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Guideline

GUIDELINES ON ORAL ANTICOAGULATION: THIRD EDITION*,†

1. INTRODUCTION

The revision of the 1990 oral anticoagulant guidelines by the British Committee for Standards in Haematology (BCSH) (British Committee for Standards in Haematology, 1990) has been undertaken to reflect changes in the current medical literature and to incorporate the outcomes of medical audit. Guidelines on heparin were published by the BCSH in 1993 (British Committee for Standards in Haematology, 1993b). These present guidelines include indications for oral anticoagulation and suggested arrangements for the management of an anticoagulant service.

These new guidelines aim to take account of the current practical difficulties involved in the safe monitoring of the rapidly expanding numbers of patients on long-term anticoagulant therapy. With patient numbers more than doubling in most anticoagulant clinics in the past 5 years and the trend set to continue, the organizational problems are immense (Baglin, 1994; Rose, 1996). However, it remains the haematologist's responsibility to ensure that local arrangements for laboratory testing and dosage of oral anticoagulant therapy are satisfactory. This involves regular participation in national/regional quality assessment schemes and audit of clinical practice.

The third edition of these guidelines has been prepared by the Haemostasis and Thrombosis Task force of the British Society for Haematology. The document has been circulated to members of the British Committee for Standards in Haematology. Relevant scientific papers from systematic literature review were identified from Medline for 1965 to July 1996 using the index terms oral anticoagulation or warfarin and venous thromboembolism, deep vein thrombosis, pulmonary embolus, stroke, heart valve(s), prosthesis, atrial fibrillation, peripheral vascular disease, grafts, coronary artery, myocardial infarction, coronary artery graft, angioplasty and stents, central venous catheters and chemotherapy. Further publications were obtained from the references cited and reviews known to members of the Task Force. Evidence and graded recommendations are according to the US Agency for Health Care Policy and Research (US Department of Health and Human Services, Public Health Service and Agency Care Policy and Research, 1992) (Appendix I).

2. TARGET INR

The international normalized ratio (INR) is a recommended method for reporting prothrombin time results for control of oral anticoagulation (British Committee for Standards in Haematology, 1990). Since adoption of the INR system it has been usual practice to adjust the dose of warfarin, or other oral vitamin K antagonist, to maintain the INR within a therapeutic range. The range was often one INR unit, e.g. INR between 2·0 and 3·0. However, in practice many clinicians and computer support systems regulate dosage according to deviation of INR from a single target taken as the midpoint of the designated range, e.g. target INR of 2·5 for a range of 2·0–3·0. Furthermore, extensive audit indicates that only 50% of INRs in a population of patients taking warfarin are usually within the range at any one time, i.e. 0·5 INR units of the target (Rose, 1996), whereas 80% of patients are within 0·75 INR units of the target. With this experience it now seems more practical to designate a target INR and encourage dose adjustment dependent on deviation of INR from the target and also individual patient characteristics such as reason for anticoagulation, stability of INRs over time, previous bleeding and thrombotic events.

In view of this we have elected to recommend target INRs throughout these guidelines. We recommend that appropriate dose adjustment is made dependent on deviation of INR from the target. An INR within 0·5 INR units of the target is generally satisfactory and deviations of 0·5 and 0·75 INR units can be used as standards for audit (see also section 11).

3. INDICATIONS FOR ANTICOAGULATION

The indications for oral anticoagulation and recommended target INRs are summarized in Table I for ease of access. The evidence basis for these recommendations is summarised within the document.

3.1. *Venous thromboembolism in non-pregnant patients*

First event of pulmonary embolus or proximal vein thrombosis: INR 2·5 for 6 months (grade A, level Ib). Calf vein thrombosis in non-surgical patients with no persistent risk factors: INR 2·5 for 3 months (grade A, level Ib). Post-operative calf vein thrombosis without persistent risk factors:

*Prepared by the Haemostasis and Thrombosis Task Force for the British Committee for Standards in Haematology. Members of the working party: T. P. Baglin and P. E. Rose. Members of the Haemostasis and Thrombosis Task Force: I. D. Walker (Chair), S. Machin (Secretary), T. P. Baglin, T. W. Barrowcliffe, B. T. Colvin, M. Greaves, C. A. Ludlam, I. J. Mackie, F. E. Preston and P. E. Rose.

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Correspondence: The Secretary BCSH, British Society for Haematology, 2 Carlton House Terrace, London SW1Y 5AF.

INR 2·5 for 6 weeks (grade A, level Ib). Continued treatment should be considered if risk factors are persistent (grade B, level IIb). A recurrence after stopping warfarin requires a further episode of treatment, INR 2·5. A recurrence on treatment requires intensification of treatment, INR 3·5 (grade C, level IV), or alternative anticoagulant treatment.

Initial anticoagulation with heparin and a period of at least 6 weeks oral anticoagulant therapy is necessary dependent on the extent of thrombus, on whether the thrombotic event was triggered by a precipitating event, such as surgery, and on the existence of risk factors for recurrence (Hull *et al*, 1979; Francis, 1994; Weinmann & Salzman, 1994).

Pulmonary embolus is strongly associated with proximal deep vein thrombosis of the lower limb (Sandler & Martin, 1989) but occurs infrequently when thrombosis remains confined to the calf (Hirsh, 1990; Ginsberg, 1996). There has been no randomized study to determine the optimum intensity or duration of oral anticoagulant therapy after an episode of pulmonary embolism. Recommendations are therefore derived from the results of treatment of proximal vein thrombosis in the lower limb where pulmonary embolism is typically regarded as an endpoint in interventional studies. Fatal recurrence of pulmonary embolism is extremely rare when deep vein thrombosis is treated with heparin initially followed by a prolonged period of treatment with warfarin (Coon *et al*, 1969; Hull *et al*, 1979; Carson *et al*, 1992; Schulman *et al*, 1995). An INR of 2·0–3·0 gives the lowest recurrence and bleeding rates (Hull *et al*, 1982) and is the recommended range for venous thromboembolism.

Table I. Indications for oral anticoagulation, target INR and grade of recommendation.

