0-3.0) **or a newer anticoagulant. The balance of risks and benefits of anticoagulant therapy should be assessed and discussed annually with the patient, with consideration given to patient preference.**

A **Antiplatelet therapy should only be considered where warfarin or one of the alternative new anticoagulants has been declined.**

2.3 PRIMARY PROPHYLAXIS OF VASCULAR DISEASE

A **Aspirin is not recommended for primary prevention of vascular disease when benefits are considered against the increased risk of haemorrhage.**

2.4 CEREBROVASCULAR DISEASE

A **Clopidogrel monotherapy** (75 mg daily) **or aspirin** (75 mg) **in combination with dipyridamole** (200 mg extended release twice daily) **should be prescribed after ischaemic stroke or TIA for secondary prevention of vascular events.**

3 Antiplatelet agents

3.1 ASPIRIN

Aspirin (acetyl salicylic acid) inhibits the enzyme cyclooxygenase. In platelets the acetylation of cyclooxygenase results in a reduction in the synthesis of proaggregatory thromboxane A_2 for the platelet lifespan. Therefore, low doses of aspirin administered once daily significantly reduce platelet aggregability.

3.1.1 DOSAGE

Aspirin is widely available and inexpensive. The preparations available in the UK are 75 mg and 300 mg. Standard, dispersable, and enteric-coated preparations are available.

3.1.2 ADVERSE EFFECTS

Three meta-analyses of primary or secondary prophylaxis of cardiovascular disease were identified focusing on the adverse events of low-dose aspirin in clinical trials,[14] the incidence of bleeding and ulcers with low-dose aspirin therapy,[15] and bleeding complications after different doses of aspirin.[16] Doses ranged from 75 mg to 325 mg per day or every second day.

In patients on low-dose aspirin therapy for longer than three months for cardiovascular prophylaxis, aspirin increased the risk of bleeding twofold compared to placebo. The absolute risk was small (1.3/1,000 patients treated). For a major gastrointestinal (GI) bleed the number needed to harm (NNH) at one year was 769 and for any GI bleed it was 247.[14] Aspirin increased the incidence of any intracranial bleeding by 0.03% (absolute risk) compared to placebo (0.08% *v* 0.05% per year; NNH at one year 3,333, 95% confidence interval (CI) 1,250 to 10,000).[14] **1++**

Low-dose aspirin (<100 mg/day) was associated with the lowest risk of bleeding. Aspirin doses <200 mg/day caused fewer major GI bleeding events than >200 mg/day.[16]

Non-bleeding adverse events included dyspepsia (relative risk, RR 1.09), diarrhoea (RR 3.30) and constipation (RR 1.98), when compared with clopidogrel.[14]

In a small randomised controlled trial (RCT), aspirin did not increase the incidence of perioperative bleeding, but the study was underpowered for this end point.[17] A systematic review of retrospective studies found that aspirin increased the rate of bleeding complications from invasive procedures by a factor of 1.5 (median, interquartile range 1.0 to 2.5) but the severity of bleeding was not generally increased, with the possible exceptions of intracranial and some urological procedures. Discontinuation of aspirin given as secondary prophylaxis is associated with an increased risk of vascular events.[18] **1-** **2-**

No trial was identified on monitoring of aspirin therapy, although incomplete compliance with treatment has been identified in case series. In addition, aspirin resistance has been reported, although the mechanisms and incidence are disputed.[19]

3.1.3 CONTRAINDICATIONS

Contraindications to aspirin include: known allergy to the drug; use other than as an antiplatelet in children and adolescents under 16 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, severe thrombocytopenia (eg platelets $<30x10^9$/l) and severe liver disease with coagulopathy.[13]

3.1.4 CAUTIONS

Cautions to be noted with aspirin include: asthma; moderate thrombocytopenia (eg platelets 30-80 $x10^9$/l); uncontrolled hypertension (risk of intracranial bleeding); previous peptic ulceration (risk of gastrointestinal bleeding: proton pump inhibitors or histamine (H2)-receptor antagonists (H2RAs) may be considered for prophylaxis); glucose 6-phosphate dehydrogenase deficiency (at doses of >1g/day); concomitant use of drugs that increase risk of bleeding; and dehydration.[13]

A systematic review, which included 25 studies, showed significant interactions between dietary supplements and aspirin and other antiplatelet agents. Many of the studies, however, had small sample sizes (range 4-610, median 22) and some included only healthy volunteers (11/25) or male participants (8/25) *(see section 5.7)*.[20]

A **To minimise the risk of bleeding, the lowest recommended dose of aspirin should be used for the clinical indication.**

✓ The standard dose of aspirin for thromboprophylaxis is 75 mg.

✓ Aspirin discontinuation is not generally required prior to invasive procedures. The risk-benefit ratio of interrupting aspirin prophylaxis should be assessed individually, with consideration given to the type of planned procedure.

3.2 DIPYRIDAMOLE

Dipyridamole reduces platelet reactivity by inhibiting cellular reuptake of adenosine and by inhibition of the enzymes adenosine deaminase and phosphodiesterase.

3.2.1 ADVERSE EFFECTS

A meta-analysis of dipyridamole for preventing stroke and other vascular events in patients with vascular disease was identified. Although primarily an outcome analysis, safety outcome measures, predominantly bleeding, were also assessed. There were no differences in major extracranial and fatal extracranial bleeding complications compared to controls (no drug or an antiplatelet drug other than dipyridamole).[21] **1++**

The combination of aspirin and dipyridamole had an RR of 1.08 (95% CI, 0.75 to 1.54) for bleeding complications (major extracranial and fatal extracranial) compared to aspirin.[21] An RCT comparing aspirin and dipyridamole combination to aspirin or dipyridamole alone found that 34% of patients on the aspirin and dipyridamole combination discontinued the treatment, with headache cited as a frequent reason.[22] **1++**

There are few data on bleeding risk from invasive procedures in patients using dipyridamole (often in combination with aspirin).

✓ Discontinuation of dipyridamole is not generally required prior to invasive procedures, but as is the case for aspirin, the risks of interrupting therapy, and of bleeding if continued, should be individually assessed.

3.2.2 CAUTIONS

Cautions to be noted with dipyridamole include: rapidly worsening angina; aortic stenosis; recent myocardial infarction (MI); left ventricular outflow obstruction; heart failure; may exacerbate migraine; hypotension; myasthenia gravis (risk of exacerbation); coagulation disorders and concomitant use of drugs that increase risk of bleeding.[13]

3.3 CLOPIDOGREL

Clopidogrel, a thienopyridine, reduces platelet aggregation through inhibition of the adenosine diphosphate (ADP) P2Y12 receptor. The inhibition is irreversible resulting in a long duration of action.

3.3.1 ADVERSE EFFECTS

One meta-analysis was identified which assessed the adverse events of clopidogrel or low-dose aspirin in clinical trials. The study identified no trials comparing clopidogrel to placebo but included trials where clopidogrel alone was compared to aspirin alone, aspirin/clopidogrel combination was compared to aspirin alone or aspirin/clopidogrel combination was compared to clopidogrel alone.[14] **1++**

The relative risks of all GI bleeding (RR 1.34, 95% CI, 1.11 to 1.61) and major GI bleeding (RR 1.45, 95% CI 1.00 to 2.10) were increased in patients taking aspirin compared with clopidogrel. The absolute risk increase of aspirin over clopidogrel was 0.12% per year (NNH at one year 883, 95% CI 357 to ∞). All other bleeds (intracranial and others) showed no significant difference between clopidogrel and aspirin.

Aspirin/clopidogrel combination had higher rates of bleeding than aspirin (300 mg) or clopidrogel alone. An RCT studying prevention of recurrent ischaemic events in patients with unstable angina found that the rate of major GI bleeding was 1.3% with aspirin/clopidogrel combination compared to 0.75% with aspirin alone (absolute NNH=77; NNH relative to aspirin alone=153).[23] **1++**

An RCT of aspirin/clopidogrel combination compared to clopidogrel alone after stroke or transient ischaemic attack found that the rate of major GI bleeding was 2.45% with aspirin/clopidogrel combination compared to 0.84% with clopidogrel alone (absolute NNH=41; NNH relative to clopidogrel alone=63).[24]

Clopidogrel has been associated with increased bleeding during invasive procedures. For example, coronary artery bypass graft surgery was associated with a significantly increased requirement for red cell transfusion when surgery was performed within five days of clopidogrel exposure (odds ratio (OR) 1.36, 95% CI 1.10 to 1.68).[25] **2+**

Rash is a more common adverse effect of clopidogrel (6.8%) than aspirin (4.8%).[14] **1++**

✓ Consideration should be given to temporary discontinuation of clopidogrel seven days prior to invasive procedures if the risk of increased bleeding is deemed to exceed the risk of thrombosis.

✓ If a coronary stent has been placed within the last 12 months, cardiology advice should be sought prior to discontinuation of clopidogrel.

The European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use and its Pharmacovigilance Working Party is aware of studies suggesting that clopidogrel may be less effective in patients receiving a proton pump inhibitor (PPI), which could result in patients being at an increased risk of thrombotic events, including acute myocardial infarction. The EMA has recommended that concomitant use of omeprazole or esomeprazole and clopidogrel-containing medicines should be discouraged.[26]

This advice related to a class effect with subsequent amendment relating to omeprazole and esomeprazole specifically. The concerns were based largely on pharmacodynamic data and whether there is an effect on clinical outcomes remains controversial. In a recent RCT comparing omeprazole to placebo in patients taking clopidogrel and aspirin the rate of symptomatic upper GI bleeding was reduced significantly by the PPI, with no significant difference in cardiovascular events. A clinically meaningful difference, however, could not be ruled out.[27]

A meta-analysis of mixed study designs indicated that the adverse clopidogrel/PPI interaction may vary between PPIs with an absence of consistent evidence on differential cardiovascular risk amongst individual PPIs.[28] The review identified an increased cardiovascular risk with PPIs used in the absence of clopidogrel, suggesting that confounding and bias may underlie the apparent risk.

The use of histamine (H2)-receptor antagonists (H2RAs) can suppress gastric acid production by up to 68% over 24 hours and standard doses have a modest protective effect in patients taking aspirin.[29] In a RCT of 404 Scottish patients with peptic ulcers or oesophagitis who were taking aspirin, fewer gastroduodenal ulcers developed over 12 weeks among patients assigned to famotidine (3.8%) than to placebo (23.5%; p=0.0002).[30] In another study, however, H2RAs did not significantly protect clopidogrel users (RR: 0.83; 95% CI: 0.20 to 3.51).[31] Few RCTs have directly compared PPIs with H2RAs in patients with CV disease on antiplatelet therapy.[32] However, observational data suggest PPIs may be more effective than H2RAs in preventing upper GI bleeding. In a cohort of 987 patients who were prescribed aspirin and clopidogrel, PPI use led to a greater reduction in upper GI bleeding (odds ratio [OR]: 0.04; 95% CI: 0.002 to 0.21) than H2RA use (OR: 0.43; 95% CI: 0.18 to 0.91).[33] **1+** **2+**

It has been suggested that the H2RA cimetidine may decrease the biotransformation of clopidogrel, so other H2RAs might be a better choice in patients treated with clopidogrel.[34]

4

✓ Any effect of various PPIs on the clinical efficacy of clopidogrel remains unclear; the relative risks of GI bleeding and thrombosis should be considered in each individual case.

✓ In cases where PPIs are not preferred a histamine (H2)-receptor antagonist may be a suitable alternative, although cimetidine should be avoided.

3.3.2 CONTRAINDICATIONS

Contraindications to clopidogrel include active bleeding.[13]

3.3.3 CAUTIONS

Cautions to be noted with clopidogrel include: patients at risk of increased bleeding from trauma, surgery, or other pathological conditions; concomitant use of drugs that increase risk of bleeding. The BNF advises that clopidogrel should be discontinued seven days before elective surgery if the antiplatelet effect is not desirable.[13]

4 Parenteral anticoagulation

4.1 UNFRACTIONATED HEPARIN

Unfractionated heparin (UFH) is a naturally-occurring glycosaminoglycan (porcine or bovine) with a molecular weight range of 5,000-35,000 daltons (mean 12-14,000). It inhibits at several points in the coagulation mechanism, including the key enzymes thrombin and factor Xa, by potentiating the effect of the endogenous serine protease inhibitor, antithrombin. It prolongs the activated partial thromboplastin time (APTT) when given in therapeutic doses. Unfractionated heparin is cleared principally through the reticuloendothelial system. It is administered parenterally, either by intravenous (IV) injection which has an immediate effect and short plasma half-life (30 minutes to two hours); or by subcutaneous injection which has a delayed (two hours) but more prolonged (10 hours) effect. There is wide variability among patients in response to a given dose of heparin. As a consequence, the anticoagulant effect (APTT ratio) of full-dose heparin therapy 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 minimised.[35]

4.1.1 INITIATION, DOSAGE AND MONITORING

Treatment doses of UFH (in contrast to those used for thromboprophylaxis) have been used typically to treat acute thrombosis in hospitalised patients and replaced by warfarin for subsequent outpatient anticoagulation *(see section 5)*. For most indications UFH has been superseded by low molecular weight heparins (LMWHs), although UFH may be preferred where a more rapid onset of action is desirable, for example in high risk pulmonary embolism *(see SIGN guideline 122: Prevention and management of venous thromboembolism, section 11.1.1)*, where rapid reversal of the anticoagulant effect may be required *(see SIGN 122, section 15.1)* and in renal impairment.

✓ After clinical assessment has demonstrated an indication for heparin treatment, the patient's medical and drug history should be assessed and baseline blood tests including platelet count, coagulation screen (in order to check baseline APTT ratio is normal), urea, electrolytes and liver function tests should be obtained. These may reveal contraindications or risk factors for bleeding, such as anaemia, thrombocytopenia, renal failure, or coagulopathy (eg due to severe liver disease).

✓ A baseline platelet count should be carried out for the assessment of possible subsequent development of heparin induced thrombocytopenia, an important complication of heparin use.

Low-dose UFH (5,000 international units (IU) 8-12 hourly by subcutaneous injection), given as prophylaxis for venous thromboembolism, does not require monitoring of the APTT ratio; nor does low-dose infusion for prevention of clotting in peripheral arterial catheters.

✓ Coagulation test monitoring of prophylactic doses of UFH is not required.

Trials in patients with acute deep vein thrombosis (DVT) or acute myocardial infarction showed that failure to reach the lower limit of the target range of the APTT ratio (usually 1.5 to 2.5) was associated with substantial increases in relative risk of recurrent thrombotic events.[35, 36] Randomised controlled trials showed that use of protocols for heparin dose adjustment according to APTT ratio results improves the achievement of therapeutic target ranges.[36-38] Furthermore, clinical experience has shown that the risk of bleeding increases with APTT ratios above the upper limit of the target therapeutic range.[35, 39] **1+ 4**

Reagents used for APTT testing vary in their sensitivities to heparin necessitating local calibration.

B **In patients given treatment 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 recommended.**

✓ Each laboratory should standardise its own target range for APTT ratio.

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

Heparin induced thrombocytopenia is covered in section 15.2 of SIGN guideline 122.[12]

Osteoporosis and fractures have followed prolonged UFH use, for example in pregnancy.[35] The risk is very low with LMWH.[40, 41] **1+ 2++ 3**

The effect of heparin on bone mineral density is covered in section 15.3 of SIGN guideline 122.[12]

Full-dose unfractionated heparin is usually initiated with an intravenous loading dose over five minutes (5,000 IU in an average-sized adult or a body weight-dependent dose (75 IU/kg) may be preferred in patients at the extremes of body weight). For treatment of deep vein thrombosis, pulmonary embolism, unstable angina, and acute peripheral arterial occlusion a continuous intravenous infusion is then given (18 IU/kg body weight/hour in an average-sized adult). Administration in children depends on age, indication and weight *(see BNF in Children for details)*.[42] Weight-based nomograms can provide a more accurate prediction of the patient's heparin requirements especially at the extremes of body weight and are therefore preferable to standard nomograms. In morbidly obese patients actual body weight is preferable to ideal body weight in calculating the required heparin dose, however a dose cap should be considered and heparin monitoring with dose adjustment is still required.[43] **4**

A lower initial infusion rate (1,000 IU/hour) is usually used if heparin is given following thrombolytic therapy, which produces an anticoagulant effect.

