MANAGEMENT OF WARFARIN REVERSAL

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Review Date	
Ratified by	
Consultation process	Developed in collaboration with the above authors, circulated to clinical area leads for dissemination and comment To be approved by members of the Hospital Transfusion Committee
Objective	To provide a guideline for best clinical practice when managing warfarin reversal therapy.
Clinical condition	Applies to patients who need warfarin reversal to lower their INR or who are on warfarin and bleeding, or about to enter into surgery.
Target Patient Group	Those identified as having a bleeding risk secondary to oral anticoagulants by their clinician. Those patients on oral anticoagulation who are due to undergo surgery or invasive procedures.
Target Professional Group	All clinicians
References and Source Documents	BCSH "Guidelines on oral anticoagulation", *British Journal of Haematology*, 1998, **101**, 374-387. BCSH "Guidelines on oral anticoagulation (warfarin): third edition-2005 update", draft guideline, BCSH website http://www.bcshguidelines.com/ Blood Transfusion Services of the United Kingdom (2001) BMA *British National Formulary no 50*, BMA 2005 *Handbook of Transfusion Medicine 3rd Edition* HMSO: London Octaplex: Summary of product characteristics 6/12/05, Octapharma Based on Hull and East Yorkshire Hospitals NHS Trust Guidelines
Recommendations	Flowchart should be available for use by all clinicians. Any deviation from this guideline should be discussed with the on-call Haematologist via switchboard.
Clinical algorithms	Flowchart for the management of warfarin reversal. Prescribing criteria checklist.

1. The Bleeding Patient

Bleeding while on oral anticoagulants increases significantly with INR levels > 5.0. Therapeutic decisions are dependent on the INR and whether there is minor or major bleeding. The dose of vitamin K used to reverse over-anticoagulation depends on the INR. Recommendations for management are given in Table 1.

INR range/presence of bleeding?	**Action required**
INR>3.0 and <6.0 (target INR 2.5) INR>4.0 and <6.0 (target INR 3.5) No bleeding	(1) Reduce warfarin dose or stop. (2) Restart warfarin when INR<5.0.
INR>6.0 and <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 0.5-2.5mg of vitamin K (oral). (IV if oral not available)
Major bleeding	(1) Stop warfarin. (2) Give prothrombin complex concentrate (prescribe as PCC Octaplex) **or** FFP (15 ml/kg) (if PCC Octaplex not available). (3) Give 10 mg of vitamin K (I.V).

Table 1

Note that fresh frozen plasma (FFP) only has a partial effect, is not the optimal treatment, and should never be used for the reversal of warfarin anticoagulation in the absence of severe bleeding. It has been shown that FFP contains insufficient concentration of the vitamin K factors (especially F IX) to reverse the bleeding deficiency (although it will reduce the INR).

1.1. Major/life threatening bleeding

- Relevant to patients with intracranial or rapid onset neurological signs, intra-ocular (not conjunctival), compartment syndrome, pericardial bleeds or those with active bleeding and shock in need of urgent clinical assessment.
- Contact the on-call Haematologist if required at this stage.
- Stop warfarin and reverse anticoagulation with vitamin K and prothrombin complex concentrate (PCC Octaplex) or FFP if PCC Octaplex is not available. PCC Octaplex is only available on approval of the on-call Haematologist.
- Anticoagulation can be effectively reversed with PCC Octaplex and vitamin K 10mg by slow intravenous injection.

- Patients receiving warfarin may have an underlying hypercoagulable state and infusion of prothrombin complex concentrate (PCC Octaplex) may exacerbate this resulting in thrombotic events.

- In the absence of available concentrate licensed for this use, emergency treatment with 15 ml/kg of FFP and intravenous vitamin K 10mg will partially reverse anticoagulation, though the levels of individual factors will typically remain < 20% and larger doses should be given if possible (recommend 30ml/kg of FFP).

- For patients with prosthetic heart valves, full reversal of oral anticoagulants with vitamin K may result in prolonged oral anticoagulant resistance with the possibility of valve thrombosis and thromboembolism. Consideration should be given to a lesser dose of vitamin K (1-5mg) depending on the clinical situation.

- Once PCC Octaplex has been given, wait 20 minutes and perform another clotting screen and assess the degree of correction of INR.

- Seek further advice if no improvement takes place.