Indication	Target INR	Grade of recommendation
Pulmonary embolus	2·5	A
Proximal deep vein thrombosis	2·5	A
Calf vein thrombus	2·5	A
Recurrence of venous thromboembolism when no longer on warfarin therapy	2·5	A
Recurrence of venous thromboembolism whilst on warfarin therapy	3·5	C
Symptomatic inherited thrombophilia	2·5	C
Antiphospholipid syndrome	3·5	B
Non-rheumatic atrial fibrillation	2·5	A
Atrial fibrillation due to rheumatic heart disease, congenital heart disease, thyrotoxicosis	2·5	C
Cardioversion	2·5	B
Mural thrombus	2·5	B
Cardiomyopathy	2·5	C
Mechanical prosthetic heart valve	3·5	B
Bioprosthetic valve	Not indicated	A (see text)
Ischaemic stroke without atrial fibrillation	Not indicated	A (see text)
Retinal vessel occlusion	Not indicated	C (see text)
Peripheral arterial thrombosis and grafts	Not indicated	A (see text)
Coronary artery thrombosis	Not indicated	A (see text)
Coronary artery graft thrombosis	Not indicated	A (see text)
Coronary angioplasty and stents	Not indicated	A (see text)

Retrospective studies gave conflicting results as to the optimal duration of oral anticoagulant therapy ranging from 6 weeks (Petiti *et al*, 1986) to 6 months (Coon *et al*, 1969). A series of small studies showed no difference in recurrence rates for patients treated for 4 weeks (Holmgren *et al*, 1985) or 6 weeks (O'Sullivan, 1972) compared to 6 months therapy, but not all patients had an objectively confirmed diagnosis. In addition, these studies either combined or did not distinguish patients with proximal thrombosis from those with thrombus confined to the calf. A review of duration of therapy in 1988 recommended at least 6 weeks therapy and indicated the need for prospective randomized studies. This review did not indicate the methods used for evaluating studies but stated that the confidence intervals for recurrence rates after only 6 weeks therapy were wide (Fennerty *et al*, 1988). Since then two prospective studies have randomized patients with proximal vein thrombosis to different durations of anticoagulation, one comparing 4 weeks with 3 months (Levine *et al*, 1995) and one comparing 6 weeks with 6 months (Schulman *et al*, 1995). In the 4-week/3-month study recurrence rates were 8·6% in the 4-week group compared to 0·9% in the 3-month group (OR = 10·1, 95% CI 1·3–81·4) (Levine *et al*, 1995). In the 6-week/6-month study recurrence rates after 2 years were 18·1% after 6 weeks treatment and 9·5% after 6 months treatment (OR = 2·1, 95% CI 1·4–3·1). In the 6-week group there was a sharp increase in the recurrence rate immediately after cessation of oral anticoagulant therapy (Schulman *et al*, 1995). Further clarification of the optimal duration of therapy will be obtained from the Duree Optimale du Traitement Antivitamine K (DOTAVK) study in which patients with proximal deep vein thrombosis are randomized to 3 or 6 months therapy. Therefore the present recommendation for duration of treatment of proximal deep vein thrombosis or symptomatic pulmonary embolism is 6 months (grade A recommendation, level Ib evidence). There is an opinion based on subgroup analysis that a period of 6 weeks therapy is adequate for proximal vein thrombosis in patients without permanent risk factors (grade C, level IV) (Hirsh, 1995; Ginsberg, 1996).

Thrombi below the level of the popliteal vein are not usually detected by compression ultrasound examination. Although these calf vein thrombi do not typically cause symptomatic pulmonary emboli they may extend into the popliteal and femoral veins and then cause significant emboli (Hirsh, 1990). Calf vein thrombi detected by contrast venography should either be treated with anticoagulant therapy or monitored with serial non-invasive tests, such as compression ultrasound examination (Cogo *et al*, 1998) and treated as for a proximal thrombus if extension occurs.

Untreated symptomatic calf vein thrombosis in non-surgical patients is associated with a recurrence rate of >25% and the risk of proximal extension and pulmonary embolization (Lagerstedt *et al*, 1985; Lohr *et al*, 1991; Raskob, 1996). Treatment with warfarin to maintain an INR of 2·0–3·0 for 3 months reduces these risks to 7·6% or less (Lagerstedt *et al*, 1985; Research Committee of the British Thoracic Society, 1992). This rate is lower than that achieved with 4 weeks (12·4%) (Research Committee of the British Thoracic Society, 1992) or 6 weeks anticoagulation (11·8%) (Schulman *et al*, 1995) and comparable to that achieved with 6 months treatment (5·8%) (Schulman *et al*, 1995). Therefore the best general recommendation at the present time is that symptomatic calf vein thrombosis in non-surgical patients without predisposing factors, such as cancer or thrombophilia, should be treated for 3 months (grade A, level Ib).

Post-operative calf vein thrombosis is also associated with proximal extension and pulmonary embolus (Kakkar *et al*, 1969; Pellegrini *et al*, 1993). However, a shorter period of anticoagulation appears to be sufficient to prevent recurrence after the initial precipitating event. In the BTSRC (British Thoracic Society Research Committee) study recurrence rates in surgical patients were low in patients assigned to 4 weeks (1·7%) as well as 3 months treatment (1·8%) (Research Committee of the British Thoracic Society, 1992). However, 26% of patients randomized to 4 weeks treatment actually received 6 weeks therapy, so it is prudent to recommend 6 weeks therapy until the results of further randomized studies are available (grade A, level Ib).

Continued treatment should be considered for patients with persistent risk factors for recurrence, e.g. cancer, thrombophilia (grade B, level IIb) (Research Committee of the British Thoracic Society, 1992; Hirsh, 1995; Levine *et al*, 1995; Schulman *et al*, 1995).

Patients with recurrent venous thromboembolism after stopping warfarin require further treatment with warfarin to maintain an INR of 2·5. The risk of further recurrence is high and the optimum duration of therapy is currently unknown (Schulman *et al*, 1997). Patients who have a recurrence whilst anticoagulated with warfarin should be considered for higher intensity therapy with warfarin, INR 3·5 (British Committee for Standards in Haematology, 1990) (grade C, level IV), or alternative anticoagulant therapy and evaluation for carcinoma or the antiphospholipid syndrome (Ginsberg, 1996).

3.2. *Inherited thrombophilia*

No episode of thromboembolism–antithrombotic prophylaxis for high-risk periods (grade C, level IV). After an episode of venous thromboembolism evidence of thrombophilia lowers the threshold for long-term anticoagulant therapy: INR 2·5 (grade C, level IV).

For these guidelines the term thrombophilia is used to refer to inherited disorders of the haemostatic system that result in an increased risk of venous thromboembolism (Cavenagh & Colvin, 1996; De Stefano *et al*, 1996; Lane *et al*, 1996), namely deficiencies of antithrombin, protein C, protein S and the factor V Leiden mutation (FV:R506Q). Acute thrombotic events should be treated with initial heparinization and oral anticoagulation to achieve an INR of 2·5 (Cavenagh *et al*, 1996; De Stefano *et al*, 1996; Lane *et al*, 1996). It is not yet known if after the initial treatment episode this level of anticoagulation is required long term or whether lower intensity warfarin regimens or aspirin will give equivalent protection. Until this information is available a target INR of 2·5 is recommended for those patients receiving anticoagulant therapy (grade C, level IV). Recommendations on the duration of therapy cannot be given as this will vary with the genetic defect, whether more than one defect is present, whether previous events were precipitated, and whether other family members with the defect are thrombosis-prone. Guidelines on the investigation and management of thrombophilia are currently being prepared by the Haemostasis and Thrombosis Task Force.

