

Guidelines on oral anticoagulation with warfarin – fourth edition

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The writing group was selected to be representative of UK based experts. This guidance is an update of the previous guideline written in 2005 and published in 2006 (Baglin *et al*, 2006). The guidance is updated with reference to relevant publications since 2005. Publications known to the writing group were supplemented with additional papers identified by searching PubMed for publications in the last 5 years using the key word warfarin and limits clinical trial, randomized control trial, meta-analysis, humans, core clinical journals, and English language. The writing group produced the draft guideline, which was subsequently revised by consensus by members of the Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology. The guideline was then reviewed by a sounding board of approximately 50 UK haematologists, the BCSH (British Committee for Standards in Haematology), the British Cardiovascular Society and the British Society for Haematology Committee and comments incorporated where appropriate. The 'GRADE' system was used to quote levels and grades of evidence, details of which can be found at http://www.bcsghguidelines.com/BCSH_PROCESS/EVIDENCE_LEVELS_AND_GRADES_OF_RECOMMENDATION/43_GRADE.html. The objective of this guideline is to provide healthcare professionals with clear guidance on the indications for and management of patients on warfarin.

This guideline replaces the previous BCSH guidelines on oral anticoagulants (Baglin & Rose, 1998; Baglin *et al*, 2006).

1. Indications for warfarin and recommended target international normalized ratio (INR)

This guideline refers to target INRs rather than target ranges, although the target range is generally taken to be within 0.5 of

the target, i.e. a target INR 2.5 equates to a target range of 2.0–3.0. Specifying tighter target ranges for fully anticoagulated patients e.g. 2.0–2.5 or 3.5–4.0 does not achieve tighter anticoagulation control but results in more blood tests and more INR results in ranges associated with increased risk of thrombosis and bleeding (Meier *et al*, 2007).

1.1 Venous thromboembolism (VTE)

For acute VTE warfarin should be started along with a parenteral anticoagulant, such as unfractionated heparin (UFH), low molecular weight heparin (LMWH) or fondaparinux (Brandjes *et al*, 1992), which should be continued for at least 5 d and until the INR is ≥ 2 for at least 24 h, whichever is the longer.

For the initial period of treatment the target INR should be 2.5. For patients who require anticoagulation beyond 3 months, it is not recommended to lower the target range after 3 months as this has been shown to offer poorer efficacy with comparable bleeding rates (Kearon *et al*, 2003; Ridker *et al*, 2003).

Patients who suffer a recurrence of VTE whilst on anticoagulants, where the anticoagulant control is within target, need escalation of their INR target. There are few data that relate to this scenario, but we suggest a target of 3.5.

Recommendation

- **First episodes of VTE should be treated with an INR target of 2.5 (1A).**
- **Warfarin used for treatment of VTE should be introduced along with parenteral anticoagulation (1A) which should continue for at least 5 d and until the INR is ≥ 2 for at least 24 h (1C).**
- **Recurrent VTE whilst anticoagulated and within the therapeutic range should be managed by increasing the INR target to 3.5 (2C).**

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1.2 Antiphospholipid syndrome (APS)

A retrospective study of 147 patients (54% with venous thrombosis) had suggested that a target INR of 3.5 was preferable to a target INR of 2.5 (Khamashta *et al*, 1995). There are two prospective randomized trials. Crowther *et al* (2003) randomized 114 patients with antiphospholipid antibodies (aPL) and thrombosis (76% venous, 24% arterial) to a target INR of 2.5 or 3.5 and followed them for a mean of 2.7 years. Recurrences were 2/58 (3.4%) in the low intensity group and 6/56 (10.7%) in the high intensity group. For venous thrombosis the events were 1/45 (2.2%) and 3/42 (7.1%), respectively. Finazzi *et al* (2005) randomized 109 patients with aPL and thrombosis (60% venous only, 31% arterial only, 9% both) to a target INR of 2–3 or 3–4.5 and followed them for a median of 3.6 years. Recurrences were 3/52 (5.8%) in the low intensity group and 6/54 (11.1%) in the high intensity group.

Recommendation

- **The target INR should be 2.5 in patients with antiphospholipid antibodies (1A).**

1.3 Atrial fibrillation (AF)

The risk of cardio-embolic stroke should be assessed by considering concurrent risk factors that predict stroke risk. These include a history of previous transient ischaemic attack (TIA) or stroke, hypertension, diabetes, heart failure and consideration of the patient's age. Patients at low risk of cardio-embolic stroke may be treated with aspirin while increasing stroke risk favours treatment with the more effective warfarin (Hart *et al*, 2007; Andersen *et al*, 2008). Evidence comparing the efficacy of different anticoagulation regimens and considering bleeding risk suggests an optimum INR target of 2.5 (Singer *et al*, 2008), which is more effective than low-intensity fixed dose warfarin plus aspirin (Stroke Prevention in Atrial Fibrillation III trial) (Stroke Prevention in Atrial Fibrillation Investigators, 1996).