The APTT ratio should be measured about six hours after the initial bolus injection, and the infusion rate adjusted using a local schedule. With 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.[35] **1++**

Twelve-hourly subcutaneous injection of UFH is as effective and as safe as intravenous heparin in the treatment of DVT,[38, 44] but is rarely used in view of the advantages of LMWHs. Treatment should be initiated with an intravenous bolus, as above, and monitoring of the APTT ratio (four to six hours after injection, preferably at the same time each day) and dose adjustment performed.

There has been no reported trial of subcutaneous UFH in patients with pulmonary embolism.

4.1.2 REVERSAL OF THE ANTICOAGULANT EFFECT OF UFH

Unfractionated heparin has a short half-life after intravenous administration (30-120 minutes), which is dose dependent. Stopping treatment leads to reversal over a few hours. Where more rapid reversal is required protamine sulphate should be used. Caution should be exercised in those with increased risk of allergic reaction to protamine (including previous treatment with protamine or protamine insulin, allergy to fish, men who are infertile or who have had a vasectomy).

✓
- The dose of protamine is determined by the heparin exposure (1 mg of protamine neutralises 80–100 IU of UFH when administered within 15 minutes of the heparin dose*)*.
- Less is required if protamine is given after a longer period because of the short half-life of intravenous UFH.

4.2 LOW MOLECULAR WEIGHT HEPARINS

Low molecular weight heparins are manufactured from UFH and consist of only short chains of polysaccharide with an average molecular weight of <8,000 daltons. In contrast to UFH the anti-Xa effect predominates over the antithrombin effect. They have better availability than UFH when administered by the subcutaneous route. Also, in contrast to UFH, the APTT is relatively insensitive to LMWH. The anti-Xa level can be used to monitor LMWH but its predictive value in terms of efficacy against thrombosis and bleeding risk is not high.[45]

The range of licensed indications for individual LMWH preparations varies. Although there is little evidence for differences in clinical efficacy between products there is a lack of head-to-head comparisons. In selecting a

particular LMWH, prescribers should consider the implications of recommending licensed medicines outwith their marketing authorisation *(see section 1.3.1)*.

4.2.1 MONITORING

Low molecular weight heparin is excreted principally by the kidneys. Most randomised trials of LMWH have excluded patients with renal insufficiency. Pharmokinetic studies suggest an association between creatinine clearance and higher levels of anti-Xa in plasma after administration of LMWH and increased bleeding complications have been reported when LMWH is used in patients with renal insufficiency. In a meta-analysis of 12 studies with 4,971 patients, standard therapeutic dose LMWH was associated with a statistically significant increase in the risk of major bleeding in patients with creatinine clearance of <30 ml/min.[46] A two- to threefold increase in major haemorrhage was observed. There were insufficient studies to assess the risk of major bleeding for LMWHs other than enoxaparin. The pharmacokinetics in patients with renal impairment may differ between individual LMWHs.[47] The American College of Chest Physicians (ACCP) and College of American Pathologists recommend UFH instead of LMWH in patients with creatinine clearance of <25 ml/min.[48] The British Committee for Standards in Haematology (BCSH) advises that if LMWH is used, a reduced dose should be given with careful observation for bleeding. Monitoring of the anti-Xa activity should be considered but there are limitations to this approach in that anti-Xa assays have a poor predictive value for bleeding.[49] **1+** **4**

Trials have excluded the very obese and therefore the safety and efficacy of LMWH in very obese patients is uncertain. The American College of Chest Physicians suggests that anti-Xa monitoring is prudent when administering weight-based doses of LMWH to patients who weigh more than 150 kg.[48] **4**

There is some evidence that UFH and LMWHs may cause a rise in serum potassium concentration through inhibition of aldosterone. Development of symptomatic hyperkalaemia, however, appears to be unlikely in the absence of an additional cause of hyperkalaemia.[50] **2+**

D **LMWH should be used with caution for those in whom standard or weight-adjusted dosing is likely to be unreliable, especially in:**

- **patients with acute kidney injury or stage 4-5 chronic kidney disease**
- **patients in extreme weight ranges**
- **pregnant women**
- **neonates and infants.**

✓ Monitoring of prophylactic or therapeutic doses of LMWH is not required routinely.

✓ Anti-Xa assay may also be of some value in the investigation of unexpected bleeding in a patient receiving LMWH. Local laboratory assay validation for the heparin in use should be carried out.

✓ When LMWH is to be continued after hospital discharge there should be a record of the patient's weight, renal function, indication and duration of anticoagulation.

4.2.2 REVERSAL OF THE ANTICOAGULANT EFFECT OF LMWH

Intravenous protamine reverses the anticoagulant effect of LMWHs incompletely,[51,52] perhaps reversing around 60% of the activity, and somewhat variable between LMWHs.[53] As expected from the mode of action of heparins, plasma infusion is ineffective for reversal of the anticoagulant effect and should not be used for this purpose.

✓
- The initial dose of protamine depends on the dose of LMWH given and the length of time since the last dose of LMWH was administered. The maximum recommended protamine dose is 50 mg.
- Plasma infusion is ineffective for reversal of the anticoagulant effect and should not be used for this purpose.

4.3 FONDAPARINUX

Fondaparinux is a synthetic pentasaccharide. Like heparins, it is an indirect inhibitor requiring antithrombin for its effect. However, it selectively inhibits factor Xa, with no activity against thrombin. It has a longer half-life than LMWHs of around 17 hours which is an important consideration when planning invasive procedures *(see SIGN 122, section 15.1.4)*.[54, 55]

4.3.1 MONITORING

As for LMWH, the dose of fondaparinux is weight adjusted and routine monitoring of prophylactic and therapeutic doses is not required.[54, 55] Fondaparinux is renally excreted and therefore should be used with caution in patients with moderate renal impairment (creatinine clearance 30-50 ml/min) and generally avoided in patients with severe renal impairment (creatinine clearance <30 ml/min).[56] Caution is required in the elderly due to a reduction in renal function.[57]

At the doses used for treatment, fondaparinux does not affect clotting times markedly, although some prolongation of the APTT may occur. Anti-Xa levels peak at around two hours after dosing.

4.3.2 REVERSAL OF THE ANTICOAGULANT EFFECT OF FONDAPARINUX

The anticoagulant effect is not neutralised by protamine.[58] Bleeding complications should be managed by withdrawing the drug and considering investigation for a local bleeding lesion. Whilst recombinant factor VIIa has been shown to reverse the anticoagulant effects of fondaparinux in healthy volunteers,[59] and there are anecdotal reports of possible clinical efficacy,[60] it is not licensed for this use.

4.4 DANAPAROID

Danaparoid is a heparinoid derived from pig gut mucosa. It consists of a mixture of heparan sulphate, dermatan sulphate and choindroitin sulphate. It exerts its antithrombotic effect principally through antithrombin-mediated inhibition of factor Xa. It inhibits thrombin to a much lesser extent, so, if required, monitoring is by anti-Xa assay using danaparoid calibrators. Danaparoid may be used for prophylaxis of venous thromboembolism (VTE) in patients undergoing general or orthopaedic surgery but its principal use is in the management of patients with heparin induced thrombocytopenia who require parenteral anticoagulation. Cross-reactivity with heparin may occur in heparin induced thrombocytopenia *(see SIGN 122, section 4.5)*.

5 Oral anticoagulation with vitamin K antagonists

5.1 INTRODUCTION

Warfarin is the oral vitamin K antagonist (VKA) of choice. Acenocoumarol (nicoumalone) and phenindione are licensed in the UK but rarely prescribed. VKAs act by antagonising the effect of vitamin K, resulting in reduced hepatic synthesis of the active, gamma-carboxylated forms of coagulation factors II, VII, IX and X. The prothrombin time is sensitive to this effect of VKAs and a standardised prothrombin time, the international normalised ratio (INR), is universally used for monitoring the effect and guiding adjustments of dose. It takes several days for the INR to reach typical target levels, most commonly in the range 2.0 to 3.0, but the precise interval depends on the dosing regimen employed. Hence, in acute thromboembolism, anticoagulation should be commenced with heparin. Warfarin can usually be commenced simultaneously and the heparin continued until the INR is within the target range. Heparin is not required when oral anticoagulants are started electively for prophylaxis of thromboembolism, except in certain thrombophilias.[61, 62]

The average daily dose of warfarin to achieve an INR within the desired range of the target is around 5 mg, but with wide variation (range 1 to 15 mg). Warfarin sensitivity varies widely between individuals due to genetic variation in its metabolism and in the sensitivity of the target enzyme *(see section 5.6)*. Sensitivity may vary over time within the same person, principally due to variables such as dietary content of vitamin K, and interacting co-medications.[62]

The target (desired range) INR for most indications is 2.5 (2.0 to 3.0). A higher target (3.5) may be appropriate when new thrombosis occurs despite an INR in the target range. The target INR for some patients with mechanical heart valves is higher *(see section 8.4)*.

Even with high-quality clinical support the average rate of INRs in therapeutic range for patients on VKA therapy is around 60%.

VKA use is associated with few systemic side effects. Because osteocalcin, a protein involved in bone formation, requires carboxylation and this can potentially be inhibited by VKAs, it has been postulated that VKA use may promote osteoporosis. There is some evidence for warfarin-associated osteoporosis in long term users of warfarin. In a large observational study of osteoporotic fractures the OR of fracture for men using warfarin for more than a year was 1.63 (95% CI 1.26 to 2.10) and for women was 1.05 (95% CI 0.88 to 1.26).[63] It is not possible to make recommendations on monitoring and treatment to prevent osteoporosis based on the evidence currently available.

5.1.1 CAUTIONS

Cautions with warfarin include: conditions in which risk of bleeding is increased, eg history of gastrointestinal bleeding, peptic ulcer, recent surgery, recent ischaemic stroke, recent childbirth (delay warfarin until risk of haemorrhage is low; usually five to seven days after delivery), bacterial endocarditis (use only if warfarin otherwise indicated); uncontrolled hypertension; concomitant use of drugs that increase risk of bleeding. The BNF also suggests that cranberry juice should be avoided.[13] VKAs cross the placenta, are teratogenic and may cause fetal bleeding *(see section 15.3)*.

5.1.2 CONTRAINDICATIONS

Warfarin is contraindicated in patients with haemorrhagic stroke or significant bleeding.[13]

5.2 INITIATION, DOSAGE AND MONITORING OF ORAL ANTICOAGULANTS

✓ After clinical assessment has demonstrated an indication for oral anticoagulant treatment, the patient's medical history, drug history, and compliance with medication should be assessed. Many drugs affect the response to a VKA, most by enhancing, but some by suppressing the anticoagulant effect. The drug regimen should be simplified if possible. Where possible, non-interacting drugs within a class should be selected and aspirin avoided unless combination therapy is indicated. In patients with peptic ulcer, H. pylori eradication therapy should be considered *(see SIGN guideline 68: Dyspepsia)*.

✓ 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, along with other medications.

✓ A baseline blood sample for blood count (including platelet count), coagulation screen and renal and liver function tests should be obtained prior to starting oral anticoagulants. This may show contraindications or risk factors for bleeding, such as anaemia, thrombocytopenia, renal failure, or a prolonged prothrombin time due to liver disease.

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

✓ An anticoagulant treatment booklet should be issued to patients *(available from: nhsforms@spsi.uk.com)*.

5.2.1 PATIENTS WITH ACTIVE THROMBOEMBOLISM

In patients with active thromboembolism, the starting regimen for treatment of acute thromboembolism is generally 10 mg warfarin on day one, as the target INR is achieved more rapidly than with a 5 mg regimen.[64] A lower starting dose should be considered in older patients. Annex 2 shows a sample dosing protocol according to the INR response and age.[37] The initial dosing regimen should be lower (5 mg) when there is increased sensitivity to warfarin (for example low body weight, drug therapy which increases warfarin sensitivity; for example some antibiotics, heart failure, liver failure, prolonged baseline prothrombin time). More cautious dosing should also be considered when warfarin is introduced within 7-10 days of surgery. Heparin prolongs the prothrombin time but 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. **1+ 4**

✓ Prior to hospital discharge, the hospital should communicate with the general practitioner (or other medical professional assuming the patient's care) to advise the recommended INR target range and the duration of therapy, and ensure arrangements for continued patient and INR monitoring. Prior to discharge, patients should be given clear information on the date and place of the next monitoring visit.

5.2.2 OUTPATIENTS WITHOUT ACUTE THROMBOEMBOLISM

In outpatients without acute thromboembolism who are started on long term prophylactic oral anticoagulants (eg for atrial fibrillation) a less intensive starting regimen is appropriate.[65-67]

✓
- Monitoring should be performed or supervised by experienced staff; and clinical performance should be monitored.
- Cumulative records of INR and warfarin dose should be maintained.
- A reliable patient recall and review system should be kept.
- A well stabilised patient may need an INR check only every four to eight weeks.
- Any change in clinical state or in medication should prompt more frequent checks.
- Healthcare professionals monitoring anticoagulant treatment should be aware of the indication for treatment, target therapeutic range, and the planned duration of therapy.

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

Reversal of oral anticoagulant therapy is covered in section 15.1 of SIGN guideline 122: Prevention and management of venous thromboembolism.[12]

The evidence base consists largely of non-RCT studies in patients without active bleeding.[68,69] Individualised patient management is required balancing the risk of thrombosis against haemorrhage.

The options available range from allowing the INR to fall slowly by reducing the dose or omitting the VKA until the INR falls into the desired range; accelerated lowering of the INR to the desired range with the use of vitamin K or a rapid return of the INR to normal/near normal with the use of human prothrombin complex concentrate (PCC). Fresh frozen plasma is less effective.[70] **2++** **2+**

In asymptomatic patients where the INR is <5.0, observational data would suggest the risk of bleeding is low and,[71] in general, close monitoring of the INR together with considering omitting a single dose and downward dose adjustment of the VKA is a reasonable option. **2+**

Where the INR is >5, observational data suggest the risk of haemorrhage in asymptomatic patients increases as the INR rises.[72,73] **2-**

In such circumstances the use of vitamin K has been shown to safely move the INR back to the desired range compared to omitting a VKA alone.[74] **1+**

It remains unknown if this approach confers a net benefit but in patients with additional risk factors for bleeding or a particularly high INR the administration of vitamin K is reasonable.

If vitamin K is used it may be given orally or intravenously. Vitamin K requires up to 24 hours for a full effect and at least four hours for any effect on the INR. In most patients the oral route is more convenient and is the route of choice but vitamin K acts more quickly when given intravenously, producing a significantly greater reduction in the INR at four hours than by the oral route. Where a more rapid effect is required this is the route of choice.[75] The subcutaneous administration of vitamin K leads to an unpredictable effect and is not recommended.[69,76] **2+** **3**

Partial reversal of VKA-induced anticoagulation in those with minor or no bleeding can be achieved using small doses of vitamin K (1.0 to 2.5 mg) given by the oral or intravenous route.[69] In the face of limb- or life threatening bleeding, full reversal of anticoagulation is desirable and 5-10 mg vitamin K intravenously will achieve this over 4-24 hours. In this situation PCC, which gives an immediate but transient effect, is also required.[70] See Table 1 for a suggested scheme for reversal of VKA-induced anticoagulation. **2+** **3**

Table 1: Suggested scheme for reversal of VKA-induced anticoagulation

Serious bleeding with INR > 1.1
1. Stop VKA 2. Intravenous vitamin K (5-10 mg) 3. Prothrombin complex concentrate, usually 30-50 IU/kg, but dose-adjusted according to INR (under the supervision of a haematologist whenever possible). Fresh frozen plasma (at least 15 ml/kg) may be used only if PCC is unavailable.
Minor bleeding and supratherapeutic INR
1. Interrupt VKA, reintroducing at a lower maintenance dose when the situation is under control 2. Administer oral or IV vitamin K (1.0-2.5 mg)
No bleeding and supratherapeutic INR
1. Interrupt VKA, monitor INR, restart warfarin when INR <5.0 2. Where the perceived risk of bleeding is high, eg INR >8, or other risk factors for bleeding are present, consider administration of oral vitamin K (1.0-2.5 mg).

✓ When there is an unexpectedly high INR consideration should be given to evidence of poor compliance with therapy, drug interactions and intercurrent illness. Healthcare professionals should take the opportunity to reassess the risk/benefit ratio with regard to the longer term continuation of VKA therapy.

✓ In a patient on VKA therapy with unexpected bleeding other causes should be considered especially when the bleeding is focal and the INR is in the therapeutic range or below.