3.3. *Antiphospholipid syndrome*

Guidelines on the investigation and management of the antiphospholipid syndrome are currently being prepared by the Haemostasis and Thrombosis Task Force. It should be noted, however, that patients with arterial thrombosis associated with this syndrome should be treated immediately with heparin initially and then warfarin (grade C, level V) (Greaves & Preston, 1991). The target INR has not been clarified. A target of 2·5 has often been used but a non-randomized comparative study supported a target of 3·5 (Khamashta *et al*, 1995) (grade B, level III).

3.4. *Atrial fibrillation*

3.4.1. *Non-rheumatic atrial fibrillation*

INR 2·5 (grade A, level Ia)

In five randomized primary prevention trials comparing oral anticoagulation to placebo or no treatment anticoagulation prevented two-thirds of fatal or disabling strokes due to major thromboembolism (Peterson *et al*, 1989; The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators, 1990; Connolly *et al*, 1991; Stroke Prevention in Atrial Fibrillation Investigators, 1991; Ezekowitz *et al*, 1992; Atrial Fibrillation Investigators, 1994). In these studies the target INR ranged from 1·5 to 4·5. Thromboembolic event rates were relatively higher with INRs <2·0 (European Atrial Fibrillation Trial Study Group, 1995). These studies indicate a beneficial effect of warfarin in carefully selected patients in whom anticoagulation is expertly controlled.

The Atrial Fibrillation Investigators established a common database to identify subgroups of patients whose risk of stroke was so low that warfarin is not justified. They identified patients under 65 years of age without diabetes, a history of hypertension or a previous stroke or transient ischaemic attack (TIA) as low risk. These patients had an annual event rate of 1·0% which was not reduced by warfarin (European Atrial Fibrillation Trial Study Group, 1993; Hylek *et al*, 1996). SPAF II (Stroke Prevention in Atrial Fibrillation, second study) was the first primary prevention study in which patients were randomized to either anticoagulation (target INR 2·0–4·5) or aspirin 325 mg/d and

overall aspirin was as effective as warfarin (Stroke Prevention in Atrial Fibrillation Investigators, 1994). However, the rate of intracranial haemorrhage in patients >75 on warfarin was higher than in previous studies and it is not clear if the results of SPAF II were due to patient characteristics or chance.

In SPAF III patients at high risk of thromboembolism (congestive heart failure, left ventricular dysfunction on echocardiography, previous thromboembolism, systolic hypertension at enrolment or being a woman over 75 years) had a lower primary event rate with adjusted dose warfarin (INR 2·0–3·0) compared to combined low-dose warfarin and aspirin (Stroke Prevention in Atrial Fibrillation Investigators, 1996).

Warfarin should be considered as first-line therapy in patients with atrial fibrillation and at least one risk factor (previous thromboembolism, hypertension, heart failure, abnormal left ventricular function on echocardiography) for thromboembolism. However, patients should be reviewed as the benefit/risk ratio may alter with increasing age or the development of additional illness. Low-risk patients may be treated with aspirin alone (grade A, level Ia). The Dutch PATAF study and AFASAK II will further evaluate the effectiveness of aspirin and different intensities of anticoagulant therapy (Laupacis & Albers, 1995).

3.4.2. *Rheumatic heart disease*

INR 2·5 (grade C, level IV)

The risk of stroke is 3 times greater in patients with atrial fibrillation with mitral stenosis than in those without valve disease (Wolf *et al*, 1978). Based on its apparent effectiveness in non-randomized studies and its effect in non-rheumatic atrial fibrillation, warfarin is usually given to maintain an INR of 2·5.

3.4.3. *Congenital heart disease and thyrotoxicosis*

INR 2·5 (grade C, level IV)

The risk of embolic stroke in patients with atrial fibrillation due to these disorders is unknown. Given the benefit in other patients with atrial fibrillation, warfarin is usually given to prevent stroke.

3.4.4. *Cardioversion*

INR 2·5 for 3 weeks before and 4 weeks after cardioversion (grade B, level III)

No randomized study has determined if anticoagulation reduces the risk of systemic embolization when atrial fibrillation is terminated, although non-randomized reports indicate a reduced risk with anticoagulant therapy (grade B, level III) (Bjerkelund & Orning, 1969; Weinberg & Mancini, 1989; Arnold *et al*, 1992). Embolic risk is associated with both electrical and pharmacological termination of atrial fibrillation. Therefore warfarin is typically given for 3 weeks prior to, and 4 weeks after, termination of fibrillation (Laupacis, 1996).

3.5. *Heart valve disease without atrial fibrillation*

Mitral valve prolapse, mitral annular calcification and aortic valve disease in the absence of atrial fibrillation or previous embolic events are associated with a low risk of stroke and are not routine indications for anticoagulant therapy. Rheumatic mitral valve disease is associated with a high risk of stroke even in the absence of atrial fibrillation and is an indication for anticoagulation, INR 2·5 (Levine *et al*, 1992) (grade C, level IV).

3.6. *Mural thrombus*

INR 2·5 for 3 months (grade B, level III)

Patients with mural thrombus after myocardial infarction are at greatest risk of embolization in the first 3 months, especially in the presence of a left ventricular aneurysm. Following initial heparin therapy, warfarin is recommended for 3 months to achieve an INR of 2·5 (Schecter *et al*, 1996) (grade B, level III).

3.7. *Cardiomyopathy*

INR 2.5 (grade C, level IV)

Dilated cardiomyopathy is associated with a 30–50% risk of thrombus formation and a high risk of systemic embolisation (Fuster *et al*, 1981). Prolonged anticoagulant therapy is recommended (Schecter *et al*, 1996) (grade C, level IV).

