bjh guideline

# Guidelines on oral anticoagulation (warfarin): third edition – 2005 update

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**Keywords:** warfarin, oral anticoagulation, guideline, vitamin K antagonists.

The British Committee for Standards in Haematology (BCSH) published its third edition of Guidelines on Oral Anticoagulation in 1998 (British Committee for Standards in Haematology, 1998). Most of the recommendations made in 1998 remain unchanged and a fourth edition of the guideline is considered unnecessary at the time of writing (June 2005). However, we draw attention to those areas where new informative data have been published. As in the original guideline, the term 'oral anticoagulant' used in this update refers to oral vitamin K antagonists (VKA), such as warfarin. New oral non-VKA are currently being evaluated in clinical trials but are not yet licensed for use in the UK. When these drugs become available new guidance will be issued specifically for the use of those drugs.

The guideline group was selected to be representative of UK-based medical experts. The drafting group met and communicated by email. MEDLINE was searched systematically for publications in English from 1998. The writing group convenor (T. Baglin) produced the draft guidelines which were subsequently revised by consensus. The guideline was reviewed by a multidisciplinary sounding board, the BCSH and the British Society for Haematology (BSH) and comments incorporated where appropriate. Criteria used to quote levels and grades of evidence are as in Appendix 3 of the Procedure for Guidelines Commissioned by the BCSH (http://www.bcsh-guidelines.com/process1.asp#App3).

The target audience for this guideline is healthcare professionals involved in the management of patients receiving oral anticoagulant therapy.

## Guideline update

The original paragraph numbering and format used in the 1998 guideline has been retained for ease of comparison. The original Table I was modified (Table I).

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## 3. Indications for anticoagulation

### 3.1. Venous thromboembolism

Treatment with oral VKA remains the treatment for choice for the majority of patients with venous thromboembolism (VTE) (van der Heijden *et al*, 2001). A specific exceptional patient group in which low-molecular-weight heparin therapy may be advantageous is patients with VTE complicating cancer (Meyer *et al*, 2002; Lee *et al*, 2003) (see section 3.b).

*Intensity of anticoagulation* The Prevention of Recurrent Venous Thromboembolism (PREVENT) trial randomised patients to continue anticoagulation with a reduced target international normalised ratio (INR) of 1·5–2·0 or to take placebo, following an initial period of oral anticoagulation (Ridker *et al*, 2003). The median duration of treatment before randomisation was 6·5 months. Recurrent VTE occurred in the low-intensity warfarin-treated patients at a rate of 2·6/100 patient-years and in patients receiving placebo at a rate of 7·2/100 patient-years [hazard ratio (HR) 0·36, 95% confidence interval (CI) 0·19–0·67]. Bleeding rates were not significantly different but the study was not powered to test for differences in bleeding rates.

The Extended Low-intensity Anticoagulation for Thrombo-Embolism (ELATE) investigators randomised patients who had been treated with a target INR of 2·5 for at least 3 months to continue anticoagulation with a reduced target INR of 1·5–1·9 or continue treatment with a target of 2·5 (Kearon *et al*, 2003). Recurrent VTE occurred in the low-intensity warfarin-treated patients at a rate of 1·9/100 patient-years and in patients receiving conventional treatment with a target INR of 2·5 at a rate of 0·7/100 patient-years (HR 2·8, 95% CI 1·1–7·0). Bleeding rates were not significantly different but the bleeding rate in patients on conventional intensity (0·9/100 patient-years) was lower than the anticipated rate that was used to power the study (3/100 patient-years).