✓ Where life- or organ-threatening bleeding is encountered the risk from bleeding outweighs that of thrombosis and full, rapid reversal of anticoagulation is required, even in patients with an underlying high thrombotic risk.

5.4 MANAGEMENT OF VKA THERAPY FOR INVASIVE PROCEDURES

Continuation of anticoagulation during surgery and invasive procedures is likely to increase bleeding. Discontinuation will, however, be associated with a temporary increase in thrombosis risk. There has been debate over the optimal approach to management in this situation and, in particular, whether VKA therapy should be interrupted and, if so, whether there is a need for temporary introduction of an alternative antithrombotic, usually heparin, perioperatively: so-called bridging therapy.

In a systematic review and meta-analysis including five trials and 553 patients undergoing dental surgery no significant difference in risk of minor or major bleeding was noted when the stable dose of VKA was continued compared to interruption of VKA therapy.[77] The British Committee for Standards in Haematology advises that the risk of bleeding from routine outpatient dental procedures is low if the INR is <4.0 and that in the majority of patients undergoing outpatient dental surgery, including extraction, VKA treatment need not be interrupted.[78] In some studies, tranexamic acid mouthwash (4.8%) was used for two days and appeared to be effective in reducing bleeding.[79] It is advised that use of non-steroidal anti-inflammatory drugs (NSAIDs) for post-surgery analgesia should be avoided. **1+ 4**

The risk of bleeding associated with other specific surgical interventions in patients using a VKA has been assessed, but generally in small cohorts analysed retrospectively. These limited data suggest that the risk of bleeding when VKA therapy is continued, with the INR in the target range, is low in patients undergoing standard cataract surgery,[80] biopsy of the prostate gland,[81] hand surgery,[82] diagnostic coronary angiography,[83] and percutaneous coronary intervention (PCI).[84] In contrast, a retrospective review of VKA use identified colonic polypectomy as an independent risk factor for bleeding (OR 13.4, 95% CI 4.1 to 43.6).[85] **2+ 2-**

A narrative review of bridging therapy with heparin, which included some studies directly comparing UFH and LMWH, concluded that LMWH can be used during interruption of VKA therapy in patients considered to be at high risk of thrombosis such as those with prosthetic heart valves and atrial fibrillation. In those at intermediate or low risk, bridging was considered to be unnecessary and to be potentially harmful due to the increased risk of bleeding.[86] A review of registry data from North America found that treatment doses of LMWH were used more frequently than UFH and that bridging was principally used in patients with arterial indications for VKA therapy.[87] In a prospective study of enoxaparin, 1.5 mg/kg daily as bridging therapy for surgery in patients taking VKA for atrial fibrillation or VTE, major bleeding occurred in 9 of 260 patients, mostly in association with major surgical procedures. Four arterial occlusive events occurred in 176 patients with atrial fibrillation and one venous thrombosis among 96 patients with VTE.[88] A systematic review, including eight studies, of anticoagulation during cardiac pacemaker or defibrillator implantation showed that low rates of thromboembolism were reported whether a VKA was continued or heparin used perioperatively. Higher bleeding rates were found with bridging therapy using heparin compared to continuation of VKAs.[89] **4 3 1-**

The limited evidence available indicates that decisions regarding the safety of discontinuing VKAs perioperatively, and whether an alternative antithrombotic should be introduced, and the dose, should be made after consideration of the level of thrombosis risk from brief interruption of treatment, the bleeding risk associated with continuation of VKAs or introduction of heparin, taking account of the nature of the surgical or other invasive procedure. For example, for patients receiving long term VKA therapy for VTE who require general surgery with a low or moderate risk of bleeding, substitution of a prophylactic dose

of LMWH may be appropriate. In contrast, higher doses of heparin are likely to be required to prevent thromboembolism perioperatively in a patient with a prosthetic heart valve. However, where the risk of bleeding is very high or the site of any problematic bleeding is likely to have serious deleterious effects, for example in intracranial surgery, it may be that the risk of thrombosis is outweighed by bleeding risk and mechanical thromboprophylaxis should be considered instead.

A **Vitamin K antagonists should not be discontinued in patients undergoing outpatient dental surgery, including dental extraction.**

✓ The INR should be checked preoperatively to ensure it is in the target range. Use of topical haemostatic measures such as sutures and collagen sponges, and tranexamic acid as a mouthwash, should be considered. NSAIDs should be avoided.

D **Decisions regarding interruption of VKA therapy for other surgical and invasive procedures, and whether bridging therapy is advisable, should be made on an individual basis dependent upon the perceived risks of bleeding and thrombosis associated with continuation of anticoagulation and discontinuation of anticoagulation, respectively, and the nature of the proposed procedure.**

5.5 RECOMMENCING VKA THERAPY FOLLOWING A MAJOR BLEEDING EVENT

In many cases VKA therapy will be permanently discontinued at the time of a major life threatening haemorrhage. There will be some patients, however, for whom there are compelling arguments for restarting anticoagulant therapy, for example patients with mechanical prosthetic heart valves, or those with high risk atrial fibrillation. In each case a careful risk/benefit analysis is required.

A systematic review identified six cohort studies including 120 patients with prosthetic heart valves and intracranial haemorrhage.[90] Of those surviving 48 hours, the majority restarted anticoagulant therapy, usually heparin, in the initial post-bleed phase. A VKA was restarted between two days and three months post bleed; mostly between 7-14 days, and in some cases at reduced intensity target INR. During a mean follow up time of eight months, there were only two recurrent cerebral haemorrhages but four cerebral ischaemic events. **2+**

In addition to intracranial bleeding, the other common site of major bleeding in VKA-treated patients is the GI tract. There are few data on the best timing or relative safety of restarting VKA therapy in patients after GI bleeding. Review of data from the prospective multinational VTE RIETE registry demonstrated that patients with recent gastrointestinal bleeding, within 30 days prior to developing VTE and starting anticoagulant therapy, had a 10% risk of major rebleeding within three months (hazard ratio (HR) 2.8 compared to patients with no recent bleeding, 95% CI 1.4 to 5.3).[91] More than 90% of those suffering a rebleed had had their anticoagulant therapy started within three weeks of the initial gastrointestinal bleed. Of 94 patients with recent intracranial haemorrhage, none suffered a rebleed. Evidence from randomised studies looking at the reintroduction of antiplatelet agents in patients following aspirin-related acute upper gastrointestinal ulcer bleeding suggests restarting aspirin, as long as it is combined with a proton pump inhibitor.[92, 93] Whether such a strategy is effective in patients using a VKA is unknown. **2-** **1-**

C **Patients with a mechanical prosthetic heart valve who suffer intracranial haemorrhage should, following a careful risk/benefit analysis, be considered for reintroduction of long term VKA therapy after 7-14 days, possibly at a reduced target INR.**

C **Patients who suffer gastrointestinal haemorrhage and who require to start or continue a VKA should be considered for delayed initiation or temporary cessation of therapeutic anticoagulation for 21 days or until there is evidence of healing of the bleeding lesion.**

5.6 PHARMACOGENOMICS AND WARFARIN

Recent advances in the understanding of the pharmacogenomics of warfarin have led to the suggestion that incorporating genotype information may improve dose prediction during initiation of therapy, and reduce bleeding events. Variants in the cytochrome P450 (CYP)2C9 and vitamin K epoxide reductase (VKORC1) genes have been shown to account for between around 25% and 60% of variance in warfarin sensitivity in a range of populations.[94] Dose requirements are determined in part by genotype and, therefore, dose prediction may be improved by prospective consideration of genotype data. Although the Food and Drug Administration in the USA has encouraged this approach to anticoagulant management through the approval of an updated label for coumarin which refers to genotyping, there are few data so far which demonstrate consequent improvements in anticoagulant control and a reduction in haemorrhagic complications.[95] Furthermore, the cost effectiveness and feasibility have not been explored fully. **1+**

A **Pharmacogenetic testing prior to initiation of therapy with a vitamin K antagonist is not recommended.**

5.7 INTERACTIONS

A systematic overview found that vitamin K antagonists have many interactions with commonly prescribed drugs, over-the-counter drugs, alternative therapies and dietary supplements.[96] Even some commonly used drugs which are generally considered safe for use alongside VKAs may be implicated. For example, two small RCTs looking at the interaction between paracetamol and warfarin (20 and 36 patients) have shown that regular concomitant use of paracetamol (2 g/day) significantly increases the INR. Further studies looking at lower doses are recommended.[97, 98] Although neither habitual alcohol consumption, nor heavy drinking, were associated with overanticoagulation in a case control study, a recent decrease in alcohol consumption was.[99]

No evidence was identified regarding the effect of exercise, stress or lifestyle on the action of warfarin.

✓ Patients should be advised of the importance of having their INR monitored on a regular basis as determined by healthcare staff.

✓ Patients should be advised to inform the healthcare staff prior to any changes to concomitant medications and/or dietary supplements, as more intensive monitoring of anticoagulation may be required.

✓ Patients should be advised not to use any over-the-counter medications or dietary supplements without checking with the healthcare team first.

✓ Patients should be advised not to make any substantial changes to their diet while on warfarin, and to check with their healthcare professional before starting any new dietary regimen.

✓ Patients should be advised:

- of the risks of taking concomitant NSAIDs and aspirin
- to minimise major changes in paracetamol use
- to consume alcohol only within the recommended limits.

✓ Patients taking vitamin K antagonists should be advised to inform healthcare staff immediately if they are planning a pregnancy or if they think they may be pregnant.

✓ Patients should be advised to inform healthcare staff if any abnormal bleeding occurs.

5.8 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.[100,101] Advantages of pharmacist-run anticoagulant clinics include improved continuity of care, maintenance of accurate patient records, identification of drug interactions, and identification and minimisation of adverse effects.[102,103] Guidance on how to establish such a clinic has been published.[100-103]

6 Other antithrombotic drugs

6.1 RIVAROXABAN, DABIGATRAN ETEXILATE AND APIXABAN

Rivaroxaban and dabigatran etexilate are novel oral agents which are direct inhibitors of factor Xa and thrombin respectively. Like VKAs they are effective by the oral route and have the potential advantage of standard dosing regimens and no requirement for monitoring. They are less susceptible to drug interactions than VKAs and in randomised controlled trials they have been efficacious with rates of serious bleeding comparable to those associated with VKA therapy. They have been investigated for use in the prevention of VTE after hip and knee replacement surgery, treatment of DVT and prevention of recurrent VTE and the prevention of thromboembolism in AF.

Dabigatran etexilate is a prodrug which is converted to the active direct thrombin inhibitor dabigatran by hydrolysis in the intestinal wall and liver. It is mainly (80%) eliminated by the renal route and consequently there is a risk of accumulation in severe renal impairment.

Rivaroxaban is less dependent on renal clearance (around 60%) but caution is required in severe renal impairment.

Both drugs have a short half-life, around 13 hours for dabigatran etexilate and around eight hours for rivaroxaban (12 hours in older patients). There is no recognised antidote to the anticoagulant effect of dabigatran etexilate. Because only 35% of the drug is bound to plasma proteins dialysis may be of benefit in an emergency situation. In healthy subjects dosed with rivaroxaban, 4-factor PCC effectively reversed the anticoagulant effect and it could be considered in emergency situations in patients.[104] **1+**

Although coagulation monitoring is not required it may be desirable to determine the degree of anticoagulation, for example if there is bleeding. The prothrombin time (PT, used for monitoring warfarin and expressed as the INR) is not sensitive to dabigatran etexilate. The APTT is prolonged but in a non-linear fashion. The thrombin clotting time (TCT) is the most informative test; if normal, the plasma concentration of dabigatran etexilate is likely to be low. The PT is prolonged by rivaroxaban although the degree of prolongation is reagent-dependent; if normal, the plasma concentration of rivaroxaban is likely to be low.[105] More evidence is required to ensure that surgical interventions and invasive procedures can be safely carried out based on the TCT in a patient on dabigatran etexilate and the PT in a patient on rivaroxaban.

Rivaroxaban has been compared with standard therapy of enoxaparin followed by a VKA in an RCT in patients with acute symptomatic VTE. The rivaroxaban regimen was non-inferior in relation to the primary outcome measure of recurrent VTE and there was no difference between the two regimens in clinically relevant bleeding; the net clinical benefit (recurrent VTE plus major bleeding) favoured rivaroxaban.[106] In a parallel study of rivaroxaban compared to placebo in patients who had completed 6 to 12 months of treatment for VTE, rivaroxaban was superior in the prevention of recurrent VTE (HR 0.18, 95% CI 0.09 to 0.39, $p<0.001$) with four episodes of (non-fatal) major bleeding in the rivaroxaban group (n=602; 0.7%) and none in the placebo group (n=594) (p=0.11).[106] **1+**

Dabigatran etexilate has been compared to warfarin in a randomised, double-blinded non-inferiority trial in patients with acute symptomatic VTE who were initially given parenteral anticoagulant therapy with a heparin.[107] Dabigatran etexilate was as effective as warfarin in preventing six month incidence of recurrent venous thromboembolism (HR for recurrent VTE with dabigatran etexilate was 1.10 (95% CI, 0.65 to 1.84). Significantly more patients in the warfarin group had bleeds classified as major or clinically relevant non-major. There was a significant excess of dyspepsia in the dabigatran etexilate group. **1+**

Apixaban is another orally active factor Xa inhibitor which is under assessment. In knee replacement surgery it has been demonstrated to be more efficacious than enoxaparin 40 mg daily in prevention of combined asymptomatic/symptomatic DVT, PE and all-cause death, with comparable bleeding risk.[108, 109]

Rivaroxaban and dabigatran etexilate are licensed for use in hip and knee replacement surgery and for the prevention of VTE in the UK *(see SIGN 122, section 5.5)*. These agents have been accepted by the Scottish Medicines Consortium for the prevention of stroke in non-valvular atrial fibrillation and for the prevention of VTE in elective hip or knee replacement surgery. Rivaroxaban is also accepted for the treatment of DVT and prevention of recurrent DVT and pulmonary embolism PE following an acute DVT in adults *(see section 18.3)*.

7 Atrial fibrillation: prophylaxis of systemic embolism

7.1 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 AF increases with age, from about 0.3/1,000 population at age <45 years to about 64/1,000 population at age >75 years.[2] Compared to people in sinus rhythm, those with AF have a fivefold 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 other organs or the limbs). Associated arterial disease (eg 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.[110,111]

The risk of stroke in patients with non-valvular AF appears to be similar irrespective of whether the arrhythmia is continuous or paroxysmal.[112] The risk is generally higher in women than men, however, women younger than 65 years and without other risk factors have a low risk for stroke (<1% annual stroke rate) which is not significantly different to the risk in men.[113] The role of echocardiography in risk stratification in patients with non-valvular AF remains unclear. Impaired left ventricular function and mitral valve calcification are risk predictors.[114] 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.[114]

The management of valvular disease is discussed in section 8.