3.8. *Heart valve prostheses*

3.8.1. *Mechanical prosthetic valves*

INR 3.5 (grade B, level IIa)

The recommended intensity of anticoagulation varies with different consensus statements (British Committee for Standards in Haematology, 1990; Ad Hoc Committee of the Working Group on Valvular Heart Disease European Society of Cardiology, 1993; Stein *et al*, 1995). Recent recommendations for INR ranges of 2·0–3·0 (Ad Hoc Committee of the Working Group on Valvular Heart Disease European Society of Cardiology, 1993) and 2·5–3·5 (Stein *et al*, 1995) are based on prospective randomized studies but these studies have limitations (Turpie, 1996) and none had a group of patients randomized to a range of 2·0–3·0 without additional antiplatelet therapy. An effective relatively low intensity regimen (INR 3·0–4·0) is supported by the latest analysis of a large Dutch study equating actual INRs to events (Cannegieter *et al*, 1995) (grade B, level IIa). This study also indicated the need to allow for the significant number of patients who are inadequately anticoagulated when the target INR is low. There was a clear relationship between event rates and actual INRs with a sharp rise in embolism rates with an INR <2·5 and haemorrhagic rates with an INR >5·0. Actual INRs were lower than the target range 31% of the time, so the target should be above 2·5. A target of 3·5 would maintain the majority of patients >2·5 and <5·0 and therefore maximize efficacy. The position and age of the prosthesis are also factors that determine thrombotic risk.

3.8.2. *Bioprosthetic valves*

Long-term warfarin not required in absence of atrial fibrillation (grade A, level Ib).

Oral anticoagulants are not required for valves in the aortic position in patients in sinus rhythm, although many centres anticoagulate patients for 3–6 months after any tissue valve implant (Turpie, 1996). Patients with

bioprostheses in the mitral position should receive oral anticoagulants to achieve an INR of 2·5 for the first 3 months (Turpie *et al*, 1988) (grade A, level Ib). After 3 months, patients with atrial fibrillation should receive lifelong therapy to achieve an INR of 2·5. Patients with bioprosthetic valves with a history of systemic embolism and those with intracardiac thrombus should also be anticoagulated to achieve an INR of 2·5. Patients who do not require oral anticoagulants after the first 3 months may be considered for antiplatelet therapy, e.g. aspirin (Nunez *et al*, 1984; Stein *et al*, 1992).

3.9. *Ischaemic stroke* (see also 8.2 Stroke as a contraindication to warfarin)

Aspirin should be considered as secondary prophylaxis (grade A, level Ia).

Anticoagulant therapy reduces the risk of stroke in patients with atrial fibrillation (see section 3.4) but it has also been considered for patients without atrial fibrillation who suffer transient ischaemic attacks (TIAs), stroke in evolution and completed stroke.

There have been no randomized double-blind studies to evaluate the effect of oral anticoagulants in patients with TIAs. Several small studies have given insignificant and contrasting results. Given the clear risk reduction with aspirin therapy warfarin should not be given as first-line therapy (del Zoppo, 1994; Hart *et al*, 1996) unless there is a potential cardiac source of embolism. There is no evidence for a beneficial effect of warfarin in patients with carotid artery stenosis.

No recommendation can be given for warfarin for stroke in evolution as appropriately sized randomized trials have not been performed (del Zoppo, 1994; Hart *et al*, 1996).

There is no evidence to support the use of warfarin in completed stroke. In a small randomized study the outcome of patients receiving anticoagulants was worse than those receiving placebo, with more episodes of further stroke and death due to intracerebral haemorrhage (Baker *et al*, 1962). The results of other small studies support the observation that warfarin does more harm than good in patients with stroke (Genton *et al*, 1977; Sherman *et al*, 1992).

If warfarin is given the recommended INR is unknown. Given the effectiveness of low-intensity anticoagulation, INR 2·0–3·0, in patients with atrial fibrillation and other cardiac sources of emboli and the effectiveness of an INR > 3·0 in patients with coronary thrombosis it is reasonable to adopt an INR between 2·0 and 4·0 if patients are to receive warfarin (grade C, level IV). Evidence-based guidelines may be facilitated by results from ongoing trials such as SPIRIT (Stroke Prevention in Reversible Ischaemia Trial, warfarin to INR of 3·0–4·5 versus aspirin 30 mg daily) and WARS (Warfarin-Aspirin Reinfarction Study, warfarin to INR of 1·4–2·8 versus aspirin 325 mg).

3.10. *Retinal vein thrombosis*

The value of anticoagulant therapy in retinal vein thrombosis has not been evaluated. When retinal vein thrombosis complicates the antiphospholipid syndrome anticoagulation is recommended (grade C, level V, see section 3.3).

3.11. *Peripheral arterial thrombosis and grafts*

Aspirin should be considered as secondary prophylaxis (grade A, level Ia).

Uncontrolled surveys suggest that oral anticoagulants may reduce the risk of acute thrombotic arterial occlusion without any effect on the progress of atherosclerosis (Tillgren, 1965; Gallus, 1988). Likewise the effect of anticoagulation following peripheral arterial reconstructive surgery is not established but may be beneficial (Kretschmer *et al*, 1988). Based on the intensity of anticoagulation required to prevent coronary artery thrombosis, an INR of 3·5 is usually recommended if warfarin is given (grade C, level IV). However, these patients have widespread atherosclerosis and treatment with aspirin should be considered as the risk of acute peripheral arterial occlusion, coronary thrombosis and ischaemic stroke are reduced by one third (Antiplatelet Trialists Collaboration, 1994). Large-scale studies comparing anticoagulation with aspirin after bypass surgery are now being conducted (Clagett, 1992).

3.12. *Coronary artery thrombosis* (see also 3.6 Mural thrombus)

Aspirin should be considered as secondary prophylaxis (grade A, level Ia).

Oral anticoagulant therapy to achieve an INR > 2·8 reduces the risk of reinfarction following a first event (Report of the Sixty-Plus Reinfarction Study Research Group, 1980; Smith *et al*, 1990; Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) Research Group, 1994) (level Ib). Earlier meta-analysis had revealed a 20% reduction in mortality with anticoagulant therapy during the immediate post-infarction period (Chalmers *et al*, 1977), but the management of myocardial infarction has changed dramatically with the widespread adoption of thrombolysis and aspirin therapy, and at the moment oral anticoagulation cannot be generally recommended in preference to aspirin except in patients with mural thrombus (Vaitkus & Barnathan, 1993). The effect of warfarin to achieve an INR > 3·0 is not apparently superior to the beneficial effect of aspirin and bleeding rates in anticoagulated patients are higher (The EPSIM Research Group, 1982). All patients at present should receive aspirin at 150 mg daily following coronary thrombosis or the development of angina. Low-dose warfarin (INR 1·5) to reduce factor VII coagulant activity as primary prevention of infarction is being evaluated, but no recommendation can yet be given (Meade *et al*, 1988). A large number of randomized studies combining anticoagulant and antiplatelet therapy are now being conducted (Becker & Ansell, 1996) and further meta-analysis by the Antithrombotic Trialists Collaboration will become available. At the present time if warfarin is given an of INR 3·5 is recommended (grade A, level Ib).