When comparing thrombosis rates in the trials it is evident that there is a dose–response effect. Combining PREVENT and ELATE the cumulative thrombosis rate at 4 years was 2·5% with a target of 2·5, 7·5% with a target INR range of 1·5–1·9/2·0

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**Table I.** Indications for oral anticoagulation, target international normalised ratio (INR) and grade of recommendations.

| 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 | A |
| Antiphospholipid syndrome | 2·5 | A |
| Non-rheumatic atrial fibrillation | 2·5 | A |
| Atrial fibrillation due to rheumatic heart disease, congenital heart disease and thyrotoxicosis | 2·5 | C |
| Cardioversion | 2·5 or 3·0 (see text) | B |
| Mural thrombus | 2·5 | B |
| Cardiomyopathy | 2·5 | C |
| Mechanical prosthetic heart valve – aortic | 3·0 or 2·5 (see Table II) | B |
| Mechanical prosthetic heart valve – mitral | 3·5 or 3·0 (see Table II) | B |
| Bioprosthetic valve | 2·5 if anticoagulated (see original 1998 guideline) | |
| Ischaemic stroke without atrial fibrillation | Not indicated | C |
| Retinal vessel occlusion | Not indicated | C |
| Peripheral arterial thrombosis | Not indicated | A |
| Arterial grafts | 2·5 if anticoagulated (see text) | |
| Coronary artery thrombosis | 2·5 if anticoagulated (see text) | |
| Coronary artery graft | Not indicated | A |
| Coronary angloplasty and stents | Not indicated | A |

and 20% without warfarin (Ridker, 2004). Therefore a target INR of 2·5 is the most effective. As there was no difference in bleeding between targets of 2·5 and 1·75 (target range 1·5–1·9/2·0) a target INR of 2·5 should remain the default target for patients requiring long-term oral anticoagulation for prevention of VTE.

It has been suggested that the findings do give some support for a lower intensity of therapy in patients at very high risk of bleeding (Ridker, 2004). It is possible that in high bleeding-risk patients, the bleeding rates would be different for a target of 2·5 and 1·75. Patients can be stratified for bleeding risk, for example prospectively with the Outpatient Bleeding Risk Index (Landefield & Beyth, 1993) or following a period of observation on treatment. On an exceptional basis, a target INR of 1·75 might be adopted for those patients at risk of recurrent VTE but who have a very high risk of bleeding that might ordinarily result in treatment being stopped (grade C, level IV). Such patients might be those who have already suffered a major bleed and in whom the risks for bleeding have not altered or those patients with repeated episodes of overanticoagulation, for example an INR greater than 8 requiring reversal with vitamin K or coagulation factor replacement on more than one occasion.

*Recommendation*

**A target INR of 2·5 is recommended for long-term oral anticoagulant (VKA) therapy for secondary prevention of VTE (grade A, level 1b).**

*Duration of anticoagulation*

A meta-analysis of long *versus* short duration anticoagulant therapy after a first episode of VTE indicated a relative risk of recurrence of 0·6 (95% CI 0·45 to 0·79) for a duration treatment of 3 months or greater compared to 6 weeks or less (Pinede *et al*, 2000).

Two recently published trials present data that may influence decisions regarding duration of oral anticoagulation after an episode of VTE.

The Short term Oral anticoagulation for a First Acute Secondary Thrombosis (SOFAST) investigators assessed duration of anticoagulation following a first episode of deep vein thrombosis (DVT) or pulmonary embolus (PE) provoked by a transient risk factor in a double-blind study in which patients who had completed 1 month of anticoagulant therapy were randomly assigned to continue warfarin or placebo for an additional 2 months (Kearon *et al*, 2004). The aim was to determine if the duration of treatment could be reduced



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without an increase in the rate of recurrent VTE during 11 months of follow-up. Recurrence rates were not significantly different, 6·0% with placebo and 3·7% with warfarin ($P = 0·5$). There were no major bleeds in either group. A meta-analysis of four other studies combined with the SOFAST study was also performed; in combination, the results of the five studies suggested that shortening the duration of anticoagulant therapy to 4 or 6 weeks more than doubled the frequency of recurrent VTE within a year of diagnosis (odds ratio 2·9, 95% CI 1·2–6·9). The authors' conclusion was that duration of anticoagulant therapy for VTE provoked by a transient risk factor should not be reduced from 3 months to 1 month.