7.2 EFFICACY OF WARFARIN AND ASPIRIN AS ANTITHROMBOTIC PROPHYLAXIS

7.2.1 MONOTHERAPY

In a meta-analysis of three RCTs considering aspirin in doses from 75-325 mg as antiplatelet therapy to prevent stroke in patients with non-valvular atrial fibrillation and no history of stroke or transient ischaemic attacks (TIA), with a mean follow up of 1.3 years, aspirin did not significantly lower stroke risk, OR 0.70 (95% CI 0.47 to 1.07). The combination of stroke, myocardial infarction and vascular death was significantly reduced (OR 0.71, 95% CI 0.51 to 0.97). [115] **1++**

In a meta-analysis which included five trials and 2,313 patients with a mean age of 69 years who were followed up for a mean of 1.5 years, dose-adjusted warfarin leading to an INR of between 2.0 and 3.0 reduced stroke rates in patients with non-valvular AF, OR 0.34 (95% CI 0.23 to 0.52) with wide confidence intervals for rates of extra- and intracranial haemorrhages.[116] **1++**

A meta-analysis of eight trials and 9,598 patients compared dose-adjusted VKA, mainly warfarin to platelet inhibitor, mainly aspirin alone, for patients in AF with no history of stroke or TIA, with a mean follow-up of 1.9 years. A dose-adjusted VKA was associated with a lower risk of stroke than platelet inhibitor, OR 0.68 (95% CI 0.54 to 0.85).[117] A further meta-analysis compared 29 trials, 28,044 patients, with a mean age of 71 years. This showed that dose-adjusted warfarin reduced stroke by 60% compared to 20% with antiplatelet agents in patients with non-valvular AF. The absolute increase in major extracranial haemorrhage was 0.2% per year with warfarin compared with aspirin, less than the absolute reduction in risk of a first stroke (0.7% per year).[118] **1++**

A large cohort study of 132,372 patients discharged with non-valvular AF, comparing risk of thromboembolism and bleeding in patients taking no treatment, VKAs, aspirin or both shows the efficacy of VKAs but no effect of aspirin on stroke or thromboembolism risk (HR for thromboembolism in patients treated by aspirin compared with VKA was 1.81, 95% CI 1.73 to 1.90). Combination therapy with a VKA and aspirin was not more effective than VKA monotherapy (HR 1.14, 95% CI 1.06 to 1.23).[119] **2+**

Despite its superiority in preventing embolic events in patients with AF it has been shown that warfarin is underused in these patients.[120] **1+**

Warfarin use has generally been limited in the elderly by concerns over falls and risks of haemorrhage. An RCT comparing 485 patients taking 75 mg aspirin and 488 patients taking dose-controlled warfarin with an INR of 2.0-3.0 who were followed up for a mean of 2.7 years showed that warfarin is better than aspirin at stroke prevention in patients with AF aged over 75 years (RR 0.48, 95% CI 0.28 to 0.80, p=0.003; absolute yearly risk reduction 2%, 95% CI 0.7 to 3.2). Risks of major extracranial haemorrhage were similar at 1.4% with warfarin and 1.6% with aspirin.[121] **1++**

Contraindications to warfarin include increased risk of bleeding (see section 5.1.2). A systematic review investigating risk factors for bleeding included nine studies. Advancing age, uncontrolled hypertension, history of MI or ischaemic heart disease (IHD)/cerebrovascular disease, anaemia, a history of bleeding and concomitant use of other drugs which predispose to bleeding were all identified as risk factors for anticoagulation-related bleeding.[122] **2++**

Independent predictors of stroke in patients with atrial fibrillation have been reviewed and a meta-analysis of seven studies shows prior stroke/TIA, advancing age, hypertension and diabetes as being associated with risk of stroke in patients with atrial fibrillation, with prior stroke conferring the highest risk.[123] **2++**

In light of these factors several schemes for stratification of stroke risk have been proposed. The $CHADS_2$ (Congestive heart failure, Hypertension, Age >75 years, Diabetes mellitus and prior Stroke or transient ischaemic attack) score has been validated and is used widely.[124, 125] It assigns two points for a history of ischaemic stroke or TIA and one for each of age 75 years and over, recent congestive heart failure, hypertension and diabetes mellitus *(see Table 2)* **2++ 4**

Table 2: $CHADS_2$ scheme for assessment of stroke risk in patients with non-valvular AF

Calculation of $CHADS_2$ score	
$CHADS_2$ risk factor	**Score**
Heart failure	1
Hypertension	1
Age >75 years	1
Diabetes mellitus	1
Prior stroke/TIA	2

Interpretation of stroke risk		
Risk	**$CHADS_2$ score**	**Annual stroke rate (%)**
LOW	0	1.9
INTERMEDIATE	1	2.8
	2	4.0
HIGH	3	5.9
	4	8.5
	5	12.5
	6	18.2

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Although $CHADS_2$ is simple and easy to use it is only one of numerous schemes and has limitations. One large cohort study compared the predictive ability of 15 published stratification schemes for stroke in a UK general practice setting. A c-statistic of 1.0 indicates perfect ability to predict the risk of stroke, and a score of 0.5 indicates no predictive value. Most had modest predictive value (c-statistic 0.55 to 0.69 for hospitalisation for stroke). There was wide variation between schemes in the proportion assigned to individual risk categories, the majority (>60%) being classified as 'moderate (intermediate) risk' using $CHADS_2$.[126] **3**

More detailed stroke risk assessment can be achieved by inclusion of additional risk factors: female sex, age (65-74 years or >75 years), and presence of vascular disease such as peripheral arterial disease, in addition to cardiac failure, hypertension, diabetes and previous stroke/TIA. In CHA_2DS_2-VASc two points are allocated for 'major risk factors' of a history of stroke or TIA, and for age >75 years. Using the CHA_2DS_2-VASc tool one point is allocated each for 'clinically relevant non-major risk factors' which are a history of cardiac failure, hypertension, age 65-74 years, diabetes, vascular disease and female sex. Using this scheme in a patient cohort with atrial fibrillation there was an increasing stroke rate with increasing scores.[127] **3**

D **In all patients with AF, risk factors for systemic thromboembolism should be assessed routinely using $CHADS_2$ or CHA_2DS_2-VASc score.**

B **Patients with AF who are clearly low risk,** (age<65 and lone AF) **do not require antithrombotic therapy. This applies to male patients with CHA_2DS_2-VASc score=0 and female patients with CHA_2DS_2-VASc score=1 in whom the single point is allocated due to female sex.**

A **All patients with AF who have a $CHADS_2$ or CHA_2DS_2-VASc score of ≥1** (one or more clinically relevant risk factors) **should be considered for warfarin at a target INR of 2.5** (range 2.0-3.0) **or a newer anticoagulant. The balance of risks and benefits of anticoagulant therapy should be assessed and discussed annually with the patient, with consideration given to patient preference.**

A **Antiplatelet therapy should only be considered where warfarin or one of the alternative new anticoagulants has been declined.**

7.2.2 COMBINATION THERAPY WITH ASPIRIN AND WARFARIN

The combination of aspirin and warfarin in patients with chronic atrial fibrillation alone or with concomitant coronary artery disease (CAD) does not reduce the risk of arterial thromboembolism compared with those on oral anticoagulant therapy alone but increases the risk for major bleeding. [128,129] **1++**

A
- **In patients with AF the combination of aspirin and warfarin is not recommended.**
- **If warfarin is indicated for moderate- or high-risk AF it should be used alone even in the presence of concomitant stable cardiovascular disease.**

7.3 CARDIOVERSION

Restoration of sinus rhythm may avoid the need for long term warfarin. However, cardioversion carries a moderate risk of systemic thromboembolism in patients who have been in AF for more than two days.[114, 130-132] The following recommendations are modified from a consensus statement:[114] **3 4**

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

D **Patients with very recent onset AF** (48 hours or less) **being considered for urgent cardioversion require immediate assessment and treatment with heparin.**

D **If it is certain that AF has been present for two days or less, cardioversion may be attempted electrically or pharmacologically without prior oral anticoagulation.**

D **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.**

✓ In patients undergoing cardioversion who are given warfarin to reduce the risk of thromboembolism a target INR of 2.5 (range 2.0-3.0) is advised.

By giving warfarin for three weeks prior to cardioversion, the risk of thromboembolism soon after the procedure is reduced from 5-7% to 1-2%. Whether warfarin should be given beyond four weeks following cardioversion 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 (LV) function, hypertension) or previously asymptomatic AF.[114]

7.4 NOVEL ANTITHROMBOTICS IN AF

7.4.1 DABIGATRAN ETEXILATE

In a large, randomised non-inferiority trial with blinded adjudication of events, the orally active direct thrombin inhibitor dabigatran etexilate was compared to warfarin in subjects with AF and at increased risk of stroke. At a dabigatran dose of 110 mg twice daily, efficacy in prevention of vascular events was comparable to warfarin but major bleeding was less frequent (2.87% versus 3.57%, p=0.002). At a dose of 150 mg twice daily, stroke and systemic embolism occurred significantly less frequently than with warfarin (1.11% per year versus 1.69% per year, RR 0.66; 95% CI 0.53 to 0.82, p<0.001) with similar rates of major haemorrhage (3.31% versus 3.57%, p=0.32).[133,134] **1+**

One RCT involving 18,113 patients showed that in centres where INR control was very good or excellent, warfarin performed as well as, if not better than, dabigatran in terms of stroke risk reduction and bleeding events.[135] **1+**

The SMC has accepted dabigatran for the prevention of stroke and systemic thromboembolism in adult patients with non-valvular atrial fibrillation with one or more of the following risk factors *(see section 18.3)*:

- previous stroke, transient ischaemic attack, or systemic embolism
- left ventricular ejection fraction <40%
- symptomatic heart failure, ≥New York Heart Association (NYHA) Class 2
- age ≥75 years
- age ≥65 years associated with one of the following: diabetes mellitus, coronary artery disease or hypertension.

A **Dabigatran etexilate can be considered as an alternative to warfarin in the management of patients with atrial fibrillation with one or more risk factors for stroke.**

✓ In selecting dabigatran etexilate consideration should be given to:

- the relative lack of experience of long term use compared with a VKA or aspirin
- the lack of a licensed product for rapid reversal of the anticoagulant effect of dabigatran etexilate (although the half-life is relatively short)
- the higher rates of gastrointestinal bleeding, especially with the higher dose regimen and in the elderly
- the limited data on use in patients at the extremes of body weight and those with renal and hepatic impairment.

7.4.2 RIVAROXABAN

In one RCT rivaroxaban was compared to warfarin in patients with AF at increased risk of stroke. For the primary outcome of stroke or systemic embolism there were 1.7% per year in the rivaroxaban group and 2.2% per year in the warfarin group (HR 0.79, 95% CI 0.66 to 0.96, p<0.001 for non-inferiority). There was no significant difference in major bleeding.[136] **1+**

The SMC has accepted rivaroxaban for restricted use for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and one or more stroke risk factors, such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or TIA *(see section 18.3)*.

A **Rivaroxaban can be considered as an alternative to warfarin in the management of patients with atrial fibrillation with one or more risk factors for stroke.**

✓ In selecting rivaroxaban consideration should be given to:

- the relative lack of experience of long term use compared with a VKA or aspirin
- the lack of experience with rapid reversal of the anticoagulant effect in patients, with PCC
- the higher rates of gastrointestinal bleeding, especially with the higher dose regimen and in the elderly
- the limited data on use in patients at the extremes of body weight and those with renal and hepatic impairment.

7.4.3 APIXABAN

Apixaban was compared with aspirin in an RCT of stroke prevention in patients with AF at increased risk of stroke and in whom VKA therapy was deemed to be unsuitable. The trial was stopped early due to a clear benefit of apixaban: stroke or systemic embolism occurred at 1.6% per year in those randomised to apixaban and 3.7% per year in the aspirin group. Rates of major bleeding were not significantly different between groups.[137] **1+**

In a further RCT apixaban was shown to be superior to warfarin in preventing stroke or systemic embolism, caused less bleeding and resulted in lower mortality in patients with AF and at least one additional risk factor for stroke. The rate of the primary outcome (ischaemic or haemorrhagic stroke or systemic embolism) was 1.27% per year compared with 1.65% per year for warfarin (HR 0.79, 95% CI 0.66 to 0.95, p=0.01 for superiority). Event rate for major or clinically relevant non-major bleeding was 4.07% per year in the group receiving apixaban compared with 6.01% per year in the group receiving warfarin (HR 0.68, 95% CI 0.61 to 0.75, p<0.001).[138] **1+**

The SMC has accepted apixaban for use in the prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery (*see section 18.3*).

8 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 3)*. 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. Aspirin or no treatment can be considered for lower-risk patients. Intravenous UFH may be indicated in acute thromboembolism *(see section 4.1)*, or if warfarin has to be stopped, for example, for elective surgery *(see section 5.4)*. In high-risk patients, anticoagulants should be discontinued only if justified by emergencies. Anticoagulants should generally be avoided in patients with active bacterial endocarditis.

Table 3: 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: - the patient has atrial fibrillation - the patient has had previous systemic embolism - the patient has left atrial thrombus at surgery - the valve is mitral, for first three months only. 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.

8.1 RHEUMATIC MITRAL VALVE DISEASE

Extrapolation from randomised controlled studies in non-rheumatic AF,[130] and recommendations based on expert opinion[139, 140] shows 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 and warfarin use is recommended if these risk factors are present.[141] **2+ 4**

D **Long term warfarin prophylaxis** *(target* INR 2.5, range 2.0-3.0) **should be considered in patients with rheumatic mitral valve disease and recommended if the patient is in atrial fibrillation.**

8.2 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 AF. Extrapolation of studies in non-rheumatic AF and recommendations based on expert opinion shows that warfarin prophylaxis is only indicated in the presence of previous systemic embolism or AF.[139-141] **4**

D **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.**

8.3 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 AF.[142,143] **4**

Hypertrophic cardiomyopathy carries a low embolic risk.

An RCT which included 279 patients with heart failure taking either aspirin, warfarin with a target INR of 2.5 or no antithrombotic agent showed that patients taking aspirin had poorer secondary outcomes, particularly hospitalisation due to worsening failure. The study provided no evidence to support the use of aspirin or warfarin in patients with heart failure in sinus rhythm.[144] **1+**

Meta-analysis of antiplatelet therapy and anticoagulation in heart failure patients in sinus rhythm shows no evidence to support the use of aspirin or anticoagulation.[145] **1++**

✓ 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.

8.4 MECHANICAL HEART VALVES

Systemic thromboembolism is a significant risk in patients with prosthetic heart valves but the level of risk varies depending upon factors such as the type of valve (eg the risk is greater with mechanical compared with bioprosthetic valves), the position (eg the risk is greater with mitral than aortic valves) and individual patient factors (eg atrial fibrillation or cardiac chamber dilatation).[141] More recently introduced mechanical valves have been regarded to be less thrombogenic than earlier types such as the Starr-Edwards valve.[71]

Anticoagulation with a VKA, usually warfarin, is standard practice in patients with mechanical heart valves based on the observed high rates of systemic embolism in case series.[146, 147] The recommended intensity of anticoagulation (target INR 2.5, 3.0 or 3.5) has varied depending upon perceived thrombogenicity. While a European consensus group concluded that reported thromboembolism rates do not provide sufficient guidance on the thrombogenicity of individual types of prosthesis,[148] the American College of Chest Physicians guideline makes specific recommendations based on type of valve as well as the other risk factors.[141] **3** **4**

In patients with prosthetic mechanical valves there was a significantly lower risk of arterial thromboembolism in patients who received combined aspirin/warfarin therapy compared with aspirin alone (OR 0.27, 95% CI 0.15 to 0.49), although there was no reduction in mortality; the OR for a major bleeding episode was 1.49 (95% CI 1.00 to 2.23).[128] Meta-analysis of 12 studies with 2,626 patients shows addition of an antiplatelet agent (aspirin or dipyridamole) to anticoagulation therapy in patients with prosthetic heart valves reduces the risk of thromboembolic events (OR 0.39, 95% CI 0.28 to 0.56) and total mortality (OR 0.57, 95% CI 0.41 to 0.78) but increased risk of bleeding (OR 1.68, 95% CI 1.21 to 2.35).[149] **1++**

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

D **The target INR should depend upon type and position of valve** (aortic or mitral) **and cardiac factors specific to the patient.**

A **Addition of aspirin or dipyridamole should be considered in patients with mechanical heart valves who suffer systemic embolism despite adequate intensity warfarin.**

8.4.1 ACUTE OBSTRUCTIVE PROSTHETIC HEART VALVE THROMBOSIS

A systematic review of case series and registries included nine series of thrombolytic therapy using streptokinase, urokinase or recombinant tissue plasminogen activator (rt-PA) and two series of surgical treatment.[150] In patients with acute obstructive prosthetic heart valve thrombosis, treatment with systemic thrombolytic therapy was successful in 85-90% of cases but was associated with a 2-8% risk of major haemorrhage, a 5.6%-19.1% risk of embolic complications, and mortality of 5-10%. It was associated with an 11-28% risk of re-thrombosis, which may itself be treated with further thrombolytic therapy.[150] **3**

Effective medical treatment is generally preferable to invasive surgical management, especially in debilitated patients, as the surgical treatment approach is associated with a mortality of 10-12%.[150]

D **Systemic thrombolysis is recommended for the initial treatment of acute obstructive prosthetic heart valve thrombosis.**

8.5 BIOPROSTHETIC HEART VALVES

One advantage of the placement of bioprosthetic heart valves is the avoidance of the need for long term VKA therapy in the absence of thrombotic risk factors, which is particularly beneficial to those at higher risk of bleeding. However, patients with bioprosthetic heart valves have a high risk of embolism, and, if they have AF, a history of systemic embolism, evidence of left atrial thrombus at surgery, persistent left atrial enlargement, or persistent heart failure, an indication for anticoagulation.[124, 140, 148] **4**

Recommendations for use of aspirin and warfarin in patients with bioprosthetic valves are included in the guidelines from the ACCP[141] and BCSH.[151] **4**

D **Low-dose aspirin** (75 mg daily) **is recommended in patients with a bioprosthetic valve in the aortic position who have no other indication for VKA therapy.**

D **Patients with a bioprosthetic valve in the mitral position should receive three months treatment with warfarin** (target INR 2.5) **followed by low-dose aspirin if in sinus rhythm and with no indication to continue warfarin.**

D **Patients with a bioprosthetic valve and a history of systemic embolism should receive at least three months of anticoagulation after valve insertion with warfarin, target INR of 2.5.**

D **Patients with a bioprosthetic valve and left atrial thrombus at surgery should receive warfarin** (target INR 2.5) **until the clot has resolved.**

D **Patients with a bioprosthetic valve and other risk factors such as atrial fibrillation and low ventricular ejection fraction should receive long term warfarin** (target INR 2.5).