3.13. *Coronary artery graft thrombosis*

Aspirin should be considered as secondary prophylaxis (grade A, level Ib).

Vein graft occlusion occurring in the first month is due to thrombosis. The frequency of thrombosis is 10–20% and this is reduced by aspirin, but warfarin has not been shown to be effective (Van der Meer, J., *et al*, 1993). Late occlusion is due to atherosclerosis with superimposed thrombosis. Although aspirin plus oral anticoagulation may reduce the risk of late occlusion, the value of warfarin alone is not known and anticoagulation is not routinely recommended (Pfisterer *et al*, 1989). If warfarin is given an INR of 3·5 is recommended based on the results of reinfarction studies. A lower intensity of anticoagulation has not been evaluated.

3.14. *Coronary angioplasty and coronary stents*

Aspirin should be considered as first-line therapy (grade A, level Ib).

Both aspirin and heparin reduce the risk of acute occlusion following angioplasty. Oral anticoagulation has not been shown to reduce the incidence of late stenosis (Thorton *et al*, 1984). Coronary stents do not require oral anticoagulation, but aspirin is recommended after angioplasty and stent insertion to prevent coronary and other thrombotic events in this high-risk population.

3.15. *Vena caval filters*

Filters are used to prevent pulmonary emboli in patients in whom anticoagulation is contraindicated or in whom it has failed. The use of anticoagulation in patients with filters must be determined by individual risk–benefit analysis. There are no prospective randomized studies. Vena cava thrombosis can occur in up to 20% of patients, and therefore in the absence of either bleeding or high bleeding risk anticoagulation is justified (Elliott & Eklof, 1996). Contraindications to anticoagulation may resolve after insertion of a filter allowing introduction of warfarin with a target INR of 2·5 at that stage (grade C, level IV).

3.16. *Low-dose warfarin*

Minidose warfarin has been evaluated in gynaecological and orthopaedic surgery. It did reduce the risk of DVT in a small study of patients having gynaecological surgery (Poller *et al*, 1987) but it did not reduce the risk of venous thrombosis in hip replacement surgery (Fordyce *et al*, 1991). A two-step warfarin regimen has been shown to be effective in hip surgery but was not monitored with INR (Francis *et al*, 1983). The effectiveness of fixed minidose warfarin at 1 mg/d to reduce the risk of central venous catheter associated thrombosis is unproven. In a randomized study of 121 patients final analysis was only available for 80 patients. These patients were not representative of the complete group and no recommendation can be given until further studies are completed (Bern *et al*, 1990). A very-low-dose warfarin regimen to keep the INR at 1·3–1·9 has been used to reduce the risk of venous thromboembolism in patients with advanced breast cancer (Levine *et al*, 1994).

Absolute recommendations on the indications, duration and intensity of low-dose warfarin regimens cannot be given at present.

4. COMMENCEMENT OF ORAL ANTICOAGULANT THERAPY

It is important to confirm objectively the diagnosis for which anticoagulant treatment is to be given. However, this should not delay the start of therapy. Where possible, routine blood samples for prothrombin time (PT) and activated partial thromboplastin time (APTT), platelet count and liver function tests should be taken before starting treatment, but the results are rarely needed immediately (McLinley *et al*, 1993). Oral anticoagulation can be commenced on day 1 in conjunction with heparin in most patients with deep venous thrombosis. 5 d of heparin treatment is as effective as a longer period of heparin in patients with venous thromboembolism (grade A, level Ib) (Gallus *et al*, 1986; Rosiello *et al*, 1987; Hull *et al*, 1990; Mohiuddin *et al*, 1992). As the initial period of treatment with warfarin may be associated with a procoagulant state due to a rapid reduction in protein C levels, it is recommended that patients receive heparin therapy for at least 4 d and it should not be discontinued until the INR has been in the therapeutic range for 2 consecutive days (Ginsberg, 1996) (grade C, level IV). In patients with large thromboses a longer period of heparin up to 10 d may be administered (Hull *et al*, 1990; Mohiuddin *et al*, 1992). A standard protocol for the commencement of anticoagulant treatment is recommended (grade B, level IIb) (Fennerty *et al*, 1984) (Appendix II).

A specific anticoagulant treatment chart is recommended for in-patient anticoagulation which contains the treatment protocol, the results of coagulation tests (INR and APTT ratios) and the prescribed doses based on these results. This chart can then form the basis of the anticoagulant referral form for out-patient follow-up. A standard chart is being prepared by the task force.

Modifications to the oral anticoagulant loading dose may be necessary if base-line coagulation results are abnormal. Some patients may be particularly sensitive to warfarin. These include the elderly and those with high-risk factors such as congestive cardiac failure and liver disease or those on drug therapy known to potentiate oral anticoagulants. A loading dose of < 10 mg daily is recommended under these circumstances.

For rapid anticoagulation with warfarin, daily INR measurement for a minimum of 4 d is recommended (Appendix II). Having achieved an INR in the desired therapeutic range, the INR should continue to be monitored weekly until control is stable. Thereafter the frequency of recall can be extended. Extension of recall up to 12 weeks is acceptable. In the outpatient setting or the community when rapid anticoagulation is not required, loading doses of < 10 mg daily are recommended. A slow induction of anticoagulation with warfarin can be achieved by starting at a dose of 2 mg daily

and increasing this slowly until the target INR is achieved (grade C, level IV).

It is important that discharge arrangements for anticoagulant follow-up are detailed in the hospital notes and that patients receive the yellow Department of Health anticoagulant booklets (obtained from DHSS Stores, No. 2 Site, Manchester Road, Heywood, Lancashire OL10 2PZ, or SHHD (Div. IIID), Room 9, St Andrews House, Edinburgh EH1 3DE). At discharge an appointment should be made for further INR measurement (this should not normally exceed 7 d). Responsibility for the discharge arrangements lies with the clinician referring the patient.

4.1. *Thrombophilia*

Patients with protein C deficiency are at risk of developing skin necrosis during commencement of oral anticoagulation. Introduction of warfarin therapy should proceed without a loading dose of warfarin even when heparin is given. Patients with protein S deficiency may also be at risk. Skin necrosis has not yet been reported in patients with resistance to activated protein C. It would be prudent to introduce anticoagulation with warfarin slowly in all patients and to withdraw warfarin slowly at the end of treatment (grade C, level IV).

