Nottingham University Hospitals NHS Trust

Full Title of Guideline:	2401 - Management of adult patients receiving a vitamin K antagonist (e.g. Warfarin) who are over-anticoagulated, bleeding, or in need of an urgent invasive procedure
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Explicit definition of patient group to which it applies ***(e.g. inclusion and exclusion criteria, diagnosis):***	Adult patients receiving a vitamin K antagonist who are over-anticoagulated, bleeding, or in need of an urgent invasive procedure
Changes from previous version ***(not applicable if this is a new guideline, enter below if extensive):***	Revised section relating to Major Bleeding Updated the links to other guidelines following change in system to Koha Changed terminology referring to Medway to Careflow
NICE guidance reference:	Not applicable
Summary of evidence base this guideline has been created from:	Based on BCSH Guidelines on oral anticoagulation with warfarin – fourth edition (2011) Expert opinion
This guideline has been registered with the trust. However, clinical guidelines are guidelines only. The interpretation and application of clinical guidelines will remain the responsibility of the individual clinician. If in doubt contact a senior colleague or expert. Caution is advised when using guidelines after the review date or outside of the Trust.	

Management of adult patients receiving a vitamin K antagonist who are over-anticoagulated, bleeding, or in need of an urgent invasive procedure

This document provides guidance for the management of patients receiving a vitamin K antagonist (including warfarin, acenocoumarol and phenindione), who are over-anticoagulated, bleeding or in need of an urgent invasive procedure.

Exclusions to this guideline:

- Patients receiving a vitamin K antagonist who require an elective invasive procedure (see separate guideline for peri-operative management of patients on a vitamin K antagonist (2854, Link)).

- Patients taking direct oral anticoagulants, including rivaroxaban, apixaban, dabigatran and edoxaban (see separate guidelines for patients receiving Apixaban, Rivaroxaban or Edoxaban requiring emergency surgery or treatment for haemorrhage (2805, Link), and patients receiving Dabigatran requiring emergency surgery or treatment for haemorrhage (2173, Link)).

- Paediatric patients (during normal working hours please contact paediatric haematologist for advice; out of hours please contact on call haematologist for advice).

Contents:

Over-anticoagulation in Outpatient (Not Bleeding)

- The following applies ONLY to outpatients dosed by the NUH Anticoagulation Service. Patients who are dosed by their own GP should be discussed directly with their GP surgery, or when closed the out of hours GP service.

- Oral vitamin K (phytomenadione) has been shown to reduce the INR of patients over-anticoagulated by Warfarin or other vitamin K anticoagulants.

- Investigate for cause of high INR (e.g. drug interactions, alcohol intake, liver disease, cardiac failure).

- If INR>8 patient contacted by anticoagulation clinic and attends NEMS at Platform One Surgery for repeat INR and FBC and administration of vitamin K as below

INR	**Recommended action**
INR 3-6 (target INR range 2-3)	Reduce warfarin dose
INR 4-6 (target INR range 2.5-3.5 or 3-4)	Reduce warfarin dose
INR 6-8	Stop warfarin for 1-2 days, reduce dose and check INR on day 3
INR >8 (Excluding patients with Mechanical Valves)	Stop warfarin. Patient to attend NEMS for repeat INR and FBC **Give oral vitamin K (phytomenadione) 2mg** (Konakion MM Paediatric 2mg in 0.2ml) diluted in water Check INR the following day and re-start warfarin only when INR in therapeutic range. Follow up by anticoagulation clinic.
INR >8 (Patients with Mechanical Valves only)	Stop warfarin. Patient to attend NEMS for repeat INR and FBC **Give oral vitamin K (phytomenadione) 1mg** (Konakion MM Paediatric 1mg in 0.1ml) diluted in water INR must be checked the following day (even if falls at a weekend) and re-start warfarin only when INR in therapeutic range. Follow up by anticoagulation clinic.

Over-anticoagulation in Inpatient (Not Bleeding)

- Oral vitamin K (phytomenadione) has been shown to reduce the INR of patients over-anticoagulated by Warfarin or other vitamin K anticoagulants.

- Investigate for cause of high INR (e.g. drug interactions, alcohol intake, liver disease, cardiac failure).