The addition of aspirin (100 mg/day) to warfarin therapy reduced the annual rate of major systemic embolism or vascular death from 8.5% to 1.9% (RR reduction of 77% (95% CI 44 to 91)) in one trial of consecutive patients with mechanical or prosthetic valves, but increased the risk of bleeding.[152] **1+**

B **Selected patients with prosthetic valves may receive aspirin as additional therapy.**

8.6 PREGNANCY IN PATIENTS WITH HEART VALVE DISEASE OR PROSTHESES

See section 15.3 for management of pregnant women with mechanical heart valves.

9 Primary prophylaxis of vascular disease

9.1 ASPIRIN

Aspirin reduces the risk of further cardiovascular events in patients with established occlusive vascular disease and the benefits outweigh the increased risk of bleeding.[153] Use of aspirin for secondary prevention of cardiovascular events after stroke/TIA, symptomatic peripheral arterial disease, acute coronary syndrome and stable angina is described in SIGN 108, 89, 93 and 96 respectively. Clinical trials have investigated the efficacy of aspirin for the prevention of a first cardiovascular event. The studies have been heterogeneous, both in relation to dose of aspirin and level of risk for cardiovascular events at recruitment: some have recruited patients with no risk factor and others subjects with diastolic hypertension, evidence of asymptomatic peripheral vascular disease or diabetes.

In a meta-analysis of six primary prevention trials (totalling 95,000 individuals at low average risk and 66,000 person-years of follow up) the reduction in serious vascular events was counterbalanced by an increase in gastrointestinal and extracranial bleeds: serious vascular events 0.51% per year on aspirin versus 0.57% in controls, with no reduction in vascular mortality; major bleeds 0.10% per year on aspirin and 0.07% per year in controls. The main risk factors for coronary disease were also risk factors for bleeding.[153] **1++**

A more recent meta-analysis extended the population by the inclusion of three trials in subjects with:[154] ankle brachial pressure index 0.95 or less but no vascular symptoms,[155] type 1 or 2 diabetes mellitus and ankle brachial pressure index 0.99 or less,[1] and type 2 diabetes mellitus.[156] It was concluded that primary prophylaxis with aspirin reduced the risk of total cardiovascular events, non-fatal MI and all-cause mortality.[157] However, the balance against adverse events was not considered. The analysis has been criticised on the grounds of unacceptable heterogeneity of the populations included.[158] None of the three additional studies included demonstrated a significant reduction in vascular events with aspirin. **1-** **1+**

A **Aspirin is not recommended for primary prevention of vascular disease when benefits are considered against the increased risk of haemorrhage.**

9.2 VITAMIN K ANTAGONISTS

The Thrombosis Prevention Trial assessed the effect of low-dose warfarin (INR 1.3 to 1.9, mean 1.47) with and without aspirin (75 mg/day) in prevention of IHD.[159] 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. **1+**

Low-dose warfarin combined with aspirin was associated with a greater reduction in myocardial infarction (fatal and non-fatal) than either agent alone (RR reduction 34%).[159] However, combined treatment was also associated with significantly greater risk of bleeding, including haemorrhagic stroke. **1+**

10 Peripheral arterial disease

10.1 ANTIPLATELET AGENTS

Cardiovascular risk reduction for patients with peripheral arterial disease (PAD) is covered in SIGN 89: Diagnosis and management of peripheral arterial disease.[3]

Allocation of high-risk patients (with vascular disease, including peripheral arterial disease) to antiplatelet therapy reduced the combined outcome of any serious vascular event by about one quarter; non-fatal MI by one third, non-fatal stroke by one quarter and vascular mortality by one sixth.[160] **1++**

10.1.1 INTERMITTENT CLAUDICATION

A Cochrane review of antiplatelet therapy (mainly aspirin) in patients with intermittent claudication included 12 studies with 12,168 patients.[161] Antiplatelet therapy was associated with a reduction in all-cause and cardiovascular mortality (RR 0.76, 95% CI 0.60 to 0.98, and RR 0.54, 95% CI 0.32 to 0.93, respectively). However, aspirin was associated with more adverse events than placebo, including dyspepsia (RR 2.11, 95% CI 1.23 to 3.61) and adverse effects leading to cessation of treatment (RR 2.05, 95% CI 1.53 to 2.75). **1++**

10.1.2 PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY IN THE LOWER LIMBS

A Cochrane review assessed trials of thromboprophylaxis after endovascular treatment.[162] Included studies were heterogeneous and based on limited data. The authors concluded that patients treated by angioplasty would benefit from low-dose aspirin (50-300 mg daily) and that clopidogrel may be a useful alternative. **1++**

A **Antiplatelet therapy is recommended for patients with symptomatic peripheral arterial disease.**

10.2 ORAL ANTICOAGULATION

A meta-analysis of nine trials of oral anticoagulant therapy included 4,889 patients with evidence of peripheral arterial disease.[163] Only two of the studies compared oral anticoagulation with aspirin; patients included had undergone infra-inguinal bypass surgery (n=2,781). Compared with aspirin there was no mortality reduction with oral anticoagulant (OR 1.04, 95% CI 0.85 to 1.29), nor significantly reduced graft occlusion (OR 0.91, 95% CI 0.77 to 1.06). Major bleeding was increased around twofold in those on an oral anticoagulant. **1+**

An RCT compared antiplatelet agent alone with combination therapy with a VKA in patients with atherosclerosis of the lower limbs, carotid arteries or subclavian arteries. Aspirin was principally used, with only a small proportion receiving clopidogrel or ticlopidine. Among 2,161 patients randomised there was no significant difference in the end point of myocardial infarction, stroke or death from cardiovascular causes (RR 0.92, 95% CI 0.73 to 1.16). The incidence of life threatening bleeding was increased significantly in the group receiving combination therapy (RR 3.41, 95% CI 1.84 to 6.35).[164] **1+**

A **In patients with PAD who have an indication for treatment with a vitamin K antagonist aspirin should not be added to improve anticoagulation.**

10.3 PARENTERAL ANTICOAGULATION

10.3.1 INTERMITTENT CLAUDICATION

A Cochrane review of anticoagulants for intermittent claudication identified 11 studies using heparin (five of UFH, six of LMWH) but only one study of UFH had sufficient methodological quality for inclusion.[165] This showed no benefit of heparin in treating intermittent claudication. **1+**

B **Heparin is not indicated in the management of intermittent claudication.**

10.3.2 ACUTE CRITICAL LIMB ISCHAEMIA

✓ Full dose IV UFH is standard practice in patients with acute critical lower limb ischaemia.

10.3.3 PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY IN THE LOWER LIMBS

Two RCTs have looked at the use of LMWH post-angioplasty to prevent re-stenosis.[166, 167] In the first study 172 patients with extensive dissection following percutaneous transluminal angioplasty (PTA) in the pelvic or upper leg region were randomised (open-label) to nadroparin or IV UFH for seven days post-PTA.[166] There was no difference in the primary outcome measure (degree of stenosis) in the group as a whole. On subgroup analysis patients with PTA in the superficial femoral artery (n=110) had reduced re-stenosis when treated with nadroparin. In the second study 275 patients undergoing PTA of the femoropopliteal arteries were randomised (open-label) to low-dose dalteparin (2,500 IU) plus aspirin (100 mg) versus aspirin (100 mg) alone for three months following PTA.[167] Again benefit was not seen in the primary outcome measure in the study population as a whole. Benefit was seen in the subgroup of patients with critical limb ischaemia. **1⁻**

The positive results from these studies should be viewed with caution as they were obtained on subgroup analysis only. In addition, practice in treatment of PAD has changed in two ways since these studies were performed. PTA is now often replaced by stent insertion and heparin may not be as valuable following this therapy and clopidogrel is now in widespread use and was not given in either of these studies.

10.3.4 BYPASS SURGERY FOR LOWER LIMB ISCHAEMIA

One RCT which randomised 849 patients undergoing bypass surgery in the lower limbs to receive either low-dose LMWH (40 mg enoxaparin) or UFH (5,000 IU).[168] In follow up recorded over 30 days there was no difference in the patency rate but perioperative blood loss and the requirement for protamine injection were lower in the enoxaparin group. This raises the possibility of replacing IV UFH during bypass surgery with LMWH. However, given the subjective nature of the outcome measures and the open-label nature of the study, the possibility of bias was high. **1⁻**

A second RCT looked at the effect of LMWH for three months following bypass surgery.[169] In this study 284 patients were randomised to dalteparin (5,000 IU) or placebo in addition to aspirin. There were no improvements in graft patency over a 12 month period despite the majority of the patients studied having critical limb ischaemia. **1⁺**

✓ It is standard practice to give IV UFH during bypass graft surgery in the lower limbs; LMWH may have equivalent benefit.

B **Further treatment with LMWH after bypass surgery is not recommended.**

10.4 THROMBOLYTIC THERAPY

10.4.1 ACUTE PERIPHERAL ARTERIAL OCCLUSION

When compared with systemic intravenous thrombolysis, catheter-directed intra-arterial (CDIA) thrombolytic therapy is more effective for limb salvage (80% versus 45%) and is associated with fewer major haemorrhagic adverse events (5-8% versus 20%).[170] When compared with surgical treatment, CDIA thrombolytic therapy is equally effective for limb salvage but is associated with higher rates of stroke (1.3% versus 0%) and major haemorrhagic adverse events (8.8% versus 3.8%).[171] Patients treated with CDIA thrombolytic therapy for PAD require less extensive surgical intervention than patients who proceed directly to surgical treatment. **1⁺⁺**

During CDIA thrombolytic therapy for PAD the use of low-dose continuous infusion, after initial bolus lacing of the thrombus with agent, is easier to administer than high-dose forced infusion/pulse spray regimens. Low-dose continuous infusion regimens are not associated with reduced therapeutic efficacy with regard to rates of limb salvage and the need for subsequent surgical intervention.

It is not clear what duration of ischaemic symptoms should be regarded as a limit beyond which CDIA thrombolytic therapy for PAD should not be considered.

Comparing rt-PA and urokinase for CDIA thrombolytic therapy in PAD, one systematic review which included a large proportion of non-randomised controlled trials and case series found an increased risk of major haemorrhagic adverse events (8.4% versus 6.2%) and death (5.6% versus 3.0%) with rt-PA.[172] Another systematic review involving mostly RCTs reported similar rates of major haemorrhagic adverse events between rt-PA and urokinase (OR 0.54, 95% CI 0.18 to 1.60) and no difference in mortality rates (OR 2.09, 95% CI 0.51 to 8.58). Restoration of vessel patency was improved by rt-PA compared with urokinase (OR 1.54, 95% CI 1.12 to 2.20).[173] **1+ 3**

An RCT, two cohort studies and a case series found that adjuvant administration of an intravenous infusion of abciximab along with CDIA thrombolytic therapy in PAD was not associated with an increased risk of major haemorrhagic adverse events or death.[174-177] **1- 2+ 3**

In a further case series CDIA thrombolytic therapy alone for PAD involving synthetic bypass grafts demonstrated high rates of initial success (restoration of patency in 84%) which were not durable (50% patency at 10 weeks, 20% at one year).[178] **3**

There are limited data on the durability of successful CDIA thrombolytic therapy for PAD in native vessels: one systematic review found that patency at one year for native vessels is similar to that for synthetic bypass grafts at 36%, although patients treated with thrombolytic therapy appear to be more likely to experience recurrent ischaemic symptoms than patients initially treated surgically.[171] **1+**

B **In individual patients with acute peripheral arterial occlusion CDIA is preferred to systemic thrombolysis. In assessing the individual patient the increased risk of haemorrhagic adverse events** (including stroke) **associated with CDIA thrombolytic therapy should be balanced against the risks of anaesthesia and surgery.**

✓ When CDIA thrombolytic therapy for PAD is performed, it is recommended that low-dose continuous infusion regimens be administered in preference to more intensive high-dose forced infusion/pulse spray regimens in order to minimise the complexity and frequency of angiographic re-assessment and surveillance of associated systemic thrombolysis effects.

11 Cerebrovascular disease

11.1 ACUTE PROPHYLAXIS OF FURTHER VASCULAR EVENTS

Management of patients in the acute phase of stroke is covered in SIGN 108.[9]

11.1.1 ANTIPLATELET AGENTS

A meta-analysis of antiplatelet therapy for acute ischaemic stroke identified 12 trials involving 43,041 patients.[179] Two trials contributed 94% of the data. One of these trials was an open-label trial and computed tomography (CT) imaging was not required prior to trial entry. In some smaller trials there was a possibility that the randomisation was not concealed, and that baseline characteristics between the intervention and comparison were not matched. In patients presenting with acute ischaemic stroke aspirin (160–300 mg), given within 48 hours of stroke onset and continued once daily, was associated with a significant reduction in death or dependency, recurrent stroke, and improved the likelihood of a full recovery. | **1++**

A **Aspirin 300 mg should be commenced within 48 hours of ischaemic stroke and continued for at least 14 days.**

11.1.2 PARENTERAL ANTICOAGULATION

A Cochrane review of ten trials involving 916 patients found that anticoagulants significantly reduced the rate of symptomatic and asymptomatic DVT compared to controls in patients with acute ischaemic stroke (OR 0.21; 95% CI 0.15 to 0.29).[180] Major events (pulmonary embolism (PE), death, intracranial/extracranial haemorrhage) were too infrequent to assess the overall effect of heparin. A meta-analysis suggested that the bleeding risk outweighed benefit for unselected patients but in another meta-analysis of 23,043 patients, low-dose LMWH reduced symptomatic and asymptomatic DVT rate without statistically increasing risk of haemorrhage.[181, 182] A third meta-analysis found a benefit of LMWH over UFH in reducing PE rate.[183] | **1++**

The BCSH guideline on use and monitoring of heparin, published in 2006 recommended that stroke patients should be assessed for VTE risk and considered for thromboprophylaxis.[49] Standard prophylactic doses of either UFH or LMWH should be used. | **4**

In a systematic review of acute ischaemic stroke which included 11 trials, none of UFH, LMWH, heparinoid or thrombin inhibitor had any significant effect in terms of death, or death or dependency after follow up of at least one month compared with controls.[180,184] | **1++**

A **The routine use of anticoagulants is not recommended for the treatment of acute ischaemic stroke.**

A **Anticoagulants are not recommended in patients with progressing stroke.**

A **In patients at high risk of venous thromboembolic disease LMWH should be considered in preference to UFH.**

The National Institute of Neurological Disorders and Stroke (NINDS) recombinant tissue plasminogen activator (rt-PA) for Stroke Protocol excluded the use of any heparin in the first 24 hours after thrombolysis for stroke. There is no clinical trial evidence for this, but the protocol is widely used in clinical practice[9,185] | **4**

D **Following administration of intravenous thrombolysis, heparin should not be given in any form for 24 hours.**

For carotid artery dissection there are no randomised trials comparing either anticoagulants with antiplatelet drugs or with control. Reported non-randomised trials do not show a significant difference between anticoagulants and antiplatelet drugs.[9, 186,187] | **2++** **3** **4**

Anticoagulation appears to be safe following cerebral venous thrombosis and may be associated with an improvement in outcome and reduced mortality. A meta-analysis of two small trials (n=79) found that anticoagulation treatment with UFH with APTT monitoring or weight-adjusted LMWH (commenced on average 10-32 days after diagnosis and continued for three weeks, followed by warfarin therapy for 10 weeks) was associated with a relative risk of death of 0.33 (95% CI 0.08 to 1.21).[188] No new symptomatic intracerebral haemorrhages occurred during treatment with anticoagulants. 1++

C **Intravenous UFH or subcutaneous LMWH followed by warfarin therapy should be considered in patients with cerebral venous thrombosis.**

11.1.3 ACUTE STROKE AND ATRIAL FIBRILLATION

Approximately one third of patients presenting in the acute phase of stroke are found to have AF. These patients have high mortality and morbidity. Prior to the administration of antithrombotic therapy, intracranial haemorrhage needs to be excluded, and consideration of the risk from haemorrhagic transformation in patients with large cerebral infarcts is required. While warfarin is superior to aspirin for the secondary prevention of stroke in patients with AF *(see section 7.2.1)* there is uncertainty about the optimal timing of administration of anticoagulants following acute stroke.