The Durée Optimale du Traitement AntiVitamines K (DOTAVK) study was an open-label, randomised trial comparing 3 with 6 months anticoagulation after proximal deep vein thrombosis (DVT) and comparing 6 weeks with 3 months after calf vein thrombosis (Pinede *et al*, 2001). Recurrence rates and bleeding rates were not different in patients receiving short-duration as compared to long-duration therapy. Equivalence was observed in both intention-to-treat and per-protocol analyses. Recurrence rates were lower in patients with temporary, as compared with permanent, risk factors but duration of therapy did not influence recurrence rates in either group. The authors, who also performed the meta-analysis quoted above (Pinede *et al*, 2000), concluded that 3 months of treatment may be sufficient for patients with temporary risk factors and a low risk of recurrence.

*Recommendation*

**Anticoagulation for 1 month is inadequate treatment after an episode of VTE (grade A, level 1b). At least 6 weeks anticoagulation is recommended after calf vein thrombosis (grade A, level 1b) and at least 3 months after proximal DVT or PE (grade A, level 1b). For patients with temporary risk factors and a low risk of recurrence 3 months of treatment may be sufficient. For patients with idiopathic VTE or permanent risk factors at least 6 months anticoagulation is recommended.**

### *3.3. Heritable thrombophilia*

Several studies have now been reported in which patients have been randomised to different durations of anticoagulation. In theses studies recurrence rates whilst on anticoagulant treatment with a target INR of 2·5 have been similar in patients with and without heritable thrombophilic defects (level II). Similarly, recurrence rates in studies investigating the influence of thrombophilia testing on recurrence of VTE have demonstrated low rates of recurrence whilst on treatment with a target INR of 2·5 in patients with and without heritable thrombophilia (level II). The duration of anticoagulation was not influenced by the presence of laboratory evidence of thrombophilia in most cases (British Committee for Standards in Haematology, 2001). Extended duration of anticoagulation for patients considered to be at excessive risk of recurrent VTE will generally be based on clinical criteria, such as recurrent idiopathic events and family history. Such decisions will generally be the same for patients with and without identifiable heritable defects.

### *3.3. Antiphospholipid syndrome*

Two randomised trials have compared a target INR of 2·5 (range 2·0–3·0) to a target greater than 3·0 [range 3·1–4·0 (Crowther *et al*, 2003) or 3·0–4·5 (Finazzi *et al*, 2005)]. Odds ratios for recurrent thrombosis in the high intensity compared to low-intensity groups were 3·1 (95% CI 0·6–15·0) (Crowther *et al*, 2003) and 1·97 (95% CI 0·49–7·89) (Finazzi *et al*, 2005). Major bleeding rates were not different. Based on these studies both groups of authors concluded that a target INR of 2·5 was sufficient for treatment of patients with thrombosis in association with antiphospholipid syndrome. Both studies included patients with either venous or arterial thrombosis but the majority had venous thrombosis. Therefore a target of 2·5 is recommended for patients with VTE. There are insufficient data to make an evidence-based recommendation for patients with antiphospholipid syndrome and arterial thrombosis but a higher target of 3·5 is often used and is reasonable as long as the bleeding risk at the higher intensity of anticoagulation is taken into consideration. A target of 3·5 is also recommended for patients who suffer recurrence of VTE whilst on warfarin with an INR between 2·0 and 3·0.

*Recommendation*

**A target INR of 2·5 is recommended for patients with DVT or PE associated with antiphospholipid syndrome (grade A, level Ib).**

*Intravenous drug users*

The management of iliofemoral venous thrombosis in injecting drug users is problematic because of poor venous access, non-compliance with prescribed treatment, ongoing intravenous drug use and co-existent sepsis. It is unlikely that a randomised trial of treatment with warfarin *versus* low molecular weight heparin (LMWH) alone would be practical in this patient group. Because of the great variation in response to warfarin between and within patients it is not appropriate to use oral VKA when monitoring of the patient is not possible or probable for whatever reason. There are retrospective data suggesting that treatment with LMWH alone results in a satisfactory clinical outcome (Mackenzie *et al*, 2000).

