Management of Warfarin in Adult Inpatients

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Division & Speciality:	Cancer and Associated Services (Haematology)
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Ratified by:	
Scope *(Target audience, state if Trust wide):*	All medical staff involved in the prescription and administration of Warfarin oral anticoagulation.
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Explicit definition of patient group to which it applies *(e.g. inclusion and exclusion criteria, diagnosis):*	Adult inpatients >18 years of age who are being treated with warfarin oral anticoagulation
Changes from previous version *(not applicable if this is a new guideline, enter below if extensive):*	Version 1
Summary of evidence base this guideline has been created from:	See reference section
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	

1. Background

The management of oral anticoagulant therapy remains a significant area of risk for the Trust. This is due to the underlying risk of bleeding associated with the drugs themselves and also the increased risks of thrombosis if doses are omitted. It is imperative that the management of patients being treated with these medications is safe, with robust pathways in place. The number of patients receiving long term oral anticoagulant therapy continues to increase and as such, many patients admitted to NUH will already be treated with these agents. Many patients will be treated with the Direct Oral Anticoagulants (DOACs) which do not require regular monitoring. However there remain a significant number of patients who continue to be anticoagulated with warfarin and other Vitamin K antagonists (VKA) which require regular dosing based on monitoring of the INR.

This guideline is intended for the management of patients taking warfarin however aspects of the guidance are equally applicable to other VKA such as phenindione and acenocoumarol. Most out-patients will have their warfarin monitored and dosed through the nurse led NUH anticoagulation service. However there are some GP practices within Nottinghamshire who dose their own patients and there are patients referred in from out of area who may not be known to our services.

Warfarin is available in four different strength tablets: 0.5mg, 1mg, 3mg,and 5mg. Most patients at NUH use 3mg tablets although some patients that are sensitive to warfarin may use 1mg tablets. Patients dosed by other anticoagulation services may use different or multiple strengths and should be kept on their current regime.

This guideline aims to give general advice on the management of warfarin on the inpatient wards and is not a substitute for clinical decision making. Further advice if required can be sought from the Haematology team.

2. Target INR

Warfarin and other VKA medications have a narrow therapeutic index that relies on a targeted INR range for efficacy and reduction of complications. The INR target is specific to the individual patient; this is most commonly 2.5 (range 2.0 – 3.0) but can be as high as 3.5 (range 3.0 – 4.0) for patients at the highest risk of thrombosis. If the INR is above target this increases the risk of bleeding for the patient. If the INR is sub-therapeutic this increases the risk of thrombosis. The individual target range for the patient can be found on MEDWAY if the patient is monitored by the NUH anticoagulation service, or in the hand held yellow warfarin book for patients monitored elsewhere. The target INR must be recorded on the inpatient oral anticoagulation chart.

Advice on the management of high INR can be found on the trust guidelines page at the following link

http://nuhnet/nuh_documents/Guidelines/Cancer%20and%20Associated%20Specialties/Clinical%20Haematology/2401.pdf

3. Initiation

The option to initiate oral anticoagulation is a clinical decision which should be made by the consultant with overall care for the patient. The absolute contra-indications for warfarin are few but, for some patients, the risk of bleeding may outweigh the prospect of any benefit. The lists below are not exhaustive and if you are unsure whether it is safe to start warfarin, this should be discussed with the responsible Consultant before prescribing

Contraindications to warfarin include;

- Recent haemorrhagic stroke or other intracerebral bleeding
- Significant active bleeding
- Uncontrolled severe hypertension (systolic ≥200mmHg; diastolic ≥110 mmHg)
- Bleeding peptic ulcer disease
- Excessive alcohol intake with binge drinking
- Pregnancy (occasional exceptions such as patients with mechanical heart valves see NUH guidelines for warfarin in pregnancy) http://nuhnet/nuh_documents/Guidelines/Family%20Health/Obstetrics%20and%20Maternity/2725.pdf

Relative contraindications to warfarin include;