- The degree of reversal must be decided on an individual basis. All patients with bleeding should be evaluated to identify if there is a local anatomical reason for bleeding.

1.2. Significant bleeding without haemodynamic compromise

- Stop warfarin.

- Give Vitamin K 2-10mg IV depending on severity of bleed.

- Consider using PCC Octaplex.

- Recheck clotting screen at 4 hours or sooner if there is clinical deterioration.

- Repeat if necessary and seek haematological advice.

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

1.3. Minor bleeding

Relevant to patients with INR> 8.0, no bleeding or minor bleeding.

- Stop warfarin.

- If no other risk factors for haemorrhage stop treatment until INR < 5.0. Monitor INR daily or on alternate days until < 5.0.

- If risk factors for haemorrhage or minor bleeding (e.g. age >70 years, previous bleeding complications, epistaxis) consider giving vitamin K 2mg oral or 1mg IV.

- Recheck clotting screen if there is clinical deterioration.

2. INR too high but not bleeding

2.1. INR > 3.0 and < 6.0 (target INR of 2.5)
INR > 4.0 and < 6.0 (target INR of 3.5)

- Reduce the warfarin dose or stop altogether, reassess regularly.
- Restart warfarin when INR < 5.0.

2.2. INR > 6.0 and < 8.0

- Stop warfarin, reassess regularly.
- Restart warfarin when INR < 5.0

3. The Warfarin Patient and Surgery

Many patients can undergo dental procedures, cataract surgery and diagnostic endoscopy without interruption of anticoagulant therapy; refer to departmental guidelines.

3.1. Planning for Minor Surgery (partial reversal)

- 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.
- 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, anaesthetist and haematologist together must decide if the level of anticoagulation is safe for surgery to take place.

3.2 Planning for Major Surgery

- For major surgery, oral anticoagulants should be stopped 5 days prior to surgery as once warfarin is stopped it typically takes about 4 days for the INR to reach 1.5. Pre-and post-operative “bridging anticoagulation” with heparin is not routinely required.
- Stopping warfarin for surgery in patients with prosthetic heart valves. The British Committee for Standards in Haematology guidelines point out that the statistical risk of thromboembolism is quite low in patients who are off anticoagulation for a few days. However, it is generally agreed that some subgroups of patients are at greater risk:-

  a) Mitral valve > Aortic valve

  b) Caged ball > Tilting disc valves

  c) Previous episode of arterial embolism

  d) Severe left ventricular dysfunction

  Unfortunately, this information is not usually available to the junior doctor or nurse who is given the task of arranging the surgical procedure and who contacts the haematology department for advice. In an ideal world, the patient’s cardiologist should be consulted about their relative risk of arterial embolism before planning a surgical procedure. However, this is rarely possible in practice for a variety of reasons.

If a patient cannot be confirmed as falling into a low risk group, the following options are available for peri-operative heparin cover while they are off warfarin:

i. Intravenous unfractionated heparin infusion aiming for an APTT patient: control ratio of 1.5-2.0. Commenced when INR <2.0 and discontinued 4 hours prior to surgery. (In practice, the dose/response curve is steep and it is often difficult to maintain patients in the therapeutic range).

OR

ii. Subcutaneous low molecular weight heparin at a therapeutic dose (e.g. Tinzaparin 175 unit/Kg) given once daily. Commenced when INR <2.0. No blood test monitoring required. Discontinued 24 hours prior to surgery.

Heparin is re-started post-operatively once haemostasis is achieved and at the discretion of the surgeon, particularly for high-risk procedures such as neurosurgery. Heparin is discontinued once patient has been re-warfarinised to a therapeutic INR.

- Effective management of patients receiving oral anticoagulants who are due to undergo major surgery requires adequate pre-operative planning and close liaison between surgeons, anaesthetists, haematologists and cardiologists if appropriate.

3.3 Rapid reversal necessary (urgent surgical procedure)

Urgent means clinically essential, not administratively convenient, to do immediate surgery.

For reversal in 4 to 24 hours:
- Vitamin K 2mg Oral or 1mg IV.

For reversal within 1 hour:
- Prothrombin complex concentrate.

Do not use FFP for rapid reversal unless prothrombin complex concentrate (PCC Octaplex) is not available. Always consult a Haematologist.