*Recommendation*

**Treatment with LMWH is an alternative to oral anticoagulation in patients with VTE secondary to intravenous drug use (grade C, level IV).**

### *3.4.4. Cardioversion*

British Committee for Standards in Haematology (1998) recommended a target INR of 2·5 for patients awaiting

cardioversion (grade C). This recommendation was based on extrapolation of the efficacy of a target INR of 2·5 in patients with non-rheumatic atrial fibrillation. A recent study confirmed the need for anticoagulation in patients awaiting cardioversion (Gallagher *et al*, 2002). No thromboembolic events occurred in 779 cardioversion attempts when the INR was 2·5 or greater before cardioversion, nine events occurred in 756 cardioversion attempts when the INR was less than 2·5 (seven patients) or not measured (two patients). The authors concluded that the INR should be 2·5 or greater at the time of cardioversion. A commentary accompanying the Gallagher publication recommended that this study alone was insufficient evidence to change practice (Olshansky, 2002). In this commentary, Olshanky presented data from his own unit, showing a very low risk of events (0/532) when the INR was greater than 2·0 for three consecutive weeks prior to cardioversion.

Increasing the target INR to 3·0 might reduce the stroke rate slightly and it is unlikely that this benefit would be offset by an increased incidence of bleeding over a short period of time. In the UK it is common practice to measure the INR on the day of the cardioversion and postpone the procedure if it is less than 2·0. This results in cancellation of as many as 25% of procedures. The main benefit of adopting a higher target INR, for example 3·0, would be the avoidance of a cancellation due to an INR <2·0 on the day of the procedure. Already, some centres adopt a target INR of 3·0 for the 4 weeks prior to the procedure and a target INR of 2·5 afterwards. We consider such an approach relatively safe and useful (grade C recommendation) although we can make no absolute recommendation that it should be adopted.

*Recommendation*

**A target INR of 2·5 is recommended for 3 weeks before and 4 weeks after cardioversion (grade B, level III). To minimise cardioversion cancellations due to low INRs on the day of the procedure a higher target INR, e.g. 3·0, can be used prior to the procedure.**

### 3.8. Heart valve prostheses

The frequency of thromboembolism is lower with modern valves than first generation valves but oral anticoagulation with VKA is still required. As the intensity of anticoagulation is a major determinant of bleeding risk the Seventh American College of Chest Physicians (ACCP) Conference on Antithrombotic and Thrombolytic Therapy refined the recommended target INRs for patients with modern mechanical prothestic heart valves (Salem *et al*, 2004). It is recognised that prospective studies are still needed to determine risk factors among patients with each type and location of valve, the level of anticoagulation actually achieved and the level of anticoagulation at which complications occur. Nevertheless, there is now sufficient level II evidence from which to make grade B recommendations for valve-location-specific target INRs when information on valve type and location are known (Table II).

**Table II.** Recommendations for valve-location-specific target international normalised ratios (INRs).

| Valve type | Position | Target INR |
|---|---|---|
| Bileaflet | Aortic | 2·5 |
| Tilting disk | Aortic | 3·0 |
| Bileaflet | Mitral | 3·0 |
| Tilting disk | Mitral | 3·0 |
| Caged ball or caged disk | Aortic or mitral | 3·5 |

There is limited information on caged ball or caged disk valves and so a target INR of 3·5 is still recommended. It is accepted that bleeding complications or problems with overanticoagulation may necessitate a reduction in target INR to 3·0, or even lower, in some of these patients. Few such valves are now being inserted and so this problem is self-limiting. If sufficient information is not available then a generic target INR of 3·0 is recommended for valves in the aortic position and 3·5 in the mitral position.