Recommendations

- **Patients with AF who require warfarin for the prevention of cardio-embolic should have an INR target of 2.5 (1A).**

1.4 Cardioversion

Patients who develop AF and are considered for cardioversion require anticoagulation prior to and after the event. Patients undergoing elective cardioversion should be anticoagulated with warfarin for at least 3 weeks prior to and 4 weeks post cardioversion if sinus rhythm is achieved and sustained. The target INR for this indication is 2.5. One study has suggested that there is a critical difference in

outcomes, which is dependent on the INR in the period immediately before cardioversion (Gallagher *et al*, 2002) and for this reason many units prefer the INR to be >2.5 in the period closest to the cardioversion. In the UK it is common practice to measure the INR on the day of the cardioversion and postpone the procedure if it is <2.5. This results in cancellation of as many as 25% of procedures. To avoid this, 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.

Recommendation

- **Patients undergoing elective cardioversion should be anticoagulated with warfarin for at least 3 weeks prior to and 4 weeks post cardioversion with a target INR of 2.5 (2C). To minimize cardioversion cancellations due to low INRs on the day of the procedure a target INR of 3.0 can be used prior to the procedure.**

1.5 Valvular heart disease and prosthetic valves

Structural abnormalities of the heart and foreign surfaces, such as prosthetic valves, predispose to thrombus formation, which becomes clinically manifest through systemic embolization. This is usually an issue for surgeons and cardiologists and there are specific guidelines for this situation (Vahanian *et al*, 2007; Salem *et al*, 2008). In this guideline target INRs will be stated for the most common scenarios.

1.5.1 Mitral stenosis or regurgitation.

Recommendations

- **Patients with mitral stenosis or regurgitation who have atrial fibrillation (1A) or a history of systemic embolism (1A) or left atrial thrombus (1A) or an enlarged left atrium (2C) should receive warfarin with an INR target of 2.5.**

1.5.2 Mechanical prosthetic heart valves. The risk of systemic embolism from prosthetic heart valves depends on the type of valve, its position and other factors that contribute to the patients' risk of developing thrombosis, such as cardiac rhythm and dilatation. The types of valves used in modern practice are typically less thrombogenic than older valves but there still are surviving patients with old style valves, such as the Starr-Edwards, in place. Many types of valves are available commercially and the data on anticoagulation and systemic embolism rates are mostly from prospective or retrospective case series. For new valves there are not sufficient data on the most appropriate level of anticoagulation and in these cases the valves should be regarded as medium thrombogenicity until there are adequate data to safely reduce the intensity of anticoagulation. Where studies purport to assess differences

between different degrees of anticoagulation there is often a lack of clarity about time spent in range and so these are effectively 'intention to treat' observations.

Where patients would appear to possibly benefit from a higher INR but there are features to suggest that the risk of anticoagulant-related bleeding is high, then this needs to be borne in mind when advising on optimal treatment for the patient. In situations where an embolic event occurs during 'on target' anticoagulation, elevation of the INR target or addition of anti-platelet drugs should be considered (Vahanian *et al*, 2007; Salem *et al*, 2008). We suggest the following, which is based on the European Society of Cardiology guidelines (Vahanian *et al*, 2007). We have restricted the highest recommended target INR to 3.5 as we do not feel that there is evidence for increased efficacy of higher levels offsetting the increased risk of bleeding.

Recommendations

The recommended target INRs for mechanical heart valves are given in Table I.

- **In situations where an embolic event occurs during anticoagulation within target, elevation of the INR target or the addition of anti-platelet drugs should be considered (2C).**

1.5.3 Bioprosthetic heart valves. Some patients may benefit from a bioprosthetic valve as opposed to a mechanical valve. One of the reasons for this choice is to avoid the need for anticoagulation in patients deemed to be at a high risk of bleeding (Salem *et al*, 2008). We suggest the following, based on the American College of Chest Physicians guidelines (Salem *et al*, 2008).

Recommendations

- **Patients with a bioprosthesis in the mitral position should receive 3 months of anticoagulation with warfarin with an INR target of 2.5 (1B).**
- **Patients with a bioprosthetic valve and a history of systemic embolism should have at least 3 months of anticoagulation with warfarin with an INR target of 2.5 (1C).**
- **Patients with a bioprosthetic valve and left atrial thrombus at surgery should receive warfarin until the clot has resolved with an INR target of 2.5 (1C).**
- **Patients with bioprosthetic valves and other prothrombotic risk factors, such as atrial fibrillation and low ventricular ejection fraction, should receive warfarin with an INR target of 2.5 (1C).**

1.6 Peripheral vascular disease

The majority of patients with peripheral vascular disease do not require anticoagulation. Most patients are managed with

Table I. Recommended target INRs for mechanical heart valves (GRADE 2B) [adapted from Vahanian *et al* (2007), copyright (2007), with permission from Oxford University Press].

Prosthesis Thrombogenicity*	INR target	INR target
	No patient risk factors	Patient-related risk factors†
Low	2.5	3.0
Medium	3.0	3.5
High	3.5	3.5‡

*Prosthesis thrombogenicity: Low: Carbomedics (aortic position), Medtronic Hall, St Jude Medical (without silzone); Medium: Bjork-Shiley, other bileaflet valves; High: Starr-Edwards, Omniscience, Lillehei-Kaster.

†Patient-related risk factors for thrombosis: Mitral, tricuspid or pulmonary position; Previous arterial thromboembolism; Atrial fibrillation; Left atrium diameter >50 mm; Mitral stenosis of any degree; Left ventricular ejection fraction <35%; Left atrial dense spontaneous echo contrast.