5. MANAGING ANTICOAGULATION IN THE PERI-OPERATIVE PERIOD

Stop anticoagulation or perform surgery with the INR < 2·5. If there is a risk of dangerous bleeding, e.g. internal, then stop anticoagulation at least 3 d before surgery or reverse anticoagulation with low-dose vitamin K (see section 6) (grade B, level III).

The short-term risk of thromboembolism in patients with mechanical heart valves when not anticoagulated is very small. Therefore these patients should be managed in the same way (grade B, level IIb).

In rare circumstances where it is necessary to continue anticoagulation, e.g. life-threatening thromboembolism in patients with adenocarcinoma, then reduce INR to < 2·5 and start heparin (see heparin guidelines (British Committee for Standards in Haematology, 1993b)) (grade C, level IV).

For minor surgical procedures the oral anticoagulant dose should be stopped or adjusted to achieve a target INR of approximately 2·0 on the day of surgery (Taberner *et al*, 1978; Francis *et al*, 1983) (grade B, level III). The INR should be checked pre-operatively and if < 2·5 the patient can proceed to surgery. If the INR is > 2·5 the surgeon and haematologist must decide if the level of anticoagulation is safe for surgery to take place.

Prevention of bleeding with oral tranexamic acid mouthwash (4·8%) can be achieved after dental extraction without dose modification of oral anticoagulants (Ramstrom *et al*, 1993) (grade A, level Ib).

For major surgery, oral anticoagulants should be stopped at least 3 d prior to surgery, and depending on the thrombotic risk of the condition for which the patient is receiving anticoagulant therapy, the INR can be monitored and if necessary heparin instituted once the INR is below the lower limit of the therapeutic range (e.g. < 2·0 for a target of 2·5) (grade C). After warfarin is stopped it typically takes about 4 d for the INR to reach 1·5 (White *et al*, 1995). The threshold for institution of heparin and the dose required will depend on the underlying condition, e.g. secondary prevention of venous thrombosis is low risk after the first month of anticoagulation and warfarin could be replaced with low-dose subcutaneous heparin preoperatively. A caged-ball metal mitral valve prosthesis is relatively high risk and warfarin might be replaced with a continuous infusion of heparin once the INR is < 3·0. There is, of course, a risk of bleeding associated with heparin during surgery, and some experts consider that the risk of heparin is greater than the risk of stopping anticoagulation for 4 d before surgery and restarting as soon as possible after surgery in patients with mechanical heart valves (Kearon & Hirsh, 1997) (and see below).

The timing for reinstitution of oral anticoagulants will depend on the risk of post-operative haemorrhage. The 48–72 h delay for achievement of anticoagulation with oral vitamin K antagonists will also influence this decision. In many instances oral anticoagulants can be started again as soon as the patient has an oral intake.

Certain types of surgery, such as neurosurgery, are particularly high risk for bleeding complications, and a period without any anticoagulant is preferable (Cannegieter *et al*, 1994) (grade B). Anticoagulant therapy in patients with metal heart valve prostheses can be temporarily discontinued. A meta-analysis of studies covering a period of 53 647 patient-years indicated that the risk of all thromboembolic events when not on oral anticoagulant therapy was only 8 per hundred patient-years. This equates to a risk of < 0·2% over a 7 d period (Cannegieter *et al*, 1994). However, this study did not specifically address the peri-operative period when the risk may be higher due to the prothrombotic state associated with surgery. In a retrospective analysis of 180 non-cardiac operations in 159 patients with valve prostheses (170 Starr-Edwards, 59 mitral and 108 aortic), 153 operations were performed > 12 months after valve replacement. In 62% of patients anticoagulation was discontinued 1–3 d before surgery and in 23% more than 3 d before. Anticoagulation was resumed 1–3 d later in 60% and after 4 d in 24%. Total peri-operative cessation averaged 6·6 d. No post-operative thromboembolic events occurred in relation to the surgical procedure (level III) (Tinker & Tarhan, 1978). In another study in which patients with metal prostheses underwent non-cardiac surgery with cessation of oral anticoagulation, two of 10 procedures in patients with mitral prostheses were complicated by peri-operative thromboembolism compared with 0 of 25 procedures in patients with aortic prostheses (level III) (Kathol *et al*, 1976).

6. MANAGING BLEEDING AND EXCESSIVE ANTICOAGULATION

Bleeding while on oral anticoagulants increases significantly with INR results > 5·0 (Eckman *et al*, 1993; Cannegieter *et al*, 1995). Therapeutic decisions are dependent on the INR and

Table II. Recommendations for management of bleeding and excessive anticoagulation.

3·0 < INR < 6·0 (target INR 2·5) 4·0 < INR < 6·0 (target INR 3·5)	(1) reduce warfarin dose or stop (2) restart warfarin when INR < 5·0	
6·0 < INR < 8·0, no bleeding or minor bleeding	(1) stop warfarin (2) restart when INR < 5·0	
INR > 8·0, no bleeding or minor bleeding	(1) stop warfarin (2) restart warfarin when INR < 5·0 (3) if other risk factors for bleeding give 0·5–2·5 mg of vitamin K (oral)	Level III, grade B
Major bleeding	(1) stop warfarin (2) give prothrombin complex concentrate 50 units/kg or FFP 15 ml/kg (3) give 5 mg of vitamin (oral or i.v.)	Level III, grade B

whether there is minor or major bleeding. The dose of vitamin K used to reverse over-anticoagulation depends on the INR (Shetty *et al*, 1992). Recommendations for management are given in Table II.

INR > 8.0, no bleeding or minor bleeding.

Stop oral anticoagulants. If no other risk factors for haemorrhage stop treatment until INR < 5.0. If risk factors for haemorrhage or minor bleeding (e.g. age > 70 years, previous bleeding complications, epistaxis) give vitamin K. Due to near complete absorption, oral vitamin K is as effective as intravenous with the delay in action hardly influenced by the absorption time. However, only 0·5 mg is required to reduce the INR from > 5·0 to a target level of 2·0–3·0 (Shetty *et al*, 1992). Vitamin K tablets usually contain > 5 mg which will completely reverse anticoagulation. Therefore, when partial correction is required it may be necessary to give intravenous vitamin K or alternatively give the intravenous preparation orally. Allergic reactions following intravenous administration are rare with new preparations of vitamin K. If the INR is still too high at 24 h the dose of vitamin K can be repeated.

Major bleeding.