*Recommendation*

**For patients in whom valve type and location are known specific target INRs are recommended (Table II). Otherwise a target INR of 3·0 is recommended for valves in the aortic position and 3·5 in the mitral position.**

### 3.11. Peripheral arterial thrombosis and grafts

Patients requiring infrainguinal vein bypass grafting who had risk factors for graft failure were randomised to receive aspirin (325 mg/d) or aspirin plus warfarin to a target INR of 2·5 in a prospective open-label study (Sarac *et al*, 1998). All patients received unfractionated heparin before arterial occlusion (100 u/kg) and patients randomised to warfarin continued an infusion of heparin (15 u/kg) for 6–24 h postoperatively to maintain the activated partial thromboplastin time (APTT) ratio at 1·5 times the control value. Postoperative bleeding was significantly higher in the continued anticoagulation group (32% vs. 3·7%). Immediate post-operative graft patency was higher in the continued anticoagulation group and the 3-year cumulative patency rates were higher with a significantly higher cumulative limb salvage rate (81% vs. 31%, $P = 0{\cdot}01$). The results of the study may have been due in part to the administration of heparin in the first 24-h postoperative period.

*Recommendation*

**Antiplatelet drugs remain first line intervention for secondary antithrombotic prophylaxis. If long-term anticoagulation is given to patients at high risk of femoral vein graft failure a target INR of 2·5 is recommended (grade B, level IIb).**

### 3.12. Coronary artery thrombosis

A recent meta-analysis (Rothberg *et al*, 2005) indicated that warfarin plus aspirin decreases the rate of myocardial



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infarction or stroke more than aspirin alone although the risk of bleeding is increased. The studies included in the meta-analysis were conducted before coronary artery stenting was widely established. Furthermore, there was no mortality benefit. It is likely that patients at high thrombotic risk and low bleeding risk will benefit from combined therapy compared to aspirin alone although the criteria for selecting patients, and in particular the influence of stenting, on patient management decisions regarding oral anticoagulation remain to be clarified. If oral anticoagulation with a vitamin K antagonist is given in addition to aspirin a target INR of 2·5 is recommended (grade A, level I).

*Recommendation*

**If oral anticoagulant therapy is prescribed a target INR of 2·5 is recommended (grade A, level I).**

### *3.a Paroxysmal nocturnal haemoglobinuria*

A retrospective analysis of 163 patients with paroxysmal nocturnal haemoglobinuria (PNH) followed up for a median of 6 years showed a 10-year cumulative thrombosis rate of 23% (Hall *et al*, 2003). The 10-year risk of thrombosis in patients with large PNH clones (PNH granulocytes >50%) was 44% compared with 5·8% in those with smaller clones (<50% PNH granulocytes). Warfarin prophylaxis had been offered to patients with large PNH clones and a platelet count greater than $100 \times 10^9$/l. There were no thrombotic events in 39 patients with large clones who received warfarin to a target INR of 2·5 whereas the 10-year cumulative thrombosis rate in patients with large clones not receiving warfarin was 36·5%. The incidence of major haemorrhage was 2/100 patient-years. Based on the available data it was not possible for the authors to recommend how often clones should be quantified or how to respond to changes in clone size.

*Recommendation*

**Long-term anticoagulation with a target INR of 2·5 is recommended for patients with large PNH clones (PNH granulocytes >50%) and a platelet count greater than $100 \times 10^9$/l (grade B, level III). Anticoagulation can also be considered for patients with smaller clones and platelet counts less than $100 \times 10^9$/l dependent on additional risk factors for thrombosis and bleeding (grade C, level IV).**

### *3.b Cancer*

Two prospective randomised studies have demonstrated superiority of continued LMWH over oral anticoagulant therapy with warfarin in patients with cancer.

The combined outcome measure of major bleeding or recurrent VTE was more frequent in patients treated with warfarin (target INR 2·5) compared to enoxaparin (1·5 mg/kg once daily) in the study reported by Meyer *et al* (2002), relative risk 2·02 (95% CI 0·88–4·65, $P = 0{\cdot}04$). No fatal bleeding was observed in patients receiving enoxaparin whilst six patients in the warfarin group died of bleeding ($P = 0{\cdot}03$). Only one of these patients was 'not-for-resuscitation'.