‡Was 4.0 in Vahanian *et al* (2007).

combinations of anti-platelet agents, statins and other medications used to control and treat other risk factors for arterial disease that are present.

Recommendations

- **Patients with intermittent claudication should not routinely be treated with anticoagulants (1A).**
- **Patients who suffer acute arterial embolism and proceed to embolectomy should be considered for long-term anticoagulation with warfarin with an INR target of 2.5 (2C).**

1.7 Myocardial infarction and cardiomyopathy

The use of warfarin following myocardial infarction has become less common as a result of the emergence of new management strategies. Recommendations for these two conditions remain unchanged from the 2006 version of this guideline

Recommendations

- **When warfarin is used following myocardial infarction, the INR target for anticoagulation is 2.5 (2A).**
- **Patients with dilated cardiomyopathy who are anticoagulated to prevent systemic embolism should have an INR target of 2.5 (2C).**

2. Duration of anticoagulation for pulmonary embolism (PE) and lower limb deep vein thrombosis (DVT)

A finite period of anticoagulation is required to prevent extension of thrombus and prevent early recurrence (within

the first 3–6 months). Thereafter, continued anticoagulation may be recommended to prevent late recurrence. The benefit of anticoagulation continues only for as long as therapy is continued (Agnelli *et al*, 2001, 2003; Pinede *et al*, 2001; Ost *et al*, 2005; Schulman *et al*, 2006; Campbell *et al*, 2007) therefore continued anticoagulation effectively equates to long-term treatment.

2.1 Duration of initial anticoagulation

At least 3 months of anticoagulant therapy is required to prevent extension of thrombus and recurrence in patients with proximal DVT (i.e. involvement of popliteal vein or above) and/or PE. Two studies have randomized patients with proximal DVT or PE to receive either 3 or 6 months of treatment (Pinede *et al*, 2001; Campbell *et al*, 2007) and there was no difference in recurrence rates

Many diagnostic strategies will only look for proximal DVT, and these strategies that leave isolated calf vein DVT (i.e. no extension into popliteal vein) undiagnosed and untreated are as safe as those in which isolated calf vein DVT is diagnosed and treated (Bernardi *et al*, 2008; Gibson *et al*, 2009). If symptomatic isolated calf vein DVT is diagnosed and treated then 6 weeks of treatment is as effective as 12 weeks (Pinede *et al*, 2001).

Patients with cancer-associated VTE are at high risk of recurrence and LMWH has been shown to be more effective than warfarin for the first 6 months of treatment (Lee *et al*, 2003).

Recommendations

- **Patients with proximal DVT or PE should be treated for at least 3 months (1A).**
- **If a diagnostic strategy that identifies isolated calf vein DVT is employed, treatment of such clots can be restricted to 6 weeks (1A).**
- **Patients with cancer-associated VTE should initially be treated for 6 months with therapeutic dose LMWH rather than warfarin (1A).**

2.2 Continued anticoagulation beyond the initial period of 3 months

In theory, therapy should be continued if the risk from recurrence on stopping treatment is greater than the risk from anticoagulant-related bleeding. However, these opposing risks are not easily predicted in an individual. In a patient with an average risk of warfarin-related bleeding the annual risk of recurrent VTE that would favour continued anticoagulant therapy has been estimated to be between 3% and 9% (Keeling, 2006; Rodger *et al*, 2010).

It is now clear that the circumstances in which proximal lower limb DVT and/or PE occurs is the strongest predictor of likelihood of recurrence (Baglin, 2007; Kearon, 2007; Kearon

et al, 2008). Patients with VTE provoked by surgery are at low risk of recurrence (annual risk <3%) after completion of 3 months warfarin therapy and continued anticoagulation is not recommended. Patients with non-surgical transient provoking factors (such as the combined oral contraceptive pill, pregnancy, plaster cast) have an annual risk of recurrence of between 3% and 9% and continued anticoagulant therapy is not routinely recommended. Patients with unprovoked venous thrombosis have an annual risk of recurrence of more than 9% in the first year after stopping treatment. Given that this risk exceeds the risk of warfarin-related bleeding, patients with a first unprovoked or recurrent unprovoked episodes of proximal DVT or PE should be considered for long term anticoagulation (Kearon *et al*, 2008). Whilst the cohort risk for patients with a history of unprovoked venous thrombosis is >9%, individual risk is heterogeneous. This is illustrated by a lower annual risk in patients with a normal D-dimer result after completion of initial warfarin therapy compared to those with an elevated D-dimer (3.5% vs. 9%) (Verhovsek *et al*, 2008). Risk of recurrence has also been related to the presence of post-thrombotic syndrome (Stain *et al*, 2005; Rodger *et al*, 2008) and male sex (Eichinger *et al*, 2010). The relationship between residual vein thrombosis and risk of recurrence remains uncertain. Recent evidence suggests that residual vein occlusion has no predictive value independent of measurement of D-dimer (Cosmi & Palareti, 2010). Testing for heritable thrombophilic defects does not usefully predict likelihood of recurrence after a first episode of VTE and for this reason testing for heritable thrombophilia is not routinely recommended (Baglin *et al*, 2010a). If anticoagulation is stopped after unprovoked VTE, we recommend testing for antiphospholipid antibodies as their presence may favour restarting anticoagulation.

