North West Anglia
NHS Foundation Trust

Guidelines for the Management of Anticoagulant Reversal in Adults

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Summary of key points in this document

- To provide best management for patients who are anticoagulated on Warfarin, Low Molecular Weight Heparins (Dalteparin), Dabigatran, Rivaroxaban, Apixaban in order to reduce the risk of bleeding and to treat active bleeding in those in whom it has occurred.

- The guidance is in keeping with the recommendations of the British Committee for Standards in Haematology (Mike Makris et al Nov 2012).

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Guidelines for the Management of Anticoagulant Reversal in Adults

1. Introduction

1.1 Patients who are taking warfarin may need, for various reasons, to have the effects of warfarin reversed. Major or life-threatening bleeding is seen in 2% of patients on warfarin each year. Fatal haemorrhage complicates warfarin use in 0.25% of patients annually. This document covers management of bleeding associated with other anticoagulants: Low Molecular Weight Heparins (Dalteparin), Dabigatran, Rivaroxaban, Apixaban, Edoxaban

1.2 These guidelines are based on scientific evidence and professional consensus, but are not intended to replace clinical judgement.

2. Purpose

The purpose of these guidelines is to provide best clinical practice when managing anticoagulant reversal therapy.

3. Scope

3.1 They apply to all adult patients identified as at risk of bleeding by their clinician:

- Who are on an anticoagulant and bleeding or
- Who require immediate surgery.

3.2 These guidelines should be used Trust wide by all clinicians involved in the care of adult patients who need reversal of their warfarin therapy.

3.3 Any deviation from these guidelines should be discussed with a Haematologist.

3.4 For paediatric guidelines, the advice of a Consultant Haematologist should be sought.

4. Patients who are bleeding

4.1 The decisions must be made on an individual basis and should consider:

4.1.1 The presence of major/minor bleeding and risk of bleeding;

4.1.2 Patient factors (including risk of falls);

4.1.3 External factors (need for urgent/semi-urgent invasive procedure and type of procedure);

4.1.4 The current International Normalised Ratio (INR) – the risk of bleeding increases exponentially with an INR >5;

4.1.5 The reason for anticoagulation – e.g. atrial fibrillation, prosthetic heart valve, the risk of thrombosis.

4.2 Bleeding while on warfarin increases significantly with INR levels >5.0.

4.3 Please 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). FFP also carries the risk of transfusion transmitted infection and other transfusion complications. The rationale for prescribing FFP must be recorded in the patient's notes.

5. Vitamin K (phytomenadione)

5.1 Vitamin K is an antidote for warfarin. Due to near complete absorption, oral vitamin K is as effective as intravenous with the delay in action hardly influenced by the absorption time.

5.2 Only 500 microgrammes is required to reduce the INR from > 5.0 to a target level of 2.0 – 3.0.

5.3 Vitamin K preparations can be administered orally.

5.4 Allergic reactions following intravenous administration are rare with newer preparations of vitamin K. If the INR is still too high at 24hours the dose of vitamin K can be repeated.

5.5 Subcutaneous absorption of vitamin K is erratic and not recommended.

5.6 Slow intravenous injection doses should be diluted with 55ml of glucose 5% vitamin K. A sustained response is achieved with intravenous vitamin K. Oral or intravenous administration of vitamin K can be expected to reverse warfarin 4 - 6 hours after administration. Only 0.5mg vitamin K is required to reduce the INR from about 5.0 to a target level of 2.0-3.0. Reverse anticoagulation.

6. Prothrombin Complex Concentrate (PCC) e.g. Octaplex

Please see also Guidelines on the use of OCTAPLEX® (Prothrombin complex concentrate/PCC) for rapid reversal of warfarin in association with life threatening bleeding (C0254).

6.1 Octaplex is a prothrombin complex concentrate (PCC) licensed for warfarin reversal. It is derived from human plasma (non-UK) and contains the clotting factors II, VII, IX and X. PCCs provide immediate reversal of warfarin but the

effect will begin to wear off after 6-12 hours. Octaplex is a virally inactivated product which reduces the risk of transmission of viral infections especially enveloped viruses such as HIV. Like other plasma products however, there remains a risk of prion diseases namely variant Creutzfeldt-Jakob Disease (vCJD).

6.2 The dose of octaplex is 25-50 units per kg body weight; (maximum dose 3,000 units).The patient's weight is required.

Wt(Kg)	INR 2-2.5	INR 2.5-3	INR 3-3.5	INR>3.5
50	1500 iu	2000 iu	2500 iu	2500 iu
60	2000 iu	2000 iu	2500 iu	3000 iu
70	2500 iu	2500 iu	3000 iu	3000 iu
80	2500 iu	3000 iu	3000iu	3000 iu
90	2500 iu	3000 iu	3000 iu	3000 iu
100	3000 iu	3000 iu	3000 iu	3000 iu

6.3 Phone the Blood Bank to request the Octaplex, giving full patient details, your name and contact number, the name of the duty haematology doctor you spoke to and the agreed number of units required.