The Clinical Leaders Of Thrombosis Investigators compared 6 months of dalteparin (200 IU/kg/d reducing to 150 IU/kg/d after 1 month) to oral anticoagulation with a vitamin K antagonist, usually warfarin (target INR 2·5). The primary outcome measure was recurrent VTE during the 6-month study period. Secondary outcomes were clinical bleeding and death. The hazard ratio for recurrent VTE in patients receiving dalteparin was 0·48 (95% CI 0·30–0·77, $P = 0{\cdot}002$) (Lee *et al*, 2003). Major bleeding was not significantly different ($P = 0{\cdot}27$). In a *post hoc* analysis, patients treated with dalteparin with solid tumours without metastatic disease at the time of diagnosis of VTE had superior survival (Lee *et al*, 2005).

*Recommendation*

**Warfarin is generally inferior to therapeutic LMWH for treatment of VTE in patients with cancer (grade A, level Ib).**

## 4. Commencement and discontinuation of anticoagulation

### *Slow induction of anticoagulation in out-patients not requiring heparin*

An outpatient slow-loading regimen was assessed in 200 outpatients requiring anticoagulation for atrial fibrillation (Janes *et al*, 2004). Patients were started on 3 mg of warfarin daily for 1 week and subsequent doses determined by weekly INR measurement. By day 15, 86% of patients had an INR greater than 2 and 58% had reached a stable maintenance dose by day 22 and 85% by day 29. The day 8 INR was predictive of maintenance dose. Only 11 patients had an INR greater than 4 and no patient suffered a thrombotic or bleeding complication in the first month.

An alternative outpatient regimen in which patients received 2 mg warfarin daily for 2 weeks was able to predict the maintenance dose from the 2-week INR (Oates *et al*, 1998). In the prospective evaluation only one patient (total 107) had an INR greater than 3·0 in the first 2 weeks and five had INRs greater than 4 at some time after week 2. More than 50% of INRs were between 2·0 and 3·0 after week 2.

A 5 mg loading schedule has been evaluated in 36 out-patients with atrial fibrillation. The regimen requires measurement of the INR on days 5 and 8 (Tait & Sefcick, 1998). Compared to 33 inpatients treated with the conventional Fennerty protocol recommended in the earlier guideline (British Committee for Standards in Haematology, 1998), this regimen resulted in a lower maximum INR during the first 21 d of therapy (median 2·9 vs. 4·0, $P = 0{\cdot}0001$) and fewer INRs greater than 4·5 (2/36 vs. 9/33). Time to reach stable

anticoagulation was similar with each regimen; however, the 5 mg regimen gave a more accurate prediction of maintenance dose (correlation coefficient for predicted *versus* actual maintenance dose, $r = 0{\cdot}985$).

### *Induction regimens for patients requiring heparin*

A low-dose warfarin induction regimen was compared with the Fennerty regimen in elderly inpatients in an age-stratified randomised open-label prospective study (Gedge *et al*, 2000). In both regimens patients were given 10 mg on day 1 and subsequent doses were determined by daily INR measurement up to day 4. For equivalent INRs the average dose of warfarin was approximately 2·5 mg lower on day 2 and 1·4 mg lower on day 3 with the trial regimen. The time to achieve therapeutic anticoagulation was longer with the trial regimen but fewer patients had INRs >4·5 in the first 8 d. This difference was greatest for patients aged more than 75 years. The ability to predict the maintenance dose within 1 mg was 55% for both regimens. A number of other papers have also examined loading regimens (Harrison *et al*, 1997; Crowther *et al*, 1999; Ageno *et al*, 2003; Kovacs *et al*, 2003). Harrison *et al* (1997) and Crowther *et al* (1999) suggested that a 5-mg starting dose achieved a therapeutic INR as quickly as a 10-mg starting dose with less excessive anticoagulation. Kovacs *et al* (2003), however, found that if 10 mg was given for the first 2 d a more rapid response was achieved (INR into therapeutic range 1·4 d sooner). Ageno *et al* (2003) suggested a lower dose-loading regimen should be used in those above 60 years of age.