A further consideration is the consequence of recurrent VTE. Patients with an initial unprovoked PE are 3–4 times more likely to suffer recurrence as PE rather than DVT (Murin *et al*, 2002; Schulman *et al*, 2006; Baglin *et al*, 2010b) and the risk of fatal PE is 2–4 times more likely in patients with symptomatic PE as compared to patients with symptomatic DVT alone (Douketis *et al*, 1998, 2007; Laporte *et al*, 2008).

It remains uncertain if recurrence is more likely after a second or subsequent episode of unprovoked VTE than after a first event. However, given that risk of recurrence is sufficiently high after a first event to justify consideration of continued treatment, unprovoked recurrence is at least confirmation that the recurrence risk is high in that individual patient.

Patients with DVT confined to the calf have a lower risk of recurrence than patients presenting with proximal DVT (Schulman *et al*, 1995; Lindmarker *et al*, 1999; Pinede *et al*, 2001) and have a low risk of recurrent VTE presenting as PE (Baglin *et al*, 2010b).

Recommendations

- **Long-term anticoagulant therapy is not recommended in patients with VTE provoked by surgery (1B).**

- Long-term anticoagulant therapy is not recommended in patients with VTE provoked by non-surgical transient trigger factors (1B).
- Patients with unprovoked proximal DVT or PE should be considered for long-term anticoagulation, taking into account information that may help predict risk of recurrence and risk of bleeding in the individual patient (2B).
- Long-term anticoagulant therapy is not recommended in patients with VTE confined to the calf (i.e. not extending into the popliteal vein) (1A).

3. Initiation of treatment

3.1 Rapid induction regimens for patients with acute thrombosis

Patients with acute thrombosis should have parenteral anticoagulation, for example with UFH, LMWH or fondaparinux, until oral anticoagulation with warfarin is established. In these patients the time to stable anticoagulation is an important factor. Heneghan *et al* (2010) systematically reviewed the literature on the most effective methods for initiating warfarin. Overall, they found no evidence to suggest a 10 mg loading dose is superior to 5 mg. In the elderly, lower initiation doses or age-adjusted doses may be more appropriate (Roberts *et al*, 1999; Gedge *et al*, 2000). In these studies, significantly fewer patients on an age-adjusted regimen had high out-of-range INRs, compared to standard dosing. There is insufficient evidence to warrant genotype-guided initiation. Although it has been shown that genetic testing can predict the maintenance dose, for initiation, information from previous dosing rapidly becomes more important (Ferder *et al*, 2010) and response to a standard dosing algorithm can accurately predict maintenance dose without genotyping (Lazo-Langner *et al*, 2009; Le Gal *et al*, 2010).

Recommendations

- Overall there is no evidence to suggest a 10 mg loading dose is superior to a 5 mg loading dose. However in the elderly lower initiation doses or age-adjusted doses may be more appropriate as they lead to fewer high INRs (2B).
- There is insufficient evidence to warrant genotype-guided initiation as response to a standard dosing algorithm can equally accurately predict maintenance dose (2B).

3.2 Induction of anticoagulation in outpatients with atrial fibrillation

Three papers describing outpatient slow-loading regimens (Oates *et al*, 1998; Tait & Sefcick, 1998; Janes *et al*, 2004) were discussed in our last guideline. They showed that for out-

patients 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.

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 (2C).

4. Peri-operative anticoagulation

For some invasive procedures, such as joint injections (Thumboo & O'Duffy, 1998), cataracts (Dunn & Turpie, 2003) and certain endoscopic procedures (including mucosal biopsy) (Eisen *et al*, 2002), warfarin does not need to be stopped. If anticoagulation has to be stopped for surgery or an invasive procedure, the risk of thrombosis, the consequence of thrombosis, by how much bridging therapy with treatment dose LMWH or UFH reduces the risk, the excess bleeding due to pre-operative or post-operative bridging and the consequences of bleeding all need to be considered. There have been many reviews and attempts to estimate the risk of peri-operative thrombosis (Kearon & Hirsh, 1997; Dunn & Turpie, 2003; Kearon, 2003; Dunn *et al*, 2007; Douketis *et al*, 2008; O'Donnell & Kearon, 2008).

For patients with VTE the risk of recurrence without anticoagulation is very high in the first 3 months (Kearon & Hirsh, 1997) and surgery will greatly increase the risk. If the annual risk of stroke in untreated AF or in a patient with an aortic mechanical heart valve (MHV) is 4% per annum, this will translate to approximately 0.5 events per 1000 patients who have 5 d without anticoagulation. For AF with previous stroke or a mitral MHV, the figures are approximately 12% per annum or approximately 1.6 cases per 1000 patients for 5 d without anticoagulation. However, typical rates of peri-operative arterial thromboembolism that have been reported are ten times these calculated figures (Dunn & Turpie, 2003; Dunn *et al*, 2007; Garcia *et al*, 2008).