Consensus recommendations based on a clinical guideline from NICE exist.[189]

D **In patients with AF and acute stroke:**

- **in the absence of haemorrhage, anticoagulant therapy should begin after two weeks but may be delayed in the presence of a large infarct**
- **in the presence of haemorrhage, anticoagulant therapy should not be given.**

✓ In all patients with AF who have had an acute stroke, any uncontrolled hypertension should be appropriately managed before antithrombotic therapy is started.

✓ In patients with AF and acute TIA in the absence of cerebral infarction or haemorrhage, anticoagulation therapy should begin as soon as possible.

11.1.4 PARENTERAL THROMBOLYTIC THERAPY

The following evidence statements and recommendations relating to intravenous thrombolysis have been reproduced from SIGN 108.[9]

A Cochrane review of IV thrombolysis includes data from RCTs of streptokinase and the alteplase form of rt-PA. Initial trials evaluated streptokinase, which has since been excluded from routine clinical use due to safety concerns and lack of evidence of efficacy.[190] 1++

Thrombolytic therapy with rt-PA (alteplase 0.9 mg/kg up to maximum 90 mg) administered within four and a half hours of stroke onset according to protocols stated in the product licence significantly reduces death and disability at 90 days.[190,191] 1++

The odds of a favourable outcome (full or nearly full recovery from stroke) are strongly related to the time to treatment and are significantly greater the earlier that treatment is delivered. The odds ratio for favourable outcome is 2.8 (95% CI 1.8 to 4.5) for 0–90 minutes, 1.6 (95% CI 1.1 to 2.2) for 91–180 minutes, and 1.4 (95% CI 1.1 to 1.9) for 181–270 minutes in favour of rt-PA treatment.[192] Administration later than 4.5 hours is associated with an increased risk of mortality and the risk:benefit ratio has not been established.[192] 1++

The incidence of symptomatic neurological deterioration due to intracerebral haemorrhage is increased approximately threefold to around 2% with IV alteplase.[191,193,194] 1++ 2++ 2-

A **Patients admitted with stroke within four and a half hours of definite onset of symptoms, who are considered suitable, should be treated with 0.9 mg/kg** (up to maximum 90 mg) **intravenous rt-PA.**

A
- **Onset to treatment time should be minimised.**
- **Systems should be optimised to allow the earliest possible delivery of intravenous rt-PA within the defined time window.**

A **Streptokinase should not be used for treatment of patients in the acute phase of stroke.**

11.2 SECONDARY PREVENTION AFTER ACUTE ISCHAEMIC STROKE OR TRANSIENT CEREBRAL ISCHAEMIC ATTACK

11.2.1 ANTIPLATELET THERAPY

A meta-analysis[21] and subsequent RCT[22] comparing the combination of aspirin and dipyridamole with aspirin in patients with vascular disease found that the combination therapy significantly reduced the risk of the composite end point of MI, stroke or vascular death compared with aspirin alone (OR 0.82, 95% CI 0.74 to 0.91; absolute risk reduction (ARR) 1% per year, 95% CI 0.1 to 1.8; number needed to treat (NNT) 104, 95% CI 55 to 1006) without an increase in bleeding complications.

An RCT comparing clopidogrel to aspirin in patients at high risk of vascular events including stroke (recruits had recent ischaemic stroke, recent myocardial infarction or symptomatic PAD) found that clopidogrel was more effective than aspirin alone in reducing the combined endpoint of ischaemic stroke, myocardial infarction or vascular death (RRR 8.7%, p=0.043; ARR 0.51%, NNT 196) except in the subgroup recruited with prior stroke (RRR 7.3%, p=0.26; ARR 0.56, NNT 179).[195] **1++**

An RCT comparing the combination of aspirin and dipyridamole to clopidogrel monotherapy found that the combination therapy was as effective as clopidogrel alone in the prevention of recurrent ischaemic stroke.[196] An angiotensin receptor blocker (ARB, telmisartan) was included in the multifactorial design of this trial.

A **Clopidogrel monotherapy** (75 mg daily) **or aspirin** (75 mg) **in combination with dipyridamole** (200 mg extended release twice daily) **should be prescribed after ischaemic stroke or TIA for secondary prevention of vascular events.**

11.2.2 WARFARIN

Secondary prevention in patients with TIA or ischaemic stroke who have atrial fibrillation or other cardiac source of embolism is covered in sections 7 and 8.

In an RCT comparing oral anticoagulants (target INR 2-3) to aspirin (50-325 mg daily) started within six months of TIA or stroke of arterial origin there was no benefit in oral anticoagulants for secondary prevention.[197] A randomised trial of higher intensity warfarin (target INR 3.7, range 3.0 to 4.5) versus aspirin was terminated early because of excessive intracranial bleeding.[198]

11.3 CAROTID ENDARTERECTOMY

The following evidence statement and recommendation have been reproduced from SIGN 108.[9]

A systematic review suggested that antiplatelet treatment given after carotid endarterectomy (CEA) reduces the rate of stroke, but not of death.[199] Antiplatelet treatment was started before CEA in four of the six RCTs reviewed, but five days and up to three months after CEA in the other two studies. The individual study results do not conclusively show that one regimen is superior to the other. **1++**

A **Standard antiplatelet treatment should be given after CEA.**

12 Myeloproliferative disorders

In addition to cytoreductive therapy, patients with myeloproliferative disorders frequently receive antithrombotic therapy.

A meta-analysis identified two studies comparing aspirin to placebo. Only patients with polycythaemia rubra vera (PRV) were entered into the trials and patients were not entered if there were other indications for antiplatelet therapy.[200] Both trials were performed by the same group of investigators and were judged to have a moderate risk of bias. Outcomes measured were thrombotic complications and major and minor bleeding, and follow up was for >6 months. Treatment with aspirin (40-100 mg per day) was associated with a large but non-statistically significant reduction in the risk of fatal thrombotic events, without an increased risk of major bleeding, when compared to no treatment in those patients who had no clear alternative indication or contraindication to aspirin therapy (OR 0.20, 95% CI 0.03 to 1.14).[200] **1++**

B **Patients with polycythaemia rubra vera should be considered for treatment with aspirin, unless there are contraindications.**

In the same Cochrane review no RCT on the use of aspirin or other antiplatelet agents in patients with essential thrombocythaemia was identified although aspirin is in common usage in this condition.[200]

See section 15.4 for the management of myeloproliferative disorders in pregnancy.

13 Other indications for anticoagulant therapy

13.1 DISSEMINATED INTRAVASCULAR COAGULATION

Experimental studies have shown that heparin can partially inhibit the activation of coagulation in disseminated intravascular coagulation (DIC).[201]

The BCSH notes that although morbidity in DIC is due in part to microvascular thrombosis there are no RCTs demonstrating that the use of heparin in patients with DIC results in an improvement in clinically relevant outcomes.[202] **4**

Observational studies have shown that heparin may improve abnormal coagulation tests in DIC.[203, 204] Disseminated intravascular coagulation is associated with a risk of VTE due to the hypercoagulable state and other factors in affected patients such as sepsis, recent surgery, immobility and the presence of indwelling vascular devices. **3** **4**

Venous thromboembolism prophylaxis using UFH, LMWH, and/or mechanical methods have been employed in critically ill patients.[205, 206] **1++** **3**

A trial in patients with severe sepsis treated with activated protein C showed a non-significant benefit of low-dose heparin on 28-day mortality.[207] **1+**

The following good practice points are adapted from the British Committee for Standards in Haematology guideline.[202]

✓
- In patients with DIC where thrombosis predominates, such as arterial or venous thromboembolism, purpura fulminans, or organ failure with presumed ischaemic pathogenesis, therapeutic doses of heparin can be considered.
- In these patients, due to the coexisting high risk of bleeding, there may be benefit in using continuous infusion of UFH rather than subcutaneous UFH or LMWH due to its short half-life and reversibility.
- Monitoring the APTT in these cases may be complicated as the clotting time may be prolonged prior to introduction of heparin; clinical observation for signs of bleeding is important.
- Weight-adjusted doses (eg 10 IU/kg body weight/hr) may be used without the intention of prolonging the APTT ratio to 1.5-2.5 times the control.
- In critically ill, non-bleeding patients with DIC, prophylaxis for venous thromboembolism with UFH or LMWH can be considered.

13.2 ACUTE PROMYELOCYTIC LEUKAEMIA

The benefit of heparin or other anticoagulant (or antifibrinolytic agent) to influence the coagulopathy and reduce the haemorrhagic risk associated with acute promyelocytic leukaemia is unproven. The British Committee for Standards in Haematology advises that their use is not recommended.[208] **4**

14 Intravascular devices

14.1 PREVENTION OF DVT DUE TO CENTRAL VENOUS CATHETERS

Addition of UFH to parenteral nutrition in patients with a central venous catheter did not significantly reduce thrombotic risk.[209] 1++

C **The risk/benefit ratio of the use of thromboprophylaxis in patients with central venous catheters should be considered on an individual basis.**

C **Thromboprophylaxis in patients with central venous catheters is not routinely recommended.**

14.1.1 PATIENTS WITH CANCER

A review of nine prospective studies of thromboprophylaxis in patients with cancer with central venous catheters suggested no benefit of thromboprophylaxis in this situation.[210] A Cochrane review on the use of anticoagulants to prevent indwelling venous catheter-related thrombosis in patients with cancer reported a trend towards reduced incidence of line related symptomatic deep vein thrombosis with heparin (RR 0.43, 95% CI 0.18 to 1.06) but not with warfarin.[211] A large RCT of warfarin demonstrated no reduction in catheter thrombosis.[212] 1++ 2++

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

14.2 TREATMENT OF CATHETER-RELATED THROMBOSIS

The evidence on treatment of catheter-related thrombosis is limited. An observational study suggests that anticoagulation without removal of the line may be appropriate in some patients.[213] 3

✓ Anticoagulant treatment of catheter-associated upper extremity DVT without removal of line may be considered appropriate in some patients.

14.3 MAINTAINING PATENCY OF ARTERIAL AND VENOUS CATHETERS

14.3.1 PARENTERAL ANTICOAGULATION

One RCT found no benefit of heparinised saline over normal saline for maintaining the patency of arterial catheters.[214] 1++

B **Normal saline should be used to maintain the patency of arterial catheters.**

14.3.2 THROMBOLYTIC THERAPY

In patients with thrombosed venous catheters evidence from two RCTs and a large case series indicated that instillation of recombinant urokinase 5,000 IU/ml followed by a 30-60 minute dwell, with a second dose at 30 minutes if required, was effective at restoring luminal patency in 54-75% of patients. There was only one major haemorrhagic complication and no other significant adverse effects attributable to treatment were reported.[215-217] 1+ 3

Instillation of reteplase 0.4 IU in 2 ml followed by up to 60 minutes dwell was effective at restoring luminal patency in 88% of patients. Of 139 events in a single case series, no significant adverse effects attributable to treatment were reported.[218] A further two case series found that instillation of rt-PA 1 mg/ml or 2 mg/ml followed by up to 240 minutes dwell, with a second dose if required, was effective at restoring luminal patency in 83-87% of patients with no significant adverse effects attributable to treatment reported for 153 events.[219, 220] 3

B **For occluded non-haemodialysis central venous catheters local treatment with short dwell instillation of thrombolytic agent is recommended.**

15 Pregnancy

15.1 PROPHYLAXIS AND TREATMENT OF VENOUS THROMBOEMBOLISM

Prophylaxis and treatment of venous thromboembolism during pregnancy is covered in SIGN guideline 122: Prevention and management of venous thromboembolism.[12]

15.2 PREGNANCY FAILURE

15.2.1 WOMEN WITH ACQUIRED THROMBOPHILIA

Antiphospholipid antibodies (APA) are associated with recurrent otherwise unexplained miscarriage and fetal death. Antithrombotic therapies are used commonly in women with antiphospholipid antibodies and pregnancy failure.

A Cochrane review of the prevention of recurrent miscarriage in women with antiphospholipid antibodies (anticardiolipin antibodies with or without lupus anticoagulant) was identified.[221] Evidence derived from two small, unblinded RCTs (total n=140) demonstrated a benefit from treatment with UFH and aspirin versus aspirin alone (RR 0.46, 95% CI 0.29 to 0.71).[221] For LMWH and aspirin versus aspirin alone evidence derived from one small, unblinded RCT (n=98) demonstrated no benefit from LMWH (RR 0.78, 95% CI 0.39 to 1.57). Some patients in this study had relatively low APA titres and may have been at lower risk of recurrent pregnancy loss. Approximately 25% of patients crossed over to the other treatment arm and 25% of women were randomised after documentation of fetal cardiac activity.[221] **1++**

Additional RCTs with consistent clinical and laboratory diagnostic criteria are required. These are difficult to perform owing to the large number of patients required and concerns about withholding treatment from women with a condition known to be associated with recurrent miscarriage. The effectiveness of LMWH compared with UFH for the prevention of recurrent pregnancy loss in women with APA syndrome has not been established.

B **Prophylactic doses of heparin with or without low-dose aspirin may be considered in women with antiphospholipid antibodies and recurrent pregnancy failure or fetal death in whom no other cause is identified.**

✓ In practice, LMWH is favoured because of its safety profile and ease of patient use.

✓ In identifying women who may benefit from antithrombotic therapy to prevent pregnancy failure consideration should be given to the pattern of antibodies:

- lupus anticoagulant is more strongly associated with clinical events than anticardiolipin and anti-beta2 glycoprotein I
- high titre antibodies and those of immunoglobulin G class are more clinically relevant than lower titre antibodies and those of immunoglobulin M class, and
- persistence of antibody positivity is essential for the diagnosis of antiphospholipid syndrome.

15.2.2 WOMEN WITH INHERITED THROMBOPHILIA

A systematic review of aspirin or anticoagulants for the treatment of recurrent miscarriage in women with heritable thrombophilia without antiphospholipid antibodies and with no other identifiable cause identified two RCTs.[222] 74 women who fulfilled the pre-specified criteria of the review; at least two spontaneous miscarriages or one late intrauterine death without apparent other causes than inherited thrombophilia (ie antiphospholipid antibody negative) were included in the analysis. One study of aspirin versus placebo found no benefit from treatment on recurrent spontaneous miscarriage. The second study, a small (n=20) quasi-randomised open-label trial of enoxaparin versus aspirin, found some benefit from treatment with enoxaparin in terms of increased live birth rate in women with a history of a single loss after the 20th week of gestation (RR 10.00, 95% CI 1.56 to 64.20). In the total cohort of this study there were 160 women with thrombophilia and a single loss after the 10th week of gestation and the live birth rate was significantly higher in the women given LMWH. Both studies in the review were considered to have methodological flaws. **1++**

There is insufficient evidence to make a recommendation on anticoagulant therapy for prophylaxis of recurrent pregnancy loss in women with a thrombophilic defect other than antiphospholipid syndrome.

15.2.3 WOMEN WITH RECURRENT MISCARRIAGE AND NO KNOWN THROMBOPHILIA

Two RCTs examined the use of antithrombotics in women with unexplained recurrent miscarriage. In the first, the pregnancy loss rate was not influenced by enoxaparin plus aspirin and intensive surveillance compared with intensive surveillance only.[223] In the second, neither aspirin alone nor aspirin with nadroparin improved the live birth rate compared with placebo.[224] **1+**

A **Antithrombotic therapy is not indicated in the management of recurrent miscarriage in the absence of antiphospholipid syndrome.**

15.2.4 WOMEN UNDERGOING ASSISTED REPRODUCTION

Antithrombotics have been used widely in an attempt to improve success rates in assisted reproduction/ early pregnancy units. The evidence for this approach is limited to small trials with variable outcomes.[225, 226] **1-**

There is insufficient evidence to support use of antithrombotics to improve outcomes after assisted reproduction.