### *Recommendation*

**For outpatients who do not require rapid anticoagulation a slow-loading regimen is safe and achieves therapeutic anticoagulation in the majority of patients within 3–4 weeks (grade B, level IIb). This appears to avoid over-anticoagulation and bleeding associated with rapid loading.**

**For patients requiring rapid initiation of oral anticoagulation regimens that start with 5 mg doses or a single 10 mg dose followed by 5 mg doses may be preferable to regimens that start with repeated 10 mg doses in certain patient groups, e.g. the elderly (>60 years of age), those with liver disease or cardiac failure and those at high risk of bleeding (grade B, level IIb).**

### *Discontinuation of anticoagulation*

Concern of a 'rebound hypercoagulable state' after stopping oral anticoagulant therapy has resulted in uncertainty as to whether treatment should be stopped abruptly or gradually. Laboratory markers indicate a hypercoagulable state in some patients following withdrawal of oral anticoagulant therapy, regardless of the speed of withdrawal (Palareti *et al*, 1994; Palareti & Coccheri, 1996). In many patients this is probably the result of a pre-existing prothrombotic state that may have contributed to the thrombotic event necessitating anticoagulant treatment. A differential effect of abrupt *versus* gradual withdrawal on laboratory markers of coagulation has been suggested. This was shown for prothrombin fragment F1.2, thrombin–antithrombin complex and factor VII:protein C ratio, but not D-dimer, 1 week after randomisation when one group of patients had stopped and one group had taken two-thirds of their maintenance dose (Palareti *et al*, 1994). However, the crucial measurement was 1 week after stopping treatment completely. Regardless of speed of withdrawal there was no significant difference between the groups 1 week after stopping the treatment completely. With regard to actual clinical risk, retrospective observational studies have given conflicting results (Palareti & Coccheri, 1996). Prospective studies have not indicated a rebound prothrombotic state (Van Cleve, 1965; Michaels & Beamish, 1967) (level IIa) and thromboembolic rates are low when anticoagulation is discontinued temporarily in patients with mechanical heart valves (Tinker & Tarhan, 1978) (level III). Given this evidence there is no need for gradual withdrawal of anticoagulant therapy.

### *Recommendation*

**Oral anticoagulant therapy can be discontinued abruptly when the duration of therapy is completed (grade B, level IIb).**

## 5. Managing anticoagulation in the peri-operative period

A systematic review of the safety and efficacy of management strategies for patients on oral anticoagulants requiring surgery did not identify any randomised trials (Dunn & Turpie, 2003). From an overview of descriptive studies, 29 thromboembolic events were identified in 1868 patients (1·6%, 95% CI 1·0–2·1), including seven strokes (0·4%, 95% CI 0–0·7). According to management strategy thromboembolic rates were 0·4% for continuation of oral anticoagulation, 0·6% for discontinuation without administration of heparin, 0% for discontinuation with administration of unfractionated heparin and 0·6% for discontinuation with administration of LMWH. Major bleeding was rare despite continuation of oral anticoagulation for the following procedures: dental (4/2014), joint and soft tissue aspirations and injections (0/32), cataract surgery (0/203) and upper endoscopy or colonoscopy with or without biopsy (0/111). Limited data in relation to prosthetic mechanical valves and not knowing the indications for anticoagulation in each of the management strategies limit the usefulness of this review (Ansell, 2003). A simple nomogram for reducing the intensity of anticoagulation on the day of surgery (achieved mean INR 1·7) has been reported (Marietta *et al*, 2003). When oral anticoagulation is stopped completely consideration should be given to low dose heparin thromboprophylaxis.