INR	**Recommended action**
INR 3-6 (target INR range 2-3)	Reduce warfarin dose *NB: Reduce weekly dose by 10-20%*
INR 4-6 (target INR range 2.5-3.5 or 3-4)	Reduce warfarin dose *NB: Reduce weekly dose by 10-20%*
INR 6-8	Stop warfarin for 1-2 days, reduce dose and check INR on day 3 *NB: Reduce weekly dose by 50%*
INR >8 (Excluding patients with Mechanical Valves)	Stop warfarin. Repeat INR and check FBC **Give oral vitamin K (phytomenadione) 2mg** (Konakion MM Paediatric 2mg in 0.2ml) diluted in water Check INR the following day and re-start warfarin only when INR in therapeutic range. Follow up by anticoagulation clinic.
INR >8 (Patients with Mechanical Valves only)	Stop warfarin. Repeat INR and check FBC **Give oral vitamin K (phytomenadione) 1mg** (Konakion MM Paediatric 1mg in 0.1ml) diluted in water INR must be checked the following day (even if falls at a weekend) and re-start warfarin only when INR in therapeutic range. Follow up by anticoagulation clinic.

For further advice about the management of inpatients on Warfarin, see:

- Warfarin Guideline (3059, Link)
- Warfarin Dosing Quick Guide (3115, Link)

Bleeding or in need of Urgent Invasive Procedure

- If the patient is an outpatient and bleeding, they should be advised to come to the hospital for assessment (which should include establishing the cause of bleeding).
- Check INR urgently (please inform Haematology Lab that result required urgently, and hand deliver sample to the Lab to minimise any delays).
- Further action will be guided by the clinical situation and the INR result.

Minor Bleed (e.g. minor trauma, minor nose bleeds etc)	
INR	**Recommended action**
INR <4	Reduce warfarin dose (aiming to get INR within usual target INR range) If minor bleeding despite INR being within target INR range, then plan for anticoagulation needs to be reviewed (e.g. brief interruption of warfarin)
INR 4-8	Stop warfarin for 2 days Restart at appropriate dose reduction when INR in therapeutic range
INR >8 (Excluding patients with Mechanical Valves) **Or** if other risk factors for bleeding (e.g. age>70 years, previous history of bleeding, abnormal LFT's, malignancy, tendency to falls)	Stop warfarin. Check FBC **Give IV vitamin K (phytomenadione) 2mg** (Konakion MM Paediatric 2mg in 0.2ml) by direct injection over at least 30 seconds but usually over 3-5 minutes Check INR in 6-8 hours and re-start warfarin only when INR in therapeutic range
INR >8 (Patients with Mechanical Valves only)	Stop warfarin. Check FBC **Give IV vitamin K (phytomenadione) 1mg** (Konakion MM Paediatric 1mg in 0.1ml) by direct injection over at least 30 seconds but usually over 3-5 minutes Check INR in 6-8 hours and re-start warfarin only when INR in therapeutic range

Major Bleed or in need of Urgent Invasive Procedure (within 24 hours)

- **DO NOT WAIT FOR THE INR RESULT**
- Stop warfarin
- **Give IV vitamin K (phytomenadione) 10mg (Konakion MM 10mg in 1ml) immediately** by direct injection over at least 30 seconds but usually over 3-5 minutes
    - Vitamin K should be given irrespective of the indication for anticoagulation (ie AF, DVT or PE, mechanical valve).

- **Prothrombin complex concentrate (PCC) can be considered if Life-threatening Bleeding or in need of Emergency Surgery (within 4 hours)**, however it is important to bear in mind that there is a 5-7% risk of thrombotic complications after this treatment and this may influence the decision to use PCC in patients who are at high risk of thrombosis (eg recent proximal DVT or PE, pregnancy, mechanical heart valves).
    - **Intracranial bleeding** (spontaneous or traumatic), PCC can be obtained without the need for authorisation by Haematologist.
        - Please discuss case with Neurosurgeon on call and Haematologist on call if further advice is required about pros/cons of using PCC in a particular case.
    - **Any other context**, PCC can only be obtained once authorised by Haematologist, so please discuss case with Haematologist on call.
        - Please highlight why this is felt to be a life-threatening bleed, or why urgent intervention cannot wait for 4 hours.

NB: If anticoagulation is reversed for patients with mechanical heart valves, a plan for post reversal re-anticoagulation once the situation has stabilised MUST be discussed with Cardiac Surgery.

Further information on Prothrombin complex concentrate (including dosing table) can be found below on Pages 7 and 8.