15.3 MECHANICAL HEART VALVES

Vitamin K antagonists can cause embryopathy and fetal bleeding and their use is avoided in pregnancy, generally. However, they are the most effective antithrombotics for prevention of thrombosis on mechanical heart valves *(see section 8.4)*. A systematic review of cohort studies and case series found that for pregnant women with mechanical heart valves the lowest thromboembolic risk was associated with treatment with a VKA (4%).[227] This risk increases with UFH regimens and ranges from 9-33% depending on the stage of pregnancy at which heparin is substituted. In this review the overall risk of fetal abnormality with use of oral anticoagulants during pregnancy was 6.4% of live births. Substitution of heparin at six weeks or less gestation abolished the risk of warfarin embryopathy. The risk of spontaneous miscarriage was similar for women receiving oral anticoagulation throughout pregnancy (24.7%) compared with heparin substitution in the first trimester (24.8%). **2+ 3**

A second systematic review of observational studies of LMWH for thromboprophylaxis in pregnant women with prosthetic heart valves identified 81 women receiving LMWH at some point during their pregnancy. The overall risk of thromboembolic complication was 12.35% (9/10 events occurred on fixed dose or prophylactic doses of LMWH).[228] Low molecular weight heparin is a suitable alternative to UFH, but requires anti-Xa monitoring to ensure levels in the range of 1.0-1.2 IU/ml four hours post-injection.[228,229]

In a multicentre prospective cohort study of vitamin K antagonists and pregnancy outcome there were only two cases of coumarin embryopathy in 356 live births (0.6%),[230] suggesting that the teratogenic effect of warfarin may be less than previously thought. Withdrawal of the VKA prior to six weeks gestation appears to eliminate the risk of embryopathy.

Evidence of a lower risk of embryopathy with warfarin therapy in the first trimester than previously thought may be of relevance when discussing a management plan for those women at very high risk of maternal thromboembolism should warfarin be discontinued. The balance of risks and benefits will be altered in this situation.

On the basis of the limited data that are available, there is no management strategy that is universally accepted for pregnant women with mechanical heart valves and, in practice, one of a number of regimens can be adopted in the context of informed patient preference.[229]

C **In women with mechanical prosthetic heart valves the treatment options are:**

- **adjusted-dose, 12 hourly, subcutaneous LMWH throughout pregnancy with anti-Xa monitoring**
- **adjusted-dose, 12 hourly, subcutaneous UFH throughout pregnancy with APTT monitoring or anti-Xa monitoring**
- **adjusted-dose UFH or LMWH from ≤6 to 13 weeks gestation, followed by warfarin until two weeks before delivery when heparin is reintroduced.**

✓ In women with mechanical valves at very high risk of thromboembolic complications

- discuss the risks and benefits of continuing warfarin throughout pregnancy (with conversion to heparin close to delivery)
- consider addition of aspirin (75-100 mg per day).

15.4 MYELOPROLIFERATIVE DISORDERS

The myeloproliferative disorders essential thrombocythaemia and polycythaemia vera are associated with an increased risk of thromboembolic complications. This risk is likely to be increased further during pregnancy. In addition there is an increased risk of first trimester miscarriage in women with myeloproliferative disease.

No RCTs of antithrombotic therapy in pregnant women with essential thrombocythaemia or polycythaemia vera were identified. A non-systematic review found that the available data for essential thrombocythaemia are retrospective and variable with regard to management and outcome.[231] The review included reports of more than five patients or more than 10 pregnancies. Nine reports identified 291 pregnancies in 160 women. The rate of first trimester miscarriage was 39%. The same review identified 36 pregnancies in 18 women with polycythaemia vera. The miscarriage rate was 22%.

4

Patients with myeloproliferative diseases can be stratified according to the presence of additional risk factors. These include older age, presence or absence of previous vaso-occlusive events and degree of erythrocytosis and thrombocytosis. Treatment can be tailored accordingly in an attempt to reduce the risk of thrombosis and pregnancy failure, although there is no high quality evidence regarding the efficacy of aspirin or LMWH for these purposes in pregnant women with myeloproliferative disease.

The use of cytoreductive therapy in this context is beyond the scope of this guideline.

✓ Pregnant women with chronic myeloproliferative disorders:

- should be considered individually in terms of thrombosis risk and pregnancy failure
- should be considered for 75 mg aspirin daily during pregnancy.

✓ Thromboprophylaxis with LMWH can be considered after and/or during pregnancy when there are additional risk factors for VTE.

16 Models of care

A meta-analysis confirmed that the lowest risk of bleeding and thrombosis in patients using VKAs is during periods when the INR is in the usual target range of two to three. For example, the relative risk of haemorrhage is increased around 20-fold at INR ≥5.[232] 1++

A range of models of care for long term management of anticoagulation with VKAs is available including hospital based anticoagulant clinics, community based clinics with INR measurement in a hospital laboratory, community based clinics with point of care (POC) testing, patient self testing of INR and patient self testing and dosing, both using POC equipment. In addition, dosing decisions may be made by a range of health professionals and/or computer-assisted dosing programmes *(see section 5.8)*.

The use of POC testing is associated with improved time in the INR target range and a significant reduction in risk of thromboembolic events and death.[233-236] These benefits were most marked in studies undertaken outside the UK and may not be evident when compared to specialised anticoagulant clinic services. Self testing and management may not be applicable for the majority of patients and the apparently improved outcomes may reflect better patient education. 1++

Point of care testing is likely to be more expensive than monitoring by specialised anticoagulant clinic services in the UK.

One RCT indicated that computer-assisted dosing may be associated with a slight further improvement in time-in-range, above that achievable by manual dosing.[237] 1++

An analysis of the clinical and cost effectiveness of different models of managing long term oral anticoagulation therapy suggests that self monitoring is unlikely to be more cost effective than current usual care in the UK.[233] 1++

A **Self monitoring and self dosing is safe and effective and can be considered for some patients.**

B **Computer-assisted dosing should be considered.**

✓ For patients who are self monitoring, appropriate education and training should be provided, clinical advice should be available on request, and provision should be made for quality assurance.

✓ Healthcare professionals providing dosing advice on INR should be appropriately trained and able to provide documented evidence of competence.

✓ Healthcare professionals undertaking POC testing should be trained in its operation and maintenance prior to use, including the requirement for robust quality assurance of the INR measurements.

17 Provision of information

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

17.1 CHECKLIST FOR PROVISION OF INFORMATION TO PATIENTS STARTING TREATMENT WITH VITAMIN K ANTAGONISTS

This section gives examples of the information patients/carers may find helpful prior to commencing treatment with vitamin K antagonists. The checklist was designed by members of the guideline development group based on their experience and their understanding of the evidence base. The checklist is neither exhaustive nor exclusive.

- Explain the meaning of anticoagulant and how it affects coagulation factors in the blood resulting in blood taking longer to clot (use of terminology such as 'thins the blood' may be confusing).
- Explain the benefits of this treatment for the patient's condition.
- Explain how a VKA should be taken, ie once a day, at about the same time, with a full glass of water.
- Explain the different strengths and colours of VKA tablets and how to make up different doses.
- Explain what to do if a dose is delayed or missed or the wrong dose has been taken by mistake.
- Explain the importance of regular monitoring, how it is done and why it is necessary to minimise the risks of complications of treatment.
- Explain INR, and that adjustments to dose of VKAs may be made depending on results of this test.
- Explain potential side effects of this treatment, especially bleeding risks, what to do if these occur and when to seek immediate medical attention.
- Go through the information in the yellow anticoagulant book with the patient, and advise them to bring the small book to each anticoagulant appointment so INR results and doses can be written in it.
- Explain about carrying the anticoagulant alert card at all times and about informing other healthcare professionals, eg pharmacist/dentist, about treatment with anticoagulants.
- Explain about interactions with other medications, including over-the-counter medicines, alternative therapies and dietary supplements, and the importance of checking with the healthcare team prior to commencing or stopping any medications, as more intensive monitoring may be required.
- Explain about avoiding concomitant use of NSAIDs and aspirin, or other medications containing aspirin, unless advised to do so by healthcare staff.
- Advise the patient to tell healthcare staff if they regularly use paracetamol as this may necessitate more frequent monitoring of INR.
- Explain the interaction with alcohol, including safe limits and the importance of not binge drinking.
- Explain the importance of avoiding major changes to diet while on VKA therapy.
- Where appropriate, advise women to consult their healthcare team if they are planning a pregnancy and immediately if pregnancy is suspected.
- Advise patients of the need to avoid trauma (especially to the head) and to seek advice before engaging in contact sports or other activities with an increased risk of head trauma.

18 Implementing the guideline

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

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

18.1 RESOURCE IMPLICATIONS

Table 4 shows the results of an economic model indicating the budget impact of prescribing 150 mg dabigatran etexilate to patients with atrial fibrillation in Scotland who are not suitable for warfarin (assumed to be 20% of patients who are currently anticoagulated). All assumptions in calculations are available to view and revise online.[238]

Table 4: Budget impact of prescribing dabigatran etexilate in Scotland to AF patients unsuitable for warfarin

	Dabigatran etexilate (150 mg)	Warfarin	Incremental cost
Total drug costs	£5,354,399	£84,990	£5,269,409
Costs of GP visits	£418,844	£418,844	£0
Cost of anticoagulation clinics	£0	£1,405,106	-£1,405,106
Cost of major bleeding	£336,358	£364,725	-£28,368
Cost of minor bleeding	£83,208	£91,893	-£8,685
Cost of haemorrhagic stroke	£63,193	£240,134	-£176,941
Cost of ischaemic or unspecified stroke	£600,055	£789,202	-£189,148
Cost of myocardial infarction	£118,352	£93,512	£24,839
Total cost	**£6,974,408**	**£3,488,407**	**£3,486,001**

Data extracted from the London New Drugs Group budget impact model for Dabigatran in the prevention of stroke in atrial fibrillation patients in the United Kingdom setting.[238]

18.2 AUDITING CURRENT PRACTICE

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

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

- the proportion of patients with new onset atrial fibrillation having their risk of stroke formally assessed.
- the proportion of patients with diabetes but no evidence of established ischaemic heart disease who are taking aspirin for primary prevention of vascular events.

18.3 ADDITIONAL ADVICE TO NHSSCOTLAND FROM HEALTHCARE IMPROVEMENT SCOTLAND AND THE SCOTTISH MEDICINES CONSORTIUM

On 12 December 2011, SMC advised that:

apixaban (Eliquis®) is accepted for use within NHSScotland for the prevention of venous thromboembolic events in adult patients who have undergone elective hip or knee replacement surgery.

In two large phase III double-blind comparative studies, in patients undergoing elective hip or knee replacement surgery, apixaban was superior to a low molecular weight heparin for the incidence of VTE and all cause death whilst incidence of major bleeding events was similar between groups.

On 7 December 2009, SMC advised that:

bemiparin (Zibor®) is accepted for use within NHSScotland for the prevention of thromboembolic disease in patients undergoing orthopaedic surgery.

Bemiparin was associated with a lower incidence of thromboembolic complications than unfractionated heparin and was non-inferior to another low molecular weight heparin.

On 9 June 2008, SMC advised that:

dabigatran etexilate (Pradaxa®) is accepted for use within NHSScotland for the primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

In two large phase lll studies, in patients undergoing either total knee or total hip replacement surgery, dabigatran was non-inferior to low molecular weight heparin in the incidence of VTE and all-cause mortality with patients having a similar incidence of major bleeding events. The two drugs have similar costs per dose but dabigatran has lower administration costs and is an oral therapy. This may facilitate longer duration of thromboprophylaxis, however the risks and benefits of this longer treatment duration need to be considered on a case-by-case basis.

On 12 September 2011, SMC advised that:

dabigatran etexilate (Pradaxa®) is accepted for use within NHSScotland for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more of the following risk factors:

- previous stroke, transient ischaemic attack, or systemic embolism
- left ventricular ejection fraction <40%
- symptomatic heart failure, ≥New York Heart Association (NYHA) Class 2
- age ≥75 years
- age ≥65 years associated with one of the following: diabetes mellitus, coronary artery disease or hypertension.

Dabigatran etexilate was at least as effective as standard oral anticoagulation at preventing stroke or systemic embolism in one large, open-label study in patients with atrial fibrillation and at least one risk factor for stroke. This was not associated with an increased risk of major bleeding.

The economics case made supports the use of the proposed sequenced dosing regimen (whereby the dose is reduced from 150 mg twice daily to 110 mg twice daily in patients aged ≥80 years). This applies whether the alternative treatment is warfarin, aspirin or 'no treatment' (ie neither warfarin nor aspirin).

On 7 March 2011, SMC advised that:

dalteparin (Fragmin®) is accepted for restricted use within NHSScotland for the extended treatment of symptomatic venous thromboembolism and prevention of its recurrence in patients with solid tumours.

Restriction: initiation by healthcare professionals experienced in the treatment of VTE.

On 13 July 2009, SMC advised that.

enoxaparin (Clexane®) is accepted for use within NHSScotland for the treatment of acute ST-segment elevation myocardial infarction (STEMI) including patients to be managed medically or with subsequent percutaneous coronary intervention (PCI) in conjunction with thrombolytic drugs (fibrin or non-fibrin specific).

In clinical studies using a median of seven days of enoxaparin treatment, enoxaparin demonstrated a reduction in death or non-fatal MI compared to unfractionated heparin.

On 8 December 2008, SMC advised that:

rivaroxaban (Xarelto®) is accepted for use within NHSScotland for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery.

In three large phase III studies in patients undergoing either total knee or total hip replacement surgery, rivaroxaban was superior to low molecular weight heparin in reducing the incidence of VTE and all cause mortality with patients while having a similar incidence of major bleeding events.

On 13 February 2012, SMC advised that:

rivaroxaban (Xarelto®) is accepted for use within NHSScotland for the treatment of deep vein thrombosis (DVT), and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults.

Rivaroxaban has been shown to be non-inferior to standard anticoagulant therapy including a low molecular weight heparin in combination with a vitamin K antagonist for the treatment of proximal DVT and prevention of recurrence.

Experience with rivaroxaban in this indication for more than 12 months is limited therefore the cost effectiveness of indefinite treatment has not been demonstrated.

On 13 February 2012, SMC advised that:

rivaroxaban (Xarelto®) is accepted for restricted use within NHSScotland for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.

Restriction: Rivaroxaban is accepted for use in patients who have poor INR control despite evidence that they are complying with a coumarin anticoagulant and in patients who are allergic to or unable to tolerate coumarin anticoagulants.

19 The evidence base

19.1 SYSTEMATIC LITERATURE REVIEW

The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using an explicit search strategy devised by a SIGN Information Officer. Databases searched include Medline, Embase, Cinahl, PsycINFO and the Cochrane Library. The year range covered was 2003-2009. Internet searches were carried out on various websites including the US National Guidelines Clearinghouse. The main searches were supplemented by material identified by individual members of the development group. Each of the selected papers was evaluated by two members of the group using standard SIGN methodological checklists before conclusions were considered as evidence.

19.1.1 LITERATURE SEARCH FOR PATIENT ISSUES

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

19.2 RECOMMENDATIONS FOR RESEARCH

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

- optimal methods for reversal of anticoagulation associated with newer anticoagulants (rivaroxaban, apixaban and dabigatran etexilate).
- optimal laboratory assessment of degree of anticoagulation in emergency preoperative settings using newer anticoagulants (rivaroxaban, apixaban and dabigatran etexilate).
- management of anticoagulation in patients undergoing invasive procedures.
- assessment of the potential interaction between VKAs and low-dose paracetamol (<2 g/day).
- assessment of the effect of exercise, stress or lifestyle on the anticoagulant action of warfarin.