Resuscitate and transfer to hospital for reversal of anticoagulation with vitamin K and prothrombin complex concentrates (PCC) or fresh frozen plasma. Anticoagulation can be effectively reversed with 50 units/kg prothrombin complex concentrate, PCC (factors II, VII, IX and X or factor II, IX and X concentrate and factor VII concentrate) (Makris *et al*, 1996) and vitamin K 5 mg by slow intravenous injection (grade B, level III). However, patients receiving warfarin may have an underlying hypercoagulable state and infusion of prothrombin complex concentrate may exacerbate this. Further studies are required to determine the minimum dose of concentrate required to restore thrombin generation to normal and the safety of concentrates used for this purpose. In the absence of available concentrate licensed for this use emergency, treatment with 15 ml/kg of FFP and intravenous vitamin K 5 mg will partially reverse anticoagulation, though the levels of individual factors will typically remain < 20% (Makris *et al*, 1996) and larger doses should be given if possible.

For patients with prosthetic heart valves, full reversal of oral anticoagulants with vitamin K may result in prolonged oral anticoagulant resistance and the possibility of valve thrombosis and thromboemboli. The degree of reversal must therefore be decided on an individual basis. All patients with bleeding should be evaluated to identify if there is a local anatomical reason for bleeding.

Bleeding may occur when patients are not over-anticoagulated. In these circumstances it may still be necessary to reverse anticoagulation and identify the cause of bleeding.

7. DRUG INTERACTIONS

If the drug change lasts < 5 d either no change, minor dose reduction or omit one complete dose of warfarin if known potentiating drug given (grade C, level IV). If the drug change lasts > 5 d check INR after start of new drug and adjust warfarin dose on basis of result (grade C, level IV).

Almost any drug can interact with oral anticoagulants, the majority potentiating the anticoagulant effect (notable exceptions which reduce the effect are anti-epileptics, barbiturates, sucralfate, Rowachol, rifampicin). For further details see relevant appendix in the current British National Formulary. When prescribing, a non-interacting drug should be chosen when possible.

For short courses of new drug therapy, oral anticoagulant dose adjustment is not essential but a slight dose reduction or omission of one dose could be recommended if a known potentiator is prescribed (grade C). If medication is for > 5 d the INR should be checked 1 week after commencement and the oral anticoagulant dose adjusted accordingly, returning to the normal maintenance dose after stopping the new drug.

8. CONTRAINDICATIONS TO ANTICOAGULATION

These are seldom absolute. The risk of haemorrhage is multifactorial, though increasing age is often found to be associated with an increased risk of major bleeding (Landefeld *et al*, 1989; Fihn *et al*, 1993; van der Meer, F., *et al*, 1993; Hylek & Singer, 1994; Stroke Prevention in Atrial Fibrillation Investigators, 1994; Palareti *et al*, 1996). The following situations deserve specific mention.

8.1. *Pregnancy*

Organogenesis occurs during the 6th to 12th weeks of gestation and exposure to warfarin at this time may be associated with embryopathy (Hall *et al*, 1980; Iturbe-Alessio *et al*, 1986; Wong *et al*, 1993). However, due to immaturity of the

fetal liver there is a continuing risk of fetal bleeding throughout pregnancy. Avoiding oral anticoagulants reduces the risk of embryopathy, but heparin can cause maternal osteoporosis and thrombocytopenia. Furthermore, heparin may not be as effective during pregnancy in preventing thromboembolic events in patients with mechanical valves (Sbarouni & Oakley, 1994). Patients receiving warfarin should be told of the risk before conception and advised to have early pregnancy tests to detect pregnancy before 6 weeks gestation. The possible need for alternative treatment with heparin in the first trimester and for 2–3 weeks before delivery (British Committee for Standards in Haematology, 1993a; Ginsberg & Barron, 1994) should be explained in advance (British Committee for Standards in Haematology, 1993a) Guidelines on management of anticoagulant therapy in pregnancy have been published (British Committee for Standards in Haematology, 1993a).

8.2. *Stroke*

Haemorrhagic stroke is a contraindication to oral anticoagulant therapy (Lowe, 1996). In patients with ischaemic strokes anticoagulation increases the risk of secondary haemorrhage into the infarcted brain. In patients with atrial fibrillation long-term warfarin therapy is beneficial, but the risk of early recurrent embolism is low and initial heparin is not required. Start warfarin 48 h to 14 d after ischaemic stroke without initial heparin therapy dependent on size of infarct and blood pressure. In patients with large embolic strokes or uncontrolled hypertension anticoagulation should be postponed for 14 d. Patients with small- to moderate-sized ischaemic strokes without evidence of haemorrhage on CT scanning 48 h after the onset of the event can be anticoagulated without delay.

9. ORGANIZATION

Responsibility for ensuring a safe anticoagulant service and organizational procedures should be documented. The level of personnel involved in an anticoagulant service will be determined by local circumstances. Increasingly pharmacists, nurses, clinical scientists and technologists are involved in providing anticoagulant care. With the development of local guidelines and computer decision support systems some duties may be devolved at the discretion of the local hospital or Trust. The following organizational issues are recommended.

A lead clinician should be nominated who should be in charge of the anticoagulant service. Responsibilities are outlined in Table III.

Where non-medical personnel are involved in anticoagulant care they should have a strong clinical background with appropriate clinical qualifications, e.g. nurse practitioner, senior pharmacist. Recommendations regarding non-medical personnel are listed in Table IV.

The devolvement of anticoagulant services away from a hospital setting, using a postal service for collection of samples and return of dosage recommendations, has been practised for many years in some areas. Particular care is needed, however, to ensure patients can be quickly contacted regarding any change of dose. It is essential that patients managed in this way know how to report any complications of treatment and how to get urgent clinical advice. A system using trained staff to provide a peripatetic service to the home or general practice maintains a direct route for good communication with the patient. All previous patient results should be readily accessible with full documentation of the clinical condition and duration of treatment before further instructions are given. Records should be regularly audited.

Table III. Responsibilities of lead clinician for anticoagulant service.

1. Receive referrals and approve need for anticoagulation
2. Give advice on duration and intensity of anticoagulation
3. Ensure system is in place for patients to receive urgent medical advice relating to anticoagulation
4. Ensure participation in national laboratory quality assurance scheme and monitor performance
5. Ensure regular clinical audit
6. Ensure anticoagulant guidelines are available, including the management of over-anticoagulation
7. Provide general practitioners involved in anticoagulant care with advice and guidelines
8. Approve computer assisted management programmes prior to implementation
9. Ensure adequate training is available for all personnel
10. Provide written approval for personnel, detailing levels of responsibility

Table IV. Recommendations for non-medical personnel involved in anticoagulant service.