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*Recommendation*

**Previous recommendations remain unchanged. Unless there is a very high risk of thromboembolism anticoagulation should be temporarily discontinued in preparation for surgery. Anticoagulation does not need to be stopped for dental extraction for patients in therapeutic range, i.e. INR <3·0.**

## 6. Managing bleeding and excessive anticoagulation

Reversal of anticoagulation with vitamin K is achieved more rapidly with intravenous administration than oral administration (Watson *et al*, 2001). In the original guideline an option of 5 mg of vitamin K orally or intravenously was recommended for patients with major bleeding, in addition to factor replacement therapy with either a factor concentrate or fresh frozen plasma (FFP). We now consider that, in patients with major bleeding, reversal with intravenous vitamin K is preferable. A dose of either 5 or 10 mg is recommended. Complete and rapid reversal of over-anticoagulation is more readily achieved with a factor concentrate than with FFP (Makris *et al*, 1997; Evans *et al*, 2001). Intravenous vitamin K should be given if reversal is to be sustained (Yasaka *et al*, 2002). In a non-randomised observational study the likelihood of enlargement of intracerebral haematoma was less when the INR was less than 2·0 at the time of the bleed, or was reduced to less than 2·0 within 24 h of bleeding. Reversal with a factor concentrate was associated with a lower incidence of haematoma enlargement as compared with reversal with FFP (Yasaka *et al*, 2003).

*Recommendation*

**Reversal of anticoagulation in patients with major bleeding requires administration of a factor concentrate in preference to FFP, when this is available (grade B, level III), and administration of intravenous rather than oral vitamin K (grade B, level IIa).**

## 6. Near-patient testing and patient self-management (PSM)

An increasing number of patients are using near-patient testing (NPT) devices for monitoring long-term oral anticoagulant therapy. Some patients are also undertaking self-management. In an assessment of a formal training programme the majority of patients who were offered a self-testing option declined (Murray *et al*, 2004). Some patients have purchased NPT machines directly from manufacturers without discussion with or assessment by clinical staff supervising their anticoagulant treatment. All patients should be encouraged to discuss NPT and PSM possibilities with clinical staff and obtain machines only after assessment for suitability. It is hoped that manufacturers will engage in directing patients to their clinicians before selling instruments directly to them. New guidelines on NPT and PSM are in preparation.

*Recommendation*

**For either NPT or PSM programmes:**

- **Patients should conduct NPT, with or without PSM, within a managed programme.**
- **The same standards of total quality management as practiced in hospital-based clinics should be adhered to.**
- **Patients should be assessed for capability: only patients considered competent to follow total quality management procedures should complete training and undertake NPT, with or without PSM, as appropriate.**
- **NPT and PSM programmes should be reviewed and audited at regular intervals for both technical (INR measurement) and clinical utility. Controls assurance procedures should include regular review of proportion of INRs in range and the incidence of overanticoagulation, bleeding and thrombotic adverse events.**

## 11. Clinical audit

Standards for audit remain, as in Table VI of the British Committee for Standards in Haematology (1998) guideline with the exception that it is recommended that standard 7 be altered to a standard of time-in-range of 60%. The range is taken as 0·5 INR units of the target. The reason for the change is that the time in range is now considered to be more relevant than simply the proportion of INRs within target (Rosendaal *et al*, 1993) and clinical experience has shown that this target is achievable.

The need for audit of non-laboratory-based outcome data is emphasised. Inpatient control of anticoagulation, transfer of patients from hospital to community, management of anticoagulation during interventional procedures, compliance with dosing, drug interactions, regular review of duration of therapy and risk:benefit analysis remain areas of practice where quality of care often needs to be improved. Within a governance framework anticoagulant therapy needs to be recognised as a significant risk with large numbers of patients being exposed to both potential harm and failure of adequate treatment. Anticoagulants were included in a recent Department of Health Report (Department of Health, 2004) as high-risk medicines that require the implementation of additional safety controls. The National Patient Safety Agency is currently undertaking work to develop safer practice recommendations for anticoagulants to be issued to the National Health Service in 2006.

## Declaration of interest

None of the authors have declared a conflict of interest.

## Disclaimer

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