If bridging therapy is given it is now usually with LMWH. This is effective in VTE prevention but there are fewer data for using LMWH in patients with AF or a MHV and it appears to be less effective than warfarin in MHV patients (Chan *et al*, 2000). Giving bridging heparin will increase the risk of bleeding, 13% vs. 0.8% in those not bridged in one study (Garcia *et al*, 2008). When bridging was used the bleeding risk varied markedly by extensiveness of procedure, the incidence of major bleeding for invasive procedures was 1/148 (0.7%), for minor surgery 0/72 (0%), and for major surgery 8/40 (20%) (Dunn *et al*, 2007). It should also be appreciated that, whereas bleeding may be fatal in approximately 3% of cases, arterial thromboembolism leading to stroke is fatal in 40% of cases with severe disability in 30%.

Logistically, warfarin should not be taken for 5 d before surgery and, if possible, the INR should be determined the day before surgery to allow the administration of oral vitamin K if the INR is ≥ 1.5 , so reducing the risk of cancellation. In patients who are receiving pre-operative bridging with LMWH the last dose should be at least 24 h before surgery and some recommend that the last dose is halved for high risk surgery (Douketis *et al*, 2008). The INR should be checked on the day of surgery and warfarin can be resumed, at the normal maintenance dose, the evening of surgery or the next day if there is adequate haemostasis (Douketis *et al*, 2008).

There are two randomized trials in progress, PERIOP-2 (clinicaltrials.gov/ct2/show/NCT00432796) and BRIDGE (clinicaltrials.gov/ct2/show/NCT007864740), which should help us to make decisions on peri-operative bridging. Based on the evidence to date, we make the following recommendations:

Recommendations

- **Pre-operative bridging carries a low risk of bleeding but the use of post-operative bridging requires careful consideration due to the high risk of bleeding. We recommend that post-operative bridging should not be started until at least 48 h after high bleeding risk surgery (1C).**
- **Patients with VTE more than 3 months earlier can be given prophylactic dose LMWH (or a suitable alternative) rather than bridging therapy (2C).**
- **Patients with low risk AF (no prior stroke or TIA) do not require bridging therapy (2C).**
- **Patients with a bileaflet aortic MHV with no other risk factors do not require bridging (2C).**
- **Patients with a VTE within the previous 3 months, patients with AF and previous stroke or TIA or multiple other risk factors, and patients with a mitral MHV should be considered for bridging therapy (2C).**

5. Management of bleeding and of high INR in the absence of bleeding

5.1 Major bleeding

Major bleeding, in terms of anticoagulation reversal, can be defined as limb or life-threatening bleeding that requires complete reversal within 6–8 h. Patients on warfarin have reduced levels of factors II, VII, IX and X and rapid correction involves replacement of the preformed factors. Rapid correction is most effectively achieved by the administration of prothrombin complex concentrate (PCC) (Makris *et al*, 1997).

Although all PCCs contain factors II, IX and X, there is significant variability in their factor VII (FVII) content. PCCs with little FVII (the so called 3-factor PCCs) produce poor correction of the INR and are not recommended (Holland *et al*, 2009). The only PCCs licensed for warfarin reversal in the

UK (Beriplex and Octaplex) are 4-factor PCCs (i.e. they contain significant amounts of FVII). PCCs are able to completely reverse the warfarin-induced anticoagulation within 10 min but the infused clotting factors have a finite half-life, the shortest of which is FVII at 6 h. In view of this, 5 mg intravenous vitamin K should be given with the PCC.

Recombinant activated FVII (rFVIIa) usage has been reported for warfarin reversal but all reports are retrospective, small series or without adequate controls. Although rFVIIa rapidly corrects the INR, its impact on stopping bleeding is unclear and its use cannot be recommended for warfarin reversal (Rosovsky & Crowther, 2008; Skolnick *et al*, 2010).

Complete and rapid correction of the coagulopathy is more rapidly achieved with PCC than fresh frozen plasma (FFP) (Makris *et al*, 1997). FFP provides a dilute form of the clotting factors and it is not practical to infuse very large volumes of plasma (15–30 ml/kg) rapidly. FFP will produce inferior correction and cannot be recommended for life-threatening bleeding. All hospitals and units responsible for anticoagulant care and hospitals performing invasive procedures on patients on warfarin should stock a licensed four-factor PCC.

Recommendation

- **All hospitals managing patients on warfarin should stock a licensed four-factor prothrombin complex concentrate (1C).**
- **Emergency anticoagulation reversal in patients with major bleeding should be with 25–50 u/kg four-factor prothrombin complex concentrate and 5 mg intravenous vitamin K (1B).**
- **Recombinant factor VIIa is not recommended for emergency anticoagulation reversal (1B).**
- **Fresh frozen plasma produces suboptimal anticoagulation reversal and should only be used if prothrombin complex concentrate is not available (1C).**

5.2 Non-major bleeding

Patients with non-major bleeding can be managed with vitamin K combined with dose reduction or temporary discontinuation of warfarin. Intravenous vitamin K produces a more rapid correction of the INR than oral vitamin K and should be used in preference in the bleeding patient. Significant correction of the INR is seen within 6–8 h after intravenous vitamin K use (Watson *et al*, 2001).