1. Personnel should be responsible to the lead clinician organizing the anticoagulant service
2. Personnel should have received adequate training and should be approved prior to commencement of duties
3. Dose recommendations and recall should be made according to written protocols or computer assisted guidelines
4. Recommendations should be available for review by the clinician
5. The clinician should be alerted to patients with an INR > 8 and those with bleeding problems
6. Personnel should provide patient education regarding anticoagulant therapy

10. COMPUTER SUPPORT SYSTEMS

The computerization of anticoagulant management offers practical benefits to the laboratory and clinical staff, with standardization and continuity of recommendations. The standardization of anticoagulant control according to previous BCSH guidelines has been achieved using computer programs (Ryan *et al*, 1989; Hunt, 1993). Table V indicates facilities for inclusion when considering implementing a computer system.

Organizational advantages may include automatic generation of clinic lists, transport lists and letters to GPs/colleagues regarding commencement and discontinuation of treatment.

Table V. Recommendations for implementation of computer-assisted anticoagulation.

1. Rapid retrieval of data to screen or printer
2. Data storage in chronological order
3. Dosage recommendations according to algorithm or guidelines approved by consultant in charge of the service; this should include evaluation of results over the full range of INR results
4. An alerting system for patient results which fall outside defined criteria
5. A facility to over-ride computer recommendations
6. Patient recall for testing according to agreed criteria based on previous stability with invalid date alerts
7. An alerting system for non-attendees
8. An alerting system for discontinuation of treatment
9. A prompt system to check for bleeding problems when high INR values are obtained
10. A system to record bleeding/thrombotic events or other rare side-effects
11. A facility to audit results

A database of drug interactions with warfarin is an additional helpful facility.

11. CLINICAL AUDIT

Routine audit of clinic management with review of over-anticoagulated patients should be an integral part of the anticoagulant service. Review of patient outcome of INR values >8 (Philips *et al*, 1993), or patients requiring therapeutic interventions to reverse anticoagulant effect, are useful criteria for audit. Potential outcomes of audit may include better use of consultant time, reduction of in-patient stay to achieve stable anticoagulation, reduction in surgery-related thromboembolic problems, reduction in near-miss events and potential litigation problems. Table VI indicates some standards for audit.

Table VI. Standards for audit.

1. Provision of adequate data for safe transfer of anticoagulant follow-up
2. Provision of anticoagulant cards for patients on hospital discharge
3. Patient information: awareness of need for anticoagulation and possible side-effects of treatment
4. Hospital notes contain information that the patient is currently on warfarin
5. The use of heparin/warfarin dosage schedules in hospital setting (see Appendix II)
6. Follow-up arrangements for patients failing to attend appointments
7. Achievement of target INR: 50% of INRs within 0·5 INR units and 80% within 0·75 INR units of target

12. LABORATORY CONTROL

The INR system is used to standardize variability of response of different thromboplastin reagents to warfarin (WHO Expert Committee on Biological Standardisation, 1983). The INR is calculated from the prothrombin time ratio of test plasma to the geometric mean normal prothrombin time (GMNPT), to the power of the international sensitivity index (ISI) of the thromboplastin.

$$\mathbf{INR = (patient\ PT/GMNPT)^{ISI}}$$

Two important sources of variability remain in the INR calculation: the measurement of the GMNPT and the ISI determination of the thromboplastin reagent (Taberner *et al*, 1989; Peters *et al*, 1991). The GMNPT should be derived from the geometric mean of 20 healthy adult plasma samples, or the use of validated lyophilized normal control plasma. Low ISI thromboplastins are recommended for monitoring oral anticoagulant therapy (Moriarty *et al*, 1988). Local estimation of ISI values is not recommended, and ISI values of each thromboplastin batch should be assigned by manufacturers by comparison with an international standard. Unfortunately there remains a problem partly due to the source of reference material (human or non-human) used in the calibration. Furthermore, problems with coagulometers producing shorter PT times than manual methods are well recognized (Poller *et al*, 1989). Local calibration of coagulometers can be achieved by using plasma calibrants with manually certified PT values (Poller *et al*, 1995). Participation in a CPA (Clinical Pathology Accreditation) accredited External Quality Assurance Scheme for anticoagulation is essential for monitoring laboratory performance (Preston, 1995). Participants are encouraged to discuss technical problems with the EQAS co-ordinators.

There is no clinically significant change in INR when analysis is delayed for up to 3 d. Off-site blood sampling can accommodate a large increase in patient workload without a major revenue increase in primary care and with continued total quality management and central expert advice (Baglin & Luddington, 1997).

13. NEAR-PATIENT TESTING

There are now several near-patient testing systems available for monitoring oral anticoagulant control (Machin *et al*, 1996). These have generally shown a good correlation with manual and automated methods. The advantages include a rapid result without centrifugation of samples, using portable equipment easy to use by non-scientific staff. The monitoring of quality control may be more difficult due to lack of appropriate quality control material. Furthermore, the ISI values of some reagents incorporated in the disposable cards are higher than recommended. When near patient testing is to be used it is recommended that this is established in conjunction with local pathology services, in order to overview quality control (British Committee for Standards in Haematology, 1995).

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Keywords: anticoagulation, warfarin, INR, guidelines, thrombosis.

Appendix I. Graded recommendations.

Grade of recommendation

A (Evidence levels Ia, Ib)	Requires at least one randomized controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation
B (Evidence levels IIa, IIb, III)	Requires availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommendation
C (Evidence level IV)	Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities; indicates absence of directly applicable studies of good quality

Levels of evidence

Ia. Meta-analysis of randomized controlled trials
Ib. At least one randomized controlled trial
IIa. At least one well-designed controlled study without randomisation
IIb. At least one other type of well-designed quasi-experimental study
III. Well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case–control studies
IV. Expert committee reports or opinions and/or clinical experience of respected authorities

Appendix II. Warfarin loading schedule.

Day	INR	Warfarin dose (mg)
First	< 1·4	10
Second	< 1·8	10
	1·8	1
	> 1·8	0·5
Third	< 2·0	10
	2·0–2·1	5
	2·2–2·3	4·5
	2·4–2·5	4
	2·6–2·7	3·5
	2·8–2·9	3
	3·0–3·1	2·5
	3·2–3·3	2
	3·4	1·5
	3·5	1
	3·6–4·0	0·5
	> 4·0	0
		(Predicted maintenance dose)
Fourth	< 1·4	> 8
	1·4	8
	1·5	7·5
	1·6–1·7	7
	1·8	6·5
	1·9	6
	2·0–2·1	5·5
	2·2–2·3	5
	2·4–2·6	4·5
	2·7–3·0	4
	3·1–3·5	3·5
	3·6–4·0	3
	4·1–4·5	Miss out next day's dose then give 2 mg
	> 4·5	Miss out 2 d doses then give 1 mg