- History of GI bleeding
- Uncontrolled hypertension
- Liver disease with abnormal baseline coagulation screen
- Oesophageal varices
- End stage renal failure – discuss with renal team before prescribing if GFR <15ml/min
- Cancer – discuss with oncology team before prescribing
- Infective endocarditis
- Hereditary haemorrhagic telengectasia (HHT) – suggest discuss with haematology before prescribing
- Bleeding disorders – discuss with haemophilia team before prescribing
  - Significant thrombocytopenia - If the platelet count is <100 $x10^9$/L discuss with Haematology before prescribing
- Inability to monitor warfarin due to patient factors
- Concomitant use of drugs which increase bleeding risk – see NUH guidance http://nuhnet/nuh_documents/Guidelines/Cancer%20and%20Associated%20Specialties/Clinical%20Haematology/2371.pdf
- A history of falls is not a contraindication to treatment with Warfarin but if the patient has had a fall causing intra-cranial bleeding, the risks versus benefits of anticoagulant therapy should be carefully considered and discussed with the patient before initiation

- For patients anticoagulated due to Atrial Fibrillation, the HAS BLED score[4] can be used to determine an estimated risk of major bleeding on warfarin (see Appendix 1)

3.1 Patients being commenced on warfarin for the first time during their inpatient admission

If you are starting warfarin for the first time during an inpatient admission

- Counsel the patient to explain why the drug is being started, how it is dosed and monitored and the risks of the drug (particularly bleeding)
- Give the patient the opportunity to watch the warfarin counselling DVD; this can be viewed on the patient facing ipads which are available on every ward
- The patient should be provided with written information about warfarin (available on inpatient wards) which contains information about the drug and contact numbers for the anticoagulation clinic.(electronic version at: http://nuhnet/diagnostics_clinical_support/Haemostasis_and_Thrombosis/Anticoagulation%20Leaflets/Information%20Leaflet%20-%20Vitamin%20K%20Antagonists.pdf.
- Baseline tests should be sent;
    - FBC - review to ensure the platelet count is sufficient for prescription of warfarin
    - Coagulation screen – baseline abnormal results must be investigated before oral anticoagulation is prescribed
    - Liver function tests (LFT) - caution is required in patients with hepatic dysfunction.
    - Urea and Electrolytes
- Review the drug chart to ensure that the patient is not taking any other oral anticoagulation such as DOACs (rivaroxaban, apixaban, edoxaban, dabigatran) or antiplatelet agents
    - If the patient is taking an antiplatelet agent, this must be reviewed before commencing warfarin
    - **NO** dual prescription of an antiplatelet agent and warfarin should be made without clear clinical indication; this should be recorded on the drug chart and in the medical notes
    - Patients who are fully anticoagulated with warfarin do not need Enoxaparin thromboprophylaxis but a VTE risk assessment should still be completed
- Complete the NUH inpatient oral anticoagulation chart
    - **Remember dual signatures are required before warfarin can be prescribed**
- Warfarin should be loaded as per the NUH guideline warfarin – loading doses in adults

http://nuhnet/nuh_documents/Guidelines/Cancer%20and%20Associated%20Specialties/Clinical%20Haematology/2379.pdf

- When initiating warfarin for the treatment of VTE
    - The patient should be prescribed treatment dose Enoxaparin alongside warfarin until the INR is within the therapeutic range
    - Ensure that referral to the VTE MDT is completed via NoTis/MEDWAY
- When initiating warfarin in patients with mechanical heart valves, advice regarding the use of Enoxaparin should be sought from the cardiac surgical team

3.2 Patients being re-started on warfarin following a period of omission

It is difficult to provide generic guidance which covers all patient groups due to the heterogeneity of conditions requiring warfarin treatment and the multiple reasons why this may be stopped. It is important for all patients that before warfarin is restarted the following is assessed;

- What was the reason for omission?
- What is the current thrombotic risk?
- What is the current bleeding risk?

It is usual practice following a period of omission to restart warfarin at the usual daily dose for the patient **without** loading doses unless specified otherwise by the clinical team. However In some situations the patient may be more sensitive to warfarin due to inter current illness or medication and in this situation consideration should be given to prescribing a lower dose than usual.