4. Post-operative reintroduction of oral anticoagulants

- Timing of reintroduction of oral anticoagulants will depend on the risk of post-operative haemorrhage.
- The 48-72 hour 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.

5. Administration of Prothrombin Complex Concentrate (PCC Octaplex®)

- The PCC used in Shrewsbury and Telford Hospitals NHS Trust is Octaplex® (Octapharma), a concentrate of coagulation factors II, VII, IX and X available via the transfusion laboratory. **It will only be issued following discussion with the on-call Haematologist.**
- 25 i.u/ml in 20 ml bottles (500 i.u. bottles).
- The dose of PCC Octaplex is dependent upon the INR and the patient's body weight in kilograms (Table 2). The maximum dose is 120ml (6 x 500 i.u. bottles)

Initial INR	2-2.5	2.5-3	3-3.5	>3.5
Dose (ml PCC Octaplex /kg)	1ml/kg	1.4 ml/kg	1.7ml/kg	2ml/kg

Table 2. Administration of PCC Octaplex.

- The product is reconstituted from a dried powder using the supplied diluent, using an aseptic technique. It should then be administered as an IV infusion initially at 1ml per minute increasing to 3ml per minute in the absence of any allergic or anaphylactic reactions. Rates up to 10ml per minute have been used in emergencies but this rate is currently not licensed.
- Contraindications to PCC Octaplex include known heparin–induced thrombocytopenia or hypersensitivity to heparin or sodium citrate.
- Recognised adverse reactions to Octaplex include anaphylaxis and thrombosis. The product is a pooled plasma product and there is a theoretical risk of transmission of Hepatitis A and Parvovirus B19. Viral inactivation processes during the manufacture of Octaplex are considered effective against HIV, Hepatitis B and C. There remains the possibility that the transmission of currently unknown infectious agents could be associated with the administration of this product.
- Regular monitoring of the coagulation status is indicated during the treatment, as the use of high doses of PCC Octaplex has been associated with instances of myocardial infarction, DIC, venous thrombosis and pulmonary embolism.
- The on-call Haematologist can be contacted via switchboard.
- Further information on dosage and administration. can be found in the PCC Octaplex information leaflet which accompanies the product.
- As PCC Octaplex is a human blood product, the volume administered and batch numbers must be recorded within the patients medical notes

6. Vitamin K (phytomenadione)

- In most cases, oral vitamin K is as effective as intravenous with the delay in action hardly influenced by the absorption time.
- Only 0.5mg is required to reduce the INR from > 5.0 to a target level of 2.0-3.0.
- Vitamin K tablets usually contain 10mg per dose 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 at a reduced dose (1-2mg).
- Allergic reactions following intravenous administration are rare with new preparations of vitamin K. If the INR is still too high at 24h the dose of vitamin K can be repeated.
- Subcutaneous absorption of vitamin K is erratic and not recommended.

7. Description of a target INR

The international normalized ratio (INR) is a recommended method for reporting prothrombin time results for control of oral anticoagulation. 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 INR should not be used as a routine measure of coagulation in areas other than warfarin therapy; e.g. the prothrombin time is the primary measurement in assessing the severity of paracetamol overdose.

8. References

BCSH "Guidelines on oral anticoagulation (warfarin): third edition-2005 update", draft guideline, BCSH website http://www.bcshguidelines.com/.

BCSH 'Guidelines on oral anticoagulation', *British Journal of Haematology*, 1998, **101**, 374-387.

BCSH 'Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant', *British Journal of Haematology*, 2004, **126**, 11-28.

Gohlke-Barwolf C. VALVE DISEASE: Anticoagulation in valvar heart disease: new aspects and mangement during non-cardiac surgery. Heart 2000; **84**; 567 572.

Douketis JD. Perioperative anticoagulation management in patients who are receiving oral anticoagulation therapy: a practical guide for clinicians. Thrombosis Research, 2003, **108**, 3-13.

9. Flow chart

Please note; the following flow chart is intended to be centred on one sheet of A4 and laminated, for use as a quick reference guide.