6.4 Octaplex can be collected from the Blood Bank within 10mins of request. It does not need to be thawed but does require labelling. Please arrange for someone to collect the product from the blood bank and ensure the nurses are aware that Octaplex has been written up and is required immediately.

6.5 May not be suitable for treatment of Jehovah's Witnesses as it contains human material.

6.6 Note: Fresh Frozen Plasma (FFP) – not recommended. The British Committee for Standards in Haematology guidelines state that FFP should not be used to reverse warfarin unless no Prothrombin Complex Concentrate is available in the case of a severe bleed. FFP must be authorised by the duty Haematology doctor.

7. Low Molecular Weight Heparin (Dalteparin) Reversal

7.1 For LMWH administration within 8h of the time of requirement for correction of anticoagulation: give Protamine sulphate (1 mg per 100 anti-Xa units of LMWH). If ineffective, consider further Protamine sulphate 0.5 mg per 100 anti-Xa units. Protamine sulphate should be given slower than 5 mg/min to minimise the risk of adverse reactions.

7.2 For LMWH administration greater than 8h from the time of requirement for correction of anticoagulation: consider smaller doses of protamine.

7.3 Consider Recombinant FVIIa if there is continued life-threatening bleeding despite protamine sulphate and the time frame suggests there is residual effect from the LMWH contributing to bleeding.

7.4 There is no specific antidote for fondaparinux. Management of bleeding should be through cessation of treatment and general haemostatic measures. Recombinant FVIIa should be considered for critical bleeding.

8. Dabigatran

8.1 Management of bleeding should be through cessation of treatment and general haemostatic measures. In bleeding patients who have taken a dose of dabigatran in the last 2 hours, consider oral activated charcoal to prevent further absorption.

8.2 In situations with ongoing life-threatening bleeding, a specific antidote Idarucizumab (Praxbind) can be given IV as a bolus. Discussion with the Haematologist on call is necessary.

9. Rivaroxaban, Apixaban, Edoxaban

9.1 There is no specific antidote for Rivaroxaban, Apixaban or Edoxaban. Management of bleeding should be through cessation of treatment and general haemostatic measures.

9.2 In situations with ongoing life-threatening bleeding, PCC, APCC and rFVIIa should be considered, discuss with Haematologist.

10. Guide to Reversal of Oral Anticoagulation on Warfarin

See Appendix 1.

11. Ratification

This guideline will be approved by the Hospital Thrombosis Committee & the Formulary & Medicines Management Committee. It will be ratified by the Quality Governance Operational Committee.

12. Distribution

This guideline will be available on SharePoint.

13. References

13.1 Makris M & Watson HG, (2002), Reversal of coumarin-induced over-anticoagulation. British Journal of Haematology 2002;118:926.

13.2 Wilson SE, Watson HG, Crowther MA., (2004), The use of low dose oral vitamin K to reverse asymptomatic elevation of the INR: A systematic review. Canadian Med Journal 2004;170(5): 821-824.

13.3 David Keeling, Trevor Baglin, Campbell Tait, Henry Watson, David Perry, Caroline Baglin,Steve Kitchen and Michael Makris, (2011), British Committee for Standards in Haematology Guidelines on oral anticoagulation with warfarin – fourth edition British Journal of Haematology 2011;154(3):311-24.

13.4 Mike Makris, Joost J. Van Veen,Campbell R. Tait, Andrew D. Mumford and Mike Laffan on behalf of the British Committee for Standards in Haematology, (2012), Guideline on the management of bleeding in patients on antithrombotic agents, British Journal of Haematology, 2012, 160,35–46

14. Associated Documents

Guidelines on the use of OCTAPLEX rapid reversal of warfarin in association with life threatening bleeding (C0254).