If the warfarin cannot safely be restarted, the patient should have an electronic VTE risk assessment as per NUH policy to identify whether thromboprophylaxis with enoxaparin can be given as an interim. If thromboprophylaxis with enoxaparin has been prescribed during the time when warfarin is omitted, this should be continued until the INR is within the therapeutic range for patients who require warfarin for VTE or mechanical cardiac valves.

Further advice for specific patient groups is below;

3.2.1 Perioperative cessation of anticoagulation

If omission was to facilitate an operation or interventional procedure, NUH guidelines for adult patients taking oral warfarin therapy undergoing planned, non neurosurgical intervention should be followed, available at the following link http://nuhnet/nuh_documents/Guidelines/Cancer%20and%20Associated%20Specialties/Clinical%20Haematology/2854.pdf

- The clinical team who performed the operation or intervention are responsible for deciding when warfarin can safely be restarted
- Patients re starting warfarin following an operation or procedure should restart at their **usual daily dose without** loading doses unless specified otherwise by the clinical team
- It is important to ensure that the patient is able to tolerate and absorb oral medication when being prescribed warfarin

3.2.2 Re introduction after GI Bleeding[2]

In patients anticoagulated with warfarin, bleeding from the GI tract can occur either due to internal bleeding driven by over-anticoagulation with warfarin [recommend checking INR urgently] with no underlying GI tract lesion or the use of warfarin anticoagulation making an underlying GI tract lesion more likely to bleed. In patients presenting with acute GI bleeding the need to stop and/or reverse warfarin is well established but there is little in the literature to guide the decision of when and how to reintroduce warfarin.

- Consideration must be given to
    - What is the risk of recurrent GI bleeding?
    - Has the cause been identified and treated?
    - Does anticoagulation definitely need to be restarted?
- Overall, restarting warfarin following GI bleeding appears to be associated with a favorable risk benefit profile compared to not initiating treatment in terms of recurrent thromboembolism and overall mortality.
- Most available studies found an increased rate of recurrent GI bleeding after restarting warfarin however in general these were not statistically significant
- If GI bleed occurred in the context of a high (supra-therapeutic) INR consideration should be given to the possible reasons for poor anticoagulant control. In some circumstances, switching to a DOAC *may* be appropriate however there is some evidence that the use of DOACS may *increase* GI bleeding risk.
- Patients should have an individual risk assessment for risks of recurrent thromboembolism and recurrent GI bleeding
    - Patients receiving warfarin for AF can have a CHADS2 VASC and HAS-BLED score[4] calculated for use in risk stratification
- If warfarin is being restarted, it should be at a minimum of 7 days after cessation of bleeding
    - It is pragmatic to delay reintroduction of warfarin for as long as possible for those at the highest risk of bleeding but earlier in those at the highest risk of thrombosis
- During the time when warfarin is omitted, consideration should be given to whether enoxaparin thromboprophylaxis could be safely used

All patients restarting VKA should have a yellow anticoagulation prescription chart completed and attached to the blue drug chart

A dual signature is still required when warfarin is re-prescribed following a period of omission.

Further advice on the safety of restarting warfarin after GI bleeding should be discussed with the Gastroenterology team if required.

3.2.3 Re introduction after Intracerebral Haemorrhage (ICH)[3]

Timing of reintroduction of warfarin after ICH should be decided by the Neurosurgical team responsible for the patient.

The optimal timing for resumption of anticoagulation after ICH is uncertain, and no randomized trial data are available to guide the decision. Several observational studies of patients with anticoagulant-related ICH found low rates of cardioembolic events while not receiving anticoagulation therapy or recurrent ICH when anticoagulation was resumed but the results are limited by relatively small sample sizes and short durations of follow-up.