Vitamin K should not be given subcutaneously due to inconsistent correction and intramuscular administration should be avoided due to the risk of intramuscular haematoma in the anticoagulated patient. Anaphylactoid reactions following intravenous vitamin K have been reported following the rapid administration of the older formulation, which contained polyethoxylated castor oil, but this risk is lower

with the currently used micelle formulation (Makris *et al*, 2010).

Patients bleeding at therapeutic levels of anticoagulation should be investigated for the source of bleeding. Haematuria is not a feature of anticoagulation and patients with this symptom at therapeutic levels should be investigated for possible bladder and renal tract malignancy.

For bleeding in the oral cavity, antifibrinolytic drugs, such as tranexamic acid mouthwash, are often very helpful. For epistaxis, nasal packing is useful when simple measures fail.

Recommendation

- **Anticoagulation reversal for non-major bleeding should be with 1–3 mg intravenous vitamin K (1B).**

5.3 INRs >5.0 and >8.0 in non-bleeding patients

There is an almost exponential increase in the risk of bleeding with increasing INR (Palareti *et al*, 1996) but the exact risk in the individual patient is more difficult to define. Some patient characteristics, such as older age, uncontrolled hypertension, diabetes, renal or liver failure, previous gastrointestinal or cerebral bleed and use of anti-platelet medication, are associated with a higher risk of bleeding.

The use of vitamin K results in more rapid reduction in INR than discontinuation of the warfarin alone (Crowther *et al*, 2009). In the non-bleeding patient, oral administration of vitamin K is preferred over the intravenous route as equal correction is achieved at 24 h (Watson *et al*, 2001). Patients with INR higher than 8.0 are at a significantly high risk of bleeding. Crowther *et al* (2010) have demonstrated that patients with INR of >10 can be managed with 2.5 mg of oral vitamin K without the need for blood products or in many cases, hospitalization. Baker *et al* (2006) observed good correction with 2.5 mg of oral vitamin K for patients with INR of 8.0–12.0 and 5 mg for those with INR >12.0, with only 8% and 21% achieving an INR of <2.0 the day after vitamin K administration. It is recommended that all patients with INR of >8.0 should receive 1–5 mg of oral vitamin K. At these doses overcorrection is infrequent and resistance to re-anticoagulation does not occur (Baker *et al*, 2006).

The decision to give vitamin K to patients with an INR of <8.0 is more controversial. A recent randomized study in patients with INR <10.0 found no difference in bleeding complications in patients given 1.25 mg vitamin K compared to placebo (Crowther *et al*, 2009), but this study has been criticized in terms of study design, vitamin K preparation and dose, patient selection as well as because of the unexpected high rate of bleeding in the control group (16.3%) (Swaim & Macik, 2009). It is reasonable to consider giving oral vitamin K to patients with an INR of 5.0–8.0 if they are judged to be at high risk of bleeding, but it is not necessary to offer this routinely to all patients.

Recommendation

- **Patients with an INR >5.0 but who are not bleeding should have 1–2 doses of warfarin withheld and their maintenance dose should be reduced (1B). The cause of the elevated INR should be investigated (1C).**
- **Patients with an INR >8.0 should receive 1–5 mg of oral vitamin K (1B).**

6. Emergency surgery for patients on warfarin

Recommendation

- **For surgery that requires reversal of warfarin and that can be delayed for 6–12 h, the INR can be corrected by giving intravenous vitamin K. For surgery that requires reversal of warfarin and which cannot be delayed, for vitamin K to have time to take effect the INR can be corrected by giving PCC and intravenous vitamin K. PCC should not be used to enable elective or non-urgent surgery (2C).**

7. Head injury in patients on warfarin

Minor head injury is one of the commonest presentations to Accident and Emergency departments and although national guidelines on the management of head injury exist (Yates *et al*, 2007), these only very briefly deal with the particular problem of patients on warfarin (Prowse & Sloan, 2010). All patients on warfarin presenting to accident and emergency departments with head injuries, however minor, should have their INR measured. Individuals with loss of consciousness, amnesia or reduced Glasgow Coma scale should have an immediate head computerized tomography (CT) scan. Patients on warfarin are more likely to have a cerebral bleed with more minor injury and there should be a lower threshold for CT scanning (Prowse & Sloan, 2010). In general if the head injury was sufficient to cause facial or scalp laceration or bruising or persistent headache, the patient should have an urgent CT scan. Patients on warfarin with a strong suspicion of intracerebral haematoma after a clear head injury should have their INR reversed with PCC immediately and before the CT and INR results are available.

Delayed intracranial bleeding can occur in patients on warfarin even when the initial CT scan is normal (Cohen *et al*, 2006). In view of this, patients with a supra-therapeutic INR should have this corrected into the therapeutic range with oral vitamin K. It is suggested that the INR is maintained as close to 2.0 as possible for the 4 weeks after a significant head injury and a normal CT scan.

Recommendations

- All patients on warfarin presenting to Accident and Emergency departments with head injury should have their INR measured as soon as possible (1C).
- A lower threshold for performing a head CT scan should be used for patients on warfarin (2C).
- Patients on warfarin presenting with a strong suspicion of intracerebral bleed should have their anticoagulation reversed before the results of any investigations (2C).