20 Development of the guideline

20.1 INTRODUCTION

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

20.2 THE GUIDELINE DEVELOPMENT GROUP

Professor Mike Greaves *(Chair)*	*Professor of Haematology, University of Aberdeen*
Mr David Allan	*Orthopaedic Surgeon, Southern General Hospital, Glasgow*
Dr Janet Brennand	*Consultant in Fetal and Maternal Medicine, Southern General Hospital, Glasgow*
Dr Andrew Docherty	*Consultant Cardiologist, Wishaw General Hospital*
Mr Carl Fenelon	*Clinical Pharmacist, Glasgow Royal Infirmary*
Dr Gregor Imrie	*Consultant Anaesthetist, Southern General Hospital, Glasgow*
Dr Martin Johnson	*Consultant Respiratory Physician, Gartnavel General Hospital, Glasgow*
Ms Joan Lawson	*Lay Representative, Wick*
Dr Chris Lush	*Consultant Haematologist, Raigmore Hospital, Inverness*
Dr Brian McInnes	*Consultant Physician, Hairmyres Hospital, East Kilbride*
Mr Gordon McPherson	*Lay Representative, Langbank, Renfrewshire*
Dr Andrew Moore	*General Practitioner, Tain Health Centre*
Dr Moray Nairn	*Programme Manager, SIGN*
Mrs Lindsay Robertson	*Thrombosis Nurse, Glasgow Royal Infirmary*
Mrs Lynne Smith	*Information Officer, SIGN*
Dr Ian Zealley	*Consultant Radiologist, Ninewells Hospital, Dundee*

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

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

Miss Lisa Birch	*Distribution and Office Coordinator*
Mrs Lesley Forsyth	*Events Coordinator*
Mrs Karen Graham	*Patient Involvement Officer*
Mr Stuart Neville	*Publications Designer*
Miss Gaynor Rattray	*Guideline Coordinator*

20.2.1 PATIENT INVOLVEMENT

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

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

20.3 ACKNOWLEDGEMENTS

SIGN is grateful to the following former members of the guideline development group and others who have contributed to the development of the guideline.

Ms Beatrice Cant	*Programme Manager, SIGN*
Professor Brian Cuthbertson	*Clinical Senior Lecturer, Health Services Research Unit, University of Aberdeen*
Dr Paul Duffy	*Consultant Radiologist, Southern General Hospital, Glasgow*

20.4 CONSULTATION AND PEER REVIEW

20.4.1 NATIONAL OPEN MEETING

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

20.4.2 SPECIALIST REVIEW

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

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

Dr Julia Anderson	*Consultant Haematologist, Royal Infirmary of Edinburgh*
Professor Adrian Brady	*Consultant Cardiologist, Glasgow Royal Infirmary*
Dr Patrick Cadigan	*Registrar, Royal College of Physicians, London*
Dr Sam Chakraverty	*Consultant in Radiology, Ninewells Hospital, Dundee*
Dr Patrick Chien	*Consultant Obstetrician and Gynaecologist, Ninewells Hospital, Dundee*
Professor Martin Dennis	*Professor of Stroke Medicine, University of Edinburgh*
Dr Nicholas Fluck	*Scottish Government Health Department Specialty Adviser for Renal Medicine, Aberdeen Royal Infirmary*
Professor Keith Fox	*Professor of Cardiology, University of Edinburgh and Consultant Cardiologist, Royal Infirmary of Edinburgh, President of the British Cardiovascular Society*

Mr Colin Howie	*Consultant Orthopaedic Surgeon, Royal Infirmary of Edinburgh*
Dr Gordon Isbister	*General Practitioner, Beith*
Professor Gordon Lowe	*Emeritus Professor (formerly Professor of Vascular Medicine), University of Glasgow*
Ms Laura McIver	*Chief Pharmacist, Healthcare Improvement Scotland, Glasgow*
Dr John Murchison	*Consultant Radiologist, Royal Infirmary of Edinburgh*
Dr David Murdoch	*Consultant Physician and Cardiologist, Honorary Senior Clinical Lecturer, University of Glasgow*
Mr David Paul	*Lay representative, Glasgow (deceased)*
Dr Robert Peel	*Consultant Renal Physician, Raigmore Hospital, Inverness*
Dr Jackie Price	*Reader in Epidemiology (Honorary Consultant in Public Health) and Co-ordinating Editor of the Cochrane Collaboration Review Group on PVD, University of Edinburgh*
Dr Scott Ramsay	*Consultant Physician and Geriatrician with an Interest in Stroke, St John's Hospital, Livingston*
Dr Campbell Tait	*Consultant Haematologist, Glasgow Royal Infirmary*
Dr Andrew Thomson	*Consultant Obstetrician and Gynaecologist, Royal Alexandra Hospital, Paisley*
Dr Barry Vallance	*Consultant Cardiologist, Hairmyres Hospital, East Kilbride and Lead Clinician for Heart Disease, Scotland*
Dr Ed Wallace	*Clinical Director and Honorary Senior Lecturer, Medical School, University of St Andrews*
Dr Henry Watson	*Consultant Haematologist, Aberdeen Royal Infirmary*

10.4.3 SIGN EDITORIAL GROUP

As a final quality control check, the guideline is reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers' comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. The editorial group for this guideline was as follows. All members of the SIGN Editorial group make yearly declarations of interest and further details of these are available on request from the SIGN Executive.

Dr Keith Brown	*Chair of SIGN; Co-Editor*
Dr Roberta James	*SIGN Programme Lead; Co-Editor*
Dr Rajan Madhok	*Royal College of Physicians and Surgeons of Glasgow*
Dr Tahir Mahmood	*Royal College of Obstetricians and Gynaecologists*
Mrs Fiona McMillan	*Royal Pharmaceutical Society of Great Britain (Scottish Dept)*
Dr Mark Strachan	*Royal College of Physicians of Edinburgh*
Dr Sara Twaddle	*Director of SIGN; Co-Editor*

Abbreviations

ACCP	American College of Chest Physicians
ADP	adenosine diphosphate
AF	atrial fibrillation
APA	antiphospholipid antibody
APTT	activated partial thromboplastin time
ARB	angiotensin receptor blocker
ARR	absolute risk reduction
BCSH	British Committee for Standards in Haematology
BNF	British National Formulary
CAD	coronary artery disease
CDIA	catheter-directed intra-arterial
CEA	carotid endarterectomy
$CHADS_2$	Congestive heart failure, Hypertension, Age >75 years, Diabetes mellitus and prior Stroke or transient ischaemic attack
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CT	computed tomography
CYP	cytochrome P
DIC	disseminated intravascular coagulation
DVT	deep vein thrombosis
EF	ejection fraction
EMA	European Medicines Agency
GI	gastrointestinal
H2	histamine2
H2RA	histamine 2 receptor antagonist
HR	hazard ratio
IHD	ischaemic heart disease
INR	international normalised ratio
IU	international unit
IV	intravenous
LMWH	low molecular weight heparin
LV	left ventricular
MI	myocardial infarction
MTA	multiple technology appraisal
NICE	National Institute for Health and Clinical Excellence

NINDS	National Institute of Neurological Disorders and Stroke
NNH	number needed to harm
NNT	number needed to treat
NSAID	non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
OR	odds ratio
PAD	peripheral arterial disease
PCC	prothrombin complex concentrate
PCI	percutaneous coronary intervention
PE	pulmonary embolism
POC	point of care
PPI	proton pump inhibitor
PRV	polycythaemia rubra vera
PT	prothrombin time
PTA	percutaneous transluminal angioplasty
RCT	randomised controlled trial
RIETE	Registro Informatizado de Pacientes con Enfermedad TromboEmbólica (computerised registry of patients with venous thromboembolism)
RR	relative risk
RRR	relative risk reduction
rt-PA	recombinant tissue plasminogen activator
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
STEMI	ST-Segment Elevation Myocardial Infarction
TCT	thrombin clotting time
TIA	transient ischaemic attack
UFH	unfractionated heparin
VKA	vitamin K antagonist
VKORC1	vitamin K epoxide reductase
VTE	venous thromboembolism

Annex 1

Key questions used to develop the guideline

THE KEY QUESTIONS USED TO DEVELOP THE GUIDELINE

Key question	See guideline section
1. What are the main indications and effectiveness for antiplatelet therapy? *Consider*: secondary prophylaxis against acute coronary syndromes, stroke or vascular death in patients with the following conditions: acute or prior MI, unstable angina, stable angina, peripheral arterial disease, prior TIA or ischaemic stroke, acute ischaemic stroke. Primary prophylaxis in patients with diabetes or myeloproliferative disease and in patients undergoing stenting/PCI, anti-angiogenesis.	7.2, 8.3-8.5, 9.1, 9.2, 10.1, 11.1-11.3, 12, 15.2
2. What are the main indications and effectiveness for parenteral anticoagulation (heparins)? *Consider*: prophylaxis and treatment of VTE, treatment of acute coronary syndromes, prophylaxis of cardiac thromboembolism, management of coronary angioplasty (including stenting) or bypass surgery, acute critical limb ischaemia, peripheral angioplasty or bypass surgery, carotid endarterectomy, renal replacement therapies (haemodialysis, haemofiltration), and prevention of clotting in intravascular devices (including peripheral arterial catheters, central venous catheters), plasma phoresis.	4.1-4.4, 10.3, 11.1, 13.1, 14.1-14.3, 15.1-15.4
3. What are the main indications and effectiveness for oral anticoagulation (warfarin)? *Consider*: prophylaxis of central venous catheter thrombosis; primary prophylaxis of myocardial infarction in high-risk patients; prophylaxis and treatment of VTE; prophylaxis of cardiac thromboembolism in patients with atrial fibrillation (permanent/paroxysmal), elective cardioversion, heart valve disease, heart failure, cardiomyopathy, mechanical heart valves, bioprosthetic heart valves; intracardiac thrombosis; prophylaxis of recurrent myocardial infarction; critical limb ischaemia; prophylaxis of recurring venous, cardiac or arterial thromboembolism; chronic pulmonary hypertension.	5.1, 5.2, 5.5, 7.2, 8.1-8.5, 9.2, 10.2, 11.1, 11.2, 14.1, 15.3
4. What are the main indications and effectiveness for thrombolytic therapy? *Consider:* Acute coronary syndromes, acute cerebral ischaemia, acute pulmonary thromboembolism, deep vein thrombosis, VTE, PAD, shunt and cannular thrombosis, local versus systemic thrombolysis.	10.4, 11.1, 14.3
5. What are the contraindications, adverse effects and management issues associated with antiplatelet drugs? *Consider*: acetylsalicylic acid/aspirin, dipyridamole, clopidogrel, platelet receptor blockers, antiplatelet combinations, thiopyridines, initiation and maintenance dosage, timing of dosage, dosage titration; requirements for monitoring, formulations, bleeding, allergies, thrombocytopenia.	3.1-3.3, 5.7, 7.2, 8.5, 9.1, 9.2, 12
6. What are the contraindications, adverse effects and management issues associated with heparins? *Consider*: unfractionated heparin, LMWHs (enoxaparin, bemiparin, dalteparin, nadroparin, parnaparin, reviparin, tinzaparin) fondaparinux, danaparoid, initiation and maintenance dosage, timing of dosage, dosage titration; requirements for monitoring – APTT ratio, bone density, platelet counts, plasma anti-Xa levels, bleeding, heparin induced thrombocytopenia (HIT).	4.1-4.4, 5.4, 10.3, 11.1, 13.1, 14.1, 14.3, 15.1-15.3

7. |What are the contraindications, adverse effects and management issues associated with warfarin? *Consider*: initiation and maintenance dosage, timing of dosage, dosage titration; requirements for monitoring – INR, bleeding, drug interactions, pharmacogenetics.	5.1-5.8, 7.2, 8.4, 9.2, 10.2, 11.2, 15.3
8. What are the contraindications, adverse effects and management issues associated with thrombolytics? *Consider*: streptokinase, alteplase, urokinase, reteplase, tenecteplase, dosage and monitoring regimens, bleeding.	11.2, 11.1, 14.3
9. What are the main indications, effectiveness, contraindications and adverse effects associated with other antithrombotic drugs (dabigatran, rivaroxaban)? *Consider*: initiation and maintenance dosage, timing of dosage, dosage titration; requirements for monitoring, bleeding.	6.1, 7.4
10. What evidence is there to support concurrent treatment with more than one antithrombotic therapy? *Consider:* aspirin/warfarin, aspirin/heparin, thrombolytics/warfarin, thrombolytics/heparin.	7.2, 8.4, 8.5, 9.2, 10.4, 16.2, 16.3
11. What are the risks of antithrombotics in pregnancy and what is the evidence for continuing/stopping/switching treatment in order to prevent thrombotic events? *Consider:* teratogenicity, fetal and maternal bleeding, maternal osteoporosis, specific indications including mechanical heart valve, VTE prophylaxis, antiphospholipid syndrome, recurrent pregnancy failure, myleoproliferative disease.	16.1-16.4
12. What is the guidance and information that should be provided to patients on antithrombotics? *Consider*: absolute contraindications, lifestyle choices, diet, other drugs, stress, herbal therapies, OTC medications, contraception, alcohol.	5.7, 5.8, 16.3, 16, 17.1
13. If antithrombotic treatment is to be stopped for an invasive procedure or after acute haemorrhage how soon before and after the procedure/haemorrhage should treatment be stopped/restarted? *Consider:* major/minor surgery, endoscopy, dental procedures, stents, central venous catheters, anaesthetic use (spinal/epidural), bridging therapy, vitamin K, protamines, antifibrinolytics.	3.1, 5.3-5.5
14. In patients receiving antithrombotics who experience bleeding what measures can be taken to reverse this effect? *Consider*: stopping antithrombotic agent, administering antagonists, use of blood products, factor VIIA, all antithrombotic agents.	4.3, 5.3-5.5
15. What is the most appropriate model of care for patients on long term anticoagulants? *Consider*: point of care devices, computerised decision systems, setting and model of delivery of service (eg patient or nurse or pharmacist or GP), governance, patient preference, safety.	16

Annex 2

Sample warfarin flexible induction regimen (age-adjusted Fennerty)

The table below gives dosing advice for the first four days of warfarin initiation only. It is not appropriate for dosing from day five onwards which should be undertaken manually using clinical judgement.

On initiation:

- Perform baseline INR (unless part of initial coagulation screen), and repeat INR daily on the first four days.
- When the INR result is towards the upper end of a range in the INR column, it is recommended that a warfarin dose is chosen towards the lower end of the suggested range in the age-appropriate dose column; and vice versa when INR result is towards the lower end of an INR range.
- Beyond day four dosage adjustment may still be required, especially between days five and 14 when INR may need to be assessed every two to three days until stable and the patient has been transferred to an appropriate outpatient INR monitoring service.
- More careful dosing and monitoring may be required in elderly patients or where there is coadministration with drugs known to increase or decrease INR (consult the BNF or seek advice from clinical pharmacists).

DAY	**INR**	**Dose for age** (mg)			
		≤50 years	51-65 years	66-80 years	>80 years
1	< 1.4	10	9	7.5	6
2	< 1.6	10	9	7.5	6
	≥1.6	0.5	0.5	0.5	0.5
3	< 1.8	10	9	7.5	6
	1.8 - 2.5	4 - 5	3.5 - 4.5	3 - 4	2.5 - 3
	2.6 - 3.0	2.5 - 3.5	2.5 - 3.5	2-2.5	1.5-2
	3.1 - 3.5	1-2	1-2	0.5 - 1.5	0.5 - 1.5
	3.6 - 4.0	0.5	0.5	0.5	0.5
	> 4	0	0	0	0
4	< 1.6	10 - 15	9 - 13	7.5 - 11	6 - 9
	1.6 - 1.9	6 - 8	5.5 - 7	4.5 - 6	3.5 - 5
	2.0 - 2.6	4.5 - 5.5	4 - 5	3.5 - 4.5	2.5 - 3.5
	2.7 - 3.5	3.5 - 4	3 - 3.5	2.5 - 3	2 - 2.5
	3.6 - 4.0	3	2.5	2	1.5
	4.1 - 4.5	Omit next day's dose then:			
		1-2	0.5 - 1.5	0.5 - 1.5	0.5 - 1.5
	> 4.5	Withhold warfarin until INR back between 2.0 - 3.0 (then restart on 0.5 – 1 mg)			

Decrease the dose by 33% if the patient has one or more of the following risk factors:

- Severe congestive cardiac failure (ejection fraction (EF) <30% and/or biventricular failure)
- Severe chronic obstructive pulmonary disease (COPD) (oxygen or steroid dependent or dyspnoea at rest)
- Concurrent treatment with amiodarone.

Adapted from Therapeutics – A Handbook for Prescribing in Adults. NHS Greater Glasgow and Clyde Acute Services Division. August 2011

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