ICH recurs in survivors at a rate of 2-3% per year. Factors associated with a higher risk of recurrence include

- Uncontrolled hypertension
- Lobar ICH - particularly if there is evidence of cerebral amyloid angiopathy have a higher rate of recurrence compared to patients with deep ICH
- Anticoagulant therapy – patients taking anticoagulant therapies may have a higher risk of recurrence and are also likely to have larger haematomas and worse outcome compared to patients not taking anticoagulation
- More variably associated with recurrence are older age, male gender and microbleeds on MRI scanning

In practice, the timing of restarting anticoagulation depends on the indication for anticoagulation and a careful, individualised assessment of the risks of thrombosis compared to the risks of re bleeding. The risk of ICH expansion and recurrence is highest in the first days after ICH, while the risk of thromboembolism continues to accumulate overtime. While published opinions vary widely, most experts conclude that for most patients with an indication for anticoagulation can be restarted on therapy 7 to 14 days after ICH. Later re initiation should be considered in those with weaker risk factors for thromboembolism. Consideration should always be given to whether long term anticoagulation treatment is still indicated.

If ICH occurred in the context of a high (supra-therapeutic) INR consideration should be given to the possible reasons for poor anticoagulant control. In some circumstances, switching to a DOAC may be appropriate. Although the data

suggests that the overall risk of ICH is lower in patients taking DOACs as opposed to warfarin, there is scant evidence for this in the context of previous ICH.

All patients restarting warfarin should have a yellow anticoagulation prescription chart completed and attached to the blue drug chart

A dual signature is still required when warfarin is re-prescribed following a period of omission.

4. Maintenance dosing of warfarin

Dosing of warfarin is highly individual and based on regular monitoring of the INR. There are many factors common to hospitalized patients which can affect the INR such as changes in diet, new interacting medication, infection and malignancy for example.

When prescribing a dose of warfarin always;

- Confirm identification of the patient on the inpatient prescription chart
    - **Ensure the dual signature section of the chart is completed**
- Review any changes in clinical condition as described below
- Check whether the patient has any bleeding symptoms
- Review the usual daily dose of warfarin for the patient; this will help to guide dosing
- INR results must be checked and written on the anticoagulant prescription and referral chart before warfarin is prescribed or given.
- Request the next INR test
    - The INR does not need checking daily for stable patients

Remember that warfarin is highly protein bound with a half-life of 36-42 hours; it takes 48-72 hours after changing dose to have an effect on the INR. This should be borne in mind when making dose adjustments.

The following conditions may increase sensitivity to warfarin (increased INR) and therefore warrant a decrease in dose:

- Hepatic dysfunction and/or jaundice
- Alcohol abuse particularly “binge drinking”
- Congestive heart failure
- Anorexia
- Hyperthyroidism
- Acute pyrexial episode
- Changes in diet
- Dietary components: eg Cranberry juice
- Medicines

The following conditions may cause a decrease in sensitivity to warfarin (decreased INR) and therefore warrant an increase in dose:

- Hypothyroidism
- Changes in diet
- Herbal remedies: St John's Wort, Gingko Biloba
- Medicines

It is also important to note that when medicines are discontinued or the clinical condition of the patient changes, the dose must be readjusted

5. Discharge of patient prescribed warfarin

For anticoagulant nurse discharge (0900am – 1700pm, Monday to Friday excluding bank holidays)

- As soon as a patient is identified as fit for discharge, contact the anticoagulation clinic via nervecentre (ideally the day before planned discharge).
- An anticoagulation clinic nurse will review the patient on the ward and
  - Perform a near patient INR test (finger prick sample)
  - Dose warfarin for sufficient time until the next planned INR test and provide the patient with a written or printed discharge dosing information
  - Provide the patient with a follow up appointment in the anticoagulation clinic
    OR
    Arrange appropriate follow up with their anticoagulant service provider (if not NUH)
- Patients newly started on warfarin will be provided with a yellow card detailing their dose, contact details for the anticoagulation clinic and a written letter confirming their next appointment for INR testing.A standard TTO should be written (as per trust policy) and sent to the GP at discharge stating the arrangements which have been made for follow up
- If the patient is taking Enoxaparin eg because the INR is not yet therapeutic, this should be continued on discharge
  - It should be clearly stated on the TTO 'Enoxaparin to be stopped when INR is in therapeutic range'