8. Management of sub-therapeutic anticoagulation in the first month after acute VTE

Barritt and Jordan (1960) showed that if PE is untreated it has a high mortality in the first 14 d. When Lagerstedt *et al* (1985) randomized patients with calf vein DVT to no treatment there was a high recurrence rate over 90 d, which was particularly marked in the first 30 d. Kearon and Hirsh (1997) estimated a risk of recurrence of 40% in the first month after VTE if patients are not anticoagulated. Sub-therapeutic anticoagulation is likely to be more effective than no anticoagulation but this raises the issue as to what should be done when a patient has a significantly sub-therapeutic INR shortly after acute VTE. It also raises the issue of how low an INR has to be before most clinicians would regard it as significant; there was no clear consensus among the writing group but opinions ranged from <1.5 to <1.7.

Recommendation

- We suggest that bridging therapy be considered if the INR becomes significantly sub-therapeutic within the first month of an acute VTE (2C).

9. Combination warfarin and antiplatelet therapy

The combination of an ageing population, increased use of warfarin in all ages of patients with AF and a marked increase in dual anti-platelet therapy in patients with acute coronary syndrome (ACS) (and for extended periods following coronary artery stenting) has created clinical situations where both warfarin and antiplatelet agents may be indicated. There is clear evidence from both randomized controlled trials (RCTs) and population registries that such combination therapies are associated with an increased risk of major bleeding (Connolly *et al*, 2006, 2009; Flaker *et al*, 2006; Sorensen *et al*, 2009; Hansen *et al*, 2010) (Table II). In contrast, the only clear evidence of an increased antithrombotic efficacy of oral anticoagulant plus anti-platelet therapies is in patients with prosthetic heart valves (Little & Massel, 2003).

While the use of combination warfarin and antiplatelet therapy should be assessed on an individual patient basis, considering the disease-specific thrombotic risk and the patient-specific bleeding risk, the following examples provide evidence-based guiding principles.

Table II. Annual rates for bleeding event (fatal or non-fatal requiring hospital admission) following acute myocardial infarction (MI), according to anti-thrombotic therapy [adapted from Sorensen *et al* (2009), copyright (2009), with permission from Elsevier].

Antithrombotic regimen	Bleeding admission rate (% per year)
Aspirin	2.6
Clopidogrel	4.6
Warfarin	4.3
Aspirin + clopidogrel	3.7
Aspirin + warfarin	5.1
Clopidogrel + warfarin	12.3
Aspirin + clopidogrel + warfarin	12.0

9.1 Patients on antiplatelet therapy who develop an indication for warfarin

These are usually patients with cardiovascular disease (CVD) who develop AF (with a CHADS₂ score >1), or VTE, or who have a new mechanical prosthetic heart valve.

Recent evidence for use of aspirin as primary prophylaxis in patients at high risk of CVD suggests negligible net benefit (De Berardis *et al*, 2009; Fowkes, *et al* 2010). Combinations of warfarin and an antiplatelet agent, compared to warfarin alone, do not have superior antithrombotic efficacy in patients with AF or stable CVD (Hurlen *et al*, 2002; Hansen *et al*, 2010). Patients with peripheral arterial disease or ischaemic stroke will derive equivalent secondary antithrombotic efficacy from warfarin alone, compared to aspirin alone, or indeed aspirin and dipyridamole in ischaemic stroke (Anand *et al*, 2007; Halkes *et al*, 2007; Warfarin and Antiplatelet Vascular Evaluation (WAVE) Investigators (2006). In contrast, in patients with ACS undergoing percutaneous coronary intervention (PCI) with stent implantation, combination antiplatelet therapy has superior antithrombotic efficacy to warfarin + aspirin (Rubboli *et al*, 2005).

Recommendations

- Patients receiving an anti-platelet agent as primary prophylaxis for CVD on developing an indication for warfarin should stop their antiplatelet agent (1B).
- Patients with peripheral artery disease or previous ischaemic stroke on antiplatelet therapy should stop this agent if warfarin is commenced (1B).
- Patients on aspirin or clopidogrel as secondary prophylaxis with stable ischaemic heart disease (often defined as >12 months following acute myocardial infarction) should stop their antiplatelet agent while being treated with warfarin (2B).
- Patients on a single antiplatelet agent <12 months following an ACS, who require to start warfarin therapy should continue aspirin therapy until 12 months post ACS, unless they are regarded as having a high bleeding risk (2B).

- **Patients on aspirin and clopidogrel, following an ACS or stent placement, who develop an indication for warfarin should be carefully assessed for bleeding risk and discussed with their cardiologist, with a view to introducing warfarin and minimizing the duration of triple therapy (2C).**
- **When combined warfarin and single antiplatelet agent are indicated, consideration should be given to use of aspirin given the higher bleeding risk associated with clopidogrel (2C).**

9.2 Patients on warfarin who develop an indication for antiplatelet agents

This will include patients on warfarin for AF or following an episode of VTE who develop an acute ischaemic arterial event (e.g. ACS or non-cardioembolic stroke).

In the first instance the need for warfarin should be reviewed – if the patient has low risk AF or is already 3 months post-VTE event (assuming not intended for lifelong anticoagulation) then warfarin could be discontinued permanently, or at least while antiplatelet therapy is indicated. If there is a clear indication for warfarin to be continued, then an attempt should be made to reduce the length of time on dual or single antiplatelet therapy. The exact duration of dual or single agent antiplatelet therapy should be guided by the patient's perceived bleeding risk.