Urgent Invasive Procedure (but not within the next 24 hours)

- Stop warfarin
- **Give IV vitamin K (phytomenadione) 5mg (Konakion MM 5mg in 0.5ml) immediately** by direct injection over at least 30 seconds but usually over 3-5 minutes
- Recheck INR in 4-6 hours

Prothrombin Complex Concentrate (PCC)

PCC is a pooled factor concentrate licensed for emergency reversal of vitamin K antagonists (e.g. warfarin), when the clinical situation does not allow for the 4-6 hours for vitamin K to take full effect. It is not used to enable elective invasive procedures where warfarin should be discontinued in advance (see separate guideline referenced on page 2), or in situations where reversal with vitamin K will suffice.

It contains factors II, VII, IX and X (plus small amounts of Proteins C, S and antithrombin, as well as heparin), is virally inactivated, and is not blood group specific.

PCC has a baseline thrombotic risk of 5-7%. It should therefore be used with extreme caution in patients at high risk of thrombosis (eg recent proximal DVT or PE, pregnancy, mechanical heart valves). PCC is not recommended for use in patients with disseminated intravascular coagulation or a history of heparin-induced thrombocytopenia (HIT).

In the context of intracranial bleeding, PCC can be obtained without the need for authorisation by Haematologist, but further advice can of course be sought from Neurosurgeon on call and/or Haematologist on call if it's unclear whether proceeding with PCC is the best course of action or not.
In any other context, the case should be discussed with the Haematologist on call, as authorisation is required in order to obtain PCC.

NB: Vitamin K **must** always be given prior to PCC to prevent the INR from rising again after 6-12 hours.

If the use of PCC is required, then the appropriate dose (see below) should be requested on Careflow (see below) and collected from the Blood Transfusion (BT) laboratory.

Dosing

The dose of PCC used within NUH for the reversal of vitamin K antagonists is based on INR as shown in the table below (and differs from the dose used in other indications, which is weight-based).

The maximum dose of PCC is 3000 units.

INR	**1.6-2.9* or UNKNOWN**	**3.0-5.0**	**>5.0**
Dose of Octaplex®	**1000 units**	**2000 units**	**3000 units**

*Prothrombin complex concentrate is not indicated if INR ≤1.5

If there is life-threatening bleeding, or emergency surgery is required, and an INR is not available, 1000 units may be given in the first instance. An additional top-up dose may then be given once INR result is known if INR result is 3.0 or higher and the clinical situation dictates than this is required.

Requesting, Prescribing and Administering PCC

PCC is requested on Careflow through Blood Products/Components (Prothrombin Complex Concentrate) or, in exceptional cases on a Blood Transfusion request form.

It must be collected **immediately** from the BT laboratory. If it is not collected within 2 hours of issue, it will be returned to stock and re-authorisation will be required.

PCC must be prescribed on the Transfusion Record Sheet (TRS) and the infusion documented as per the TRS. It can also be given as a rapid IV infusion or slow IV bolus.

As this is an emergency drug, it should be given immediately. If more than 3 hours has passed since the administration of vitamin K and the commencement of PCC, then consideration should be given as to whether it is still clinically necessary, and a repeat INR checked to confirm dose of PCC is still appropriate.

Reconstitution and administration guidelines are available on the Specific Product Characteristics (Summary of Product Characteristics) / leaflet accompanying the product. Instructions are also available on the Blood Transfusion webpage on the NUH intranet (http://nuhnet/diagnostics_clinical_support/Blood_Transfusion/Pages/Reversal_Warfarin.aspx)

The BT laboratory will NOT accept PCC back in the event of failure to reconstitute. This is rarely a product malfunction and there is usually a solution to this problem. Please contact the haematologist for advice.

Post dose monitoring

Since dose effect is not universally applicable, efficacy of dosing must be determined using the surrogate marker of an INR 10-30 minutes post administration of PCC.
If the INR is not ≤1.5 and the patient is still bleeding, an additional dose may be required so discuss with the haematologist.

NB: Be aware that the risk of thrombosis can extend to up to 30 days post dose, so it is important to be vigilant for thrombosis during this period, and patients should be advised to seek medical attention if they develop any symptoms of concern.

References

RECOMMENDATIONS FOR USE OF PROTHROMBIN COMPLEX CONCENTRATES IN CANADA
Recommendations for the use of prothrombin complex concentrates in Canada, National Advisory Committee on Blood and Blood Products, May 2014