Out of hours discharges (outside of the time covered by the anticoagulation clinic)

The out of hours policy for the discharge of patients anticoagulated with a vitamin k antagonist should be followed – see appendix 2 or at the following link.
http://nuhnet/diagnostics_clinical_support/Haemostasis_and_Thrombosis/Discharge%20Documents/Out%20Of%20Hours%20Pathway%20(January%202009).pdf

- Responsibility for dosing will be that of the discharging team.
- A venous INR sample is taken on the day of discharge and the result reviewed before the patient leaves the hospital
- The inpatient oral anticoagulation chart should be sent to the anticoagulation clinic with the plan for follow up documented

  - For patients monitored by the trust anticoagulation clinic, an appointment will be made for ongoing INR monitoring
  - For patients monitored by their own GP, a follow up INR appointment will be made directly with the GP surgery; the anticoagulation team will check that this has been done
- The patient should be dosed with sufficient warfarin until their next anticoagulation clinic visit or until they are able to see their GP
  - At the weekend, the patient should be dosed sufficiently to last until the following Tuesday as a minimum
- The patient should be provided with written information about their ongoing warfarin dose and the time of their next INR test
- A standard TTO should be written (as per trust policy) and sent to the GP at discharge

6. Useful links/further information

Additional guidelines for warfarin are available on the trust guidelines page including

- Reversal of Anticoagulation – warfarin http://nuhnet/nuh_documents/Guidelines/Cancer%20and%20Associated%20Specialties/Clinical%20Haematology/2401.pdf
- Warfarin – management for elective procedures http://nuhnet/nuh_documents/Guidelines/Cancer%20and%20Associated%20Specialties/Clinical%20Haematology/2854.pdf
- Out of hours policy for the discharge of patients anticoagulated with a vitamin k antagonist http://nuhnet/diagnostics_clinical_support/Haemostasis_and_Thrombosis/Discharge%20Documents/Out%20Of%20Hours%20Pathway%20(January%202009).pdf

- NUH Anticoagulation clinics can be contacted on the following numbers

  - **QMC site**
    D floor, East block:
    Ext 66005 or Bleep 284-1594

  - **City campus**
    Physiotherapy corridor:
    Ext 53464 or Bleep 284-1594

References

1. Keeling et al (2011) Guidelines of oral anticoagulation with Warfarin – fourth edition. B J Haem 154 (3), 31 - 324

2. Scott MJ, Veitch A and Thachil J (2017) Reintroduction of anti thrombotic therapy after a gastrointestinal haemorrhage: if and when?
   B J Haem 177, 185 – 197

   Hemphill et al (2015) Guidelines for the Management of spontaneous intracerebral hemorrhage; A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2015;46:2032-2060
4. Pisters R, Lane D A, Neuwlaat R, De Vos C B, Crijns H J, Lip G Y. A novel user-friendly score (HAS-BLED) to assess 1 year risk of major bleeding in patients with atrial fibrillation. Chest. 138 (5): 1093-100

Appendix 1: HAS BLED score[4]

	Condition	Points
H	Hypertension: (uncontrolled, >160mmHg systolic)	1
A	Abnormal renal function: Dialysis, transplant, Cr >2.26mg/dl or >200umol/l Abnormal liver function: Cirrhosis or bilirubin >2x normal or AST/ALT/AP >3x normal	1 1
S	Stroke: Prior history of stroke	1
B	Bleeding: Prior major bleeding or predisposition to bleeding	1
L	Labile INR: (unstable/high INR), time in therpeutic range <60%	1
E	Elderly: Age >65 years	1
D	Prior alcohol or drug usage history (≥8 drinks/week) Medication usage predisposing to bleeding: (Antiplatelet agnets, NSAIDs)	1 1

Interpretation of the HAS BLED score

HAS BLED Score	Risk of major bleeding per year
0	1%
1	3.4%
2	4.1%
3	5.8%
4	8.9%
5	9.1%
> 5	12-15%

Appendix 2: NUH out of hours policy for discharging patients anticoagulated with Vitamin K antagonists