Flowchart for the management of warfarin reversal

The bleeding patient

Major/life threatening bleeding

- Intracranial
- Intraocular
- Compartment syndrome
- Pericardial
- Active bleeding and shock

Urgent clinical assessment
Check clotting screen
Contact Haematologist

- Stop Warfarin
- Vitamin K 10mg IV
- PCC (Octaplex®)

Check clotting screen 20 minutes post administration

- Adequate correction – recheck in 4 hours
- Inadequate correction – consider other causes, seek Haematological advice

Significant bleeding without haemodynamic compromise

- Stop Warfarin
- Vitamin K 2-10mg IV
- Consider PCC (Octaplex®)
- Check clotting screen at 4 hours or sooner if clinical deterioration

Minor bleeding

- Stop Warfarin
- Consider Vitamin K 2mg Oral or 1mg IV
- Check clotting screen at 24 hours or sooner if clinical deterioration

INR too high but not bleeding

INR >3.0 and <6.0 (target INR of 2.5)
INR >4.0 and <6.0 (target INR of 3.5)

- Reduce Warfarin dose or stop
- Restart Warfarin when INR < 5.0

INR >6.0 and <8.0

- Stop Warfarin
- Restart Warfarin when INR < 5.0

The warfarin patient and surgery

- Elective surgery- always plan in advance
- Decide on a 'safe'INR for the procedure

Full warfarin reversal

- Stop Warfarin 5 days pre-op
- Check INR on admission or morning of operation

Rapid reversal necessary (urgent surgical procedure)

Reversal in 4 to 24 hours

- Vitamin K 2mg Oral or 1mg IV

Reversal within 1 hour

- PCC (Octaplex®)

Note:

- Prothrombin Complex Concentrate (PCC) may induce a prothrombotic state. Use with caution in patients with DIC or decompensated liver disease. See product insert for more information about dosage, administration or contraindications.
- To give PCC (Octaplex®) use a slow IV infusion as detailed in trust guidance or datasheet. Obtain via the Transfusion Laboratory (ext 3542 RSH; ext 4305 PRH).
- In serious but non-life threatening bleeding (e.g. GI bleeding or epistaxis without haemodynamic compromise) prompt reversal with IV vitamin K is indicated.
- Vitamin K (phytomenadione) may rarely cause anaphylaxis. Give by slow IV bolus.
- Oral vitamin K: use the Trust preparation of IV Konakion®(Roche) given orally. The vial contains 10mg/ml; dilute appropriate dose in small amount of juice/water after drawing up in 1ml insulin syringe. Alternative the Konakion® paediatric formulation may be used.
- For more information please refer to the accompanying Trust guidelines or the BCSH Guidelines 'Guidelines on oral anticoagulation: 3rd edition', 1998.
- Lower doses of Vitamin K should be considered for patients with prosthetic heart valves (see page 3)

Prescribing Criteria Checklist for
Octaplex® Prothrombin Complex Concentrate (PCC) to reverse warfarin

1. Management	
The use of Prothrombin Complex Concentrate (PCC Octaplex) to reverse the effects of warfarin should only be initiated upon the advice of the on call Haematologist, once the following criteria have been established. ☐ Is the patient on oral anticoagulation?	☐ Yes Proceed to section 2 ☐ No Patient is NOT eligible for PCC Octaplex
2. Presence of major/life threatening bleeding	
Any of the following: ☐ Intracranial bleeding or rapid onset neurological signs ☐ Intraocular bleeding (not conjunctival) ☐ Compartment syndrome ☐ Pericardial bleed ☐ Active bleeding and shock	☐ Yes Proceed to section 5 ☐ No Proceed to section 3
3. Significant bleeding without heamodynamic compromise	
☐ Patient continues to bleed despite the stopping of warfarin and administration of vitamin K as per Trust guideline	☐ Yes Proceed to section 5 ☐ No Proceed to section 6
4.Rapid warfarin reversal required for urgent surgical procedure due to patients clinical condition (NOT FOR ADMINISTRATIVE CONVENIENCE)	
☐ Surgical/Interventional procedure required within 1 hour	☐ Yes Proceed to section 5 ☐ No Patient is NOT eligible for PCC Octaplex
5. Contact on call Consultant Haematologist via switchboard for advice regarding administration of Prothrombin Complex Concentrate (PCC Octaplex)	
6. Consult Trust Guidelines on warfarin reversal for further management	
7. Patient meets *all* the inclusion criteria and has *no* contraindications or exclusions	☐ Yes ☐ No

Patient Name: …… Hospital No.:……

Completed by: ……

Date/time: ……..:…… on …../…../…..

Referral details to Haematologist: ……