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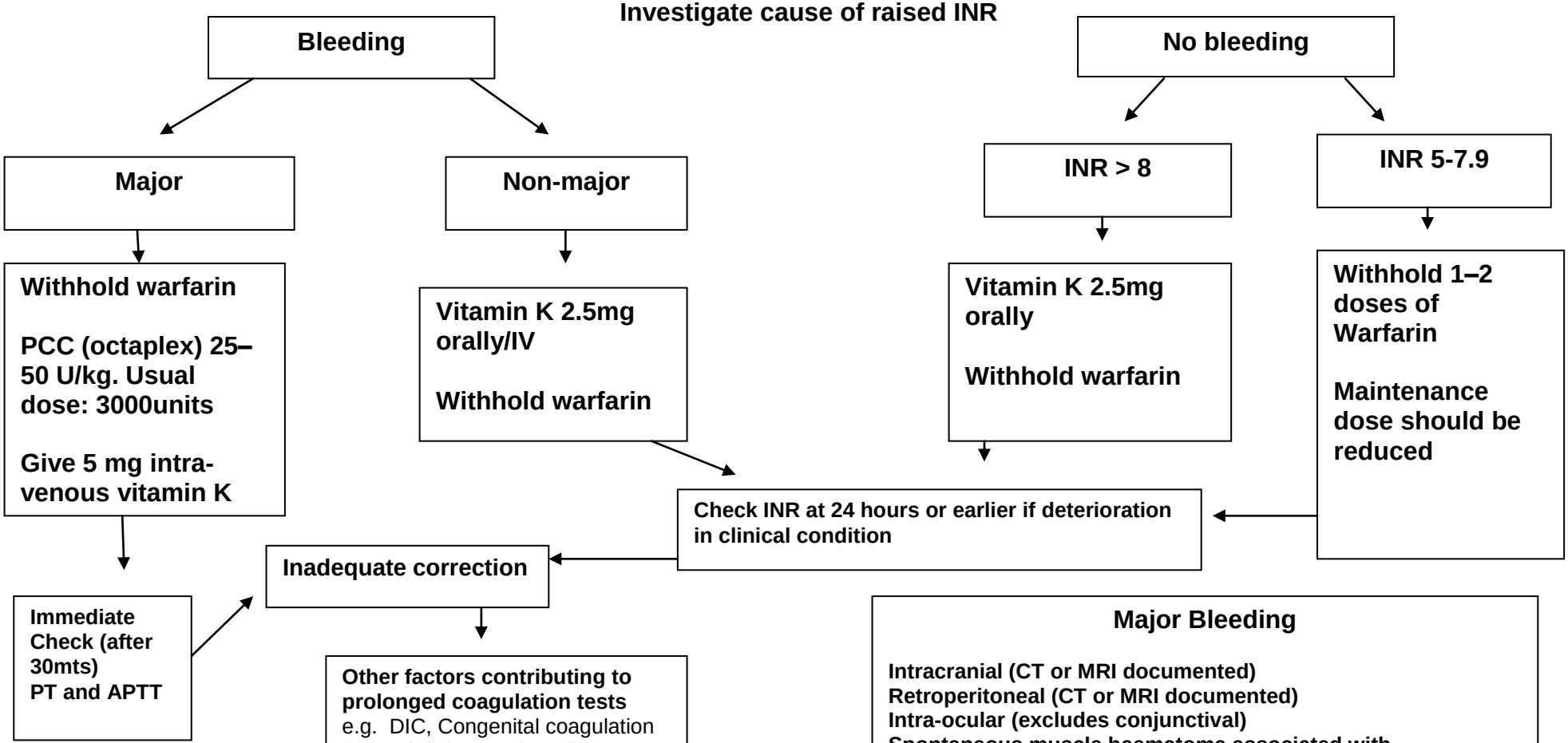
Appendix 1 Guide to Reversal of Oral Anticoagulation on Warfarin

Investigate cause of raised INR



Major Bleeding

Intracranial (CT or MRI documented)
Retroperitoneal (CT or MRI documented)
Intra-ocular (excludes conjunctival)
Spontaneous muscle haematoma associated with compartment syndrome
Pericardial
Non-traumatic intra-articular
Any invasive procedure to stop bleeding
Active bleeding from any orifice plus BP ≤ 90mmHg systolic, or oliguria or ≥20g/l fall in haemoglobin

Quality Assurance Checklist - Version Number: 3 Appendix: 2

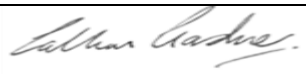
		Y/N/n/a	COMMENTS (where necessary)
1	**Title of document** Guidelines for the Management of Anticoagulant Reversal in Adults (C0161)		
2	**Type of document (e.g. guidance, code of practice)**	Guideline	
	Is it clear whether the document type is (e.g. guideline, procedure)?	Yes	
3	**Introduction**		
	Are reasons for the development of the document clearly stated?	Yes	
4	**Content**		
	Is there a standard front cover?	Yes	
	Are the key points identified?	Yes	
	Is the document in the correct format?	Yes	
	Is the purpose of the document clear?	Yes	
5	**Approval Route**		
	Does the document identify which committee/group will approve it?	Yes	
6	**Review Date**		
	Is the review date identified?	Yes	

If answers to any of the above questions is 'no', then this document is not ready for ratification, it needs further review.

Compliance Team:		
1.	Date of Compliance Team approval	27/04/2017
2.	Comments to author for any amendments	
3.	Name of compliance lead	Jim Walker, Quality Governance & Policies Assistant

Approval Committee: Hospital Thrombosis Committee, FMMC

If the committee/group is happy to approve this document would the chair please sign below and send the document and the minutes from the approval committee to the author. To aid distribution all documentation should be sent electronically wherever possible.

Name	Callum Gardner	**Date**	**23 March 2017**
Signature			

Ratifying Committee: QGOC

If the committee/group is happy to ratify this document would the chair please sign below and send the document and the minutes from the ratifying committee to the author. To aid distribution all documentation should be sent electronically wherever possible.

Name	KANCHAN REGE	**Date**	9.5.17.
Signature