The evidence base for optimal management of such patients who develop an ACS has been systematically reviewed (Lip, *et al* 2010). If PCI is required this can be undertaken while on warfarin therapy, however a radial artery approach is recommended so as to reduce bleeding risk.

Recommendations

- **Patients requiring a coronary artery stent, should be considered for bare metal stent (rather than drug-eluting stent) which would only necessitate triple therapy for 4 weeks, followed by aspirin and warfarin to 12 months (2B).**
- **Patients who do not undergo PCI should be considered for 4 weeks triple therapy, after which clopidogrel should be stopped, and aspirin continued for a further 11 months (2C).**

10. Anticoagulant monitoring and dose adjustment

10.1 Manual dosing

Historically, in many centres, anticoagulant dosing involved appropriately qualified health care professionals, e.g. medical, nursing, laboratory and pharmacy staff, to both monitor and adjust individual patient dose to achieve and maintain the

target INR. The National Patient Safety Agency (NPSA 2007) guidelines provide information on the management of anti-coagulant services and the appropriate training of staff. The use of a dosing algorithm can significantly improve anticoagulant control (Kim *et al*, 2010).

10.2 Computer-assisted dosing

The safety and effectiveness of computer-assisted dosing has been demonstrated in a number of publications, with patients achieving a stable state significantly faster than in comparison to manual dosing and with more time spent within the therapeutic range. Computerized dosing has been shown to increase the overall percentage time for which patients are in their target INR range and in some studies to reduce the frequency of testing of patients. Furthermore, it has been shown to significantly reduce the risk of bleeding and thromboembolic events and overall is a more cost-effective option to manual dosing (Fitzmaurice *et al*, 1996; Manotti *et al*, 2001; NPSA 2007; Poller *et al*, 2008a,b, Jowett *et al*, 2009). Minimum safety requirements for computer-dosing programs have been suggested (Poller *et al*, 2009).

10.3 Patient self-management

Individuals on warfarin can adopt one of two separate anticoagulant self-testing programmes: Individuals may elect to check their own INR using one of the commercially available INR monitors (Perry *et al*, 2010) and then report their INR to a healthcare professional who is then responsible for dosing advice. Such advice can be given verbally initially but should also be sent in writing or electronically (Ryan *et al*, 2009). Alternatively, patients may be trained to both monitor their INR and adjust their dose of warfarin based upon the result. In a recent Cochrane systematic review, patients who self-monitored or self-managed their anticoagulants improved the overall quality of their oral anticoagulation therapy compared to standard monitoring (Garcia-Alamino *et al*, 2010). The number of thromboembolic events and overall mortality was decreased without any increase in bleeding. However, self-monitoring or self-management may not be appropriate for most patients e.g. in those unable to complete the training programme, with no wish to participate in such a programme or with a lack of support from their general practitioner. Guidelines for patients self-testing have been published (Fitzmaurice *et al*, 2005) and that paper, the review by Perry *et al* (2010) and a BCSH guideline (Briggs *et al*, 2008) cover the important issue of quality assurance for point-of-care machines.

10.4 Dietary vitamin K intake

Both the stability of the INR and the time spent within the therapeutic INR range for patients on warfarin were shown to be influenced by dietary vitamin K intake (Sconce *et al*, 2005; Rombouts *et al*, 2010). In such patients supplementing the diet

with 100–150 µg vitamin K or altering the dietary intake of vitamin K to achieve a more consistent intake of vitamin K has been shown to reduce INR fluctuations in selected patients with unstable INRs and to improve overall anticoagulation control in patients with an unexplained instability of response to warfarin (Ford *et al*, 2007; Rombouts *et al*, 2007; Sconce *et al*, 2007; de Assis *et al*, 2009).

10.5 Patient records

All patients on warfarin should have a written copy of their INR result, which should indicate any dose changes that are necessary and the date for the next INR check. Patients should be aware of the reasons for anticoagulation, their target INR and the duration of treatment.

10.6 Drug interactions

Many drugs, whether prescribed, over the counter, herbal or alternative remedies, can interact with warfarin. Up-to-date information can be found in the British National Formulary (<http://bnf.org/bnf/index.htm>). When prescribing, a non-interacting drug should be chosen when possible. For short courses of a new drug, warfarin dose adjustment is not essential. For a drug change lasting more than 7 d an INR test should be performed 3–7 d after starting the new medication so that the warfarin dose can be adjusted on the basis of the INR result.

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Recommendations

- For patients on warfarin, computer-assisted dosing is superior to manual dosing (1A).
- Self-Testing and self-management of warfarin is associated with improved anticoagulant control but may not be suitable for most patients (2B).
- All patients on warfarin must have a written record of their results and dose changes (2C).
- In individuals with an unstable INR, supplementing the diet with 100–150 µg vitamin K may improve anticoagulant control (2B).
- All patients on warfarin who are prescribed a drug that may interact with it should have an INR performed after 3–5 d (2C).

Authorship contributions

All authors contributed to writing the manuscript and all reviewed the final document and agreed the recommendations.

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