Clinical Guideline

ANTICOAGULATION IN PATIENTS WITH SEVERE RENAL IMPAIRMENT INCLUDING AKI AND ESRF

SETTING	Trust-wide (excluding paediatrics)
FOR STAFF	Renal multidisciplinary team, doctors, nurses, pharmacists
PATIENTS	Adult patients with severe renal impairment (< 30ml/min) including acute kidney injury (AKI) and end-stage renal failure (ESRF) requiring prophylactic or therapeutic anticoagulation. This includes in the peri-procedural setting

Contents

Guidance

This guideline has been formulated with input from clinicians across NBT and UHBW and is designed to be a cross trust policy.

The purpose of this guideline is to provide guidance on anticoagulation in patients with an estimated glomerular filtration rate (eGFR) or creatinine clearance (CrCl) of < 30ml/min including dialysis patients where anticoagulation is felt to be appropriate.

The aim is to unify guidance for patients with stage 4 and 5 renal impairment with regards to prophylactic and treatment dose anticoagulation. This guidance can also be used in patients whose renal function is acutely impaired due to acute kidney injury (AKI) but with close attention to the eGFR trend so that anticoagulant doses can be adjusted with worsening or improving renal function.

Those with severe renal impairment have a risk of VTE of 2-3 times the general population and a risk of atrial fibrillation of 10-20 times the general population. Those with renal impairment

often also have co-existent cardiovascular disease. Patients have factors that make them prone to haemorrhage as well as thrombosis.
The factors making patients vulnerable to **thrombosis** include:

- Venous stasis, lines that may be inserted, altered blood components and endothelial dysfunction.

Factors making patients prone to **bleeding** include:

- Increased uraemia, increased vascular prostaglandin, decreased Von Willebrand Factor, chronic inflammation, anaemia and platelet abnormalities.

1. Definition of terms

Stage 4 CKD (chronic kidney disease): an estimated glomerular filtration rate (eGFR) of 15-29ml/ minute. This is classified as severe renal impairment.

Stage 5 CKD (chronic kidney disease): an estimated glomerular filtration rate (eGFR) of less than 15ml/ minute. This is classified as renal failure.

Stage 5 CKD-D (chronic kidney disease on dialysis): Patients with stage 5 CKD on dialysis

2. Prophylactic Anticoagulation

eGFR may be used as a guide but creatinine clearance (CrCl) should be calculated for dosing in extremes of body weight or elderly patients

RENAL FUNCTION	PROPHYLACTIC ANTICOAGULATION
eGFR or CrCl >30ml/min	See LMWH guideline
eGFR or CrCl 15-29ml/min (Stage 4 CKD)	Patients <100kg Enoxaparin 20mg SC OD Patients >100kg Enoxaparin 40mg SC OD
eGFR or CrCl <15ml/min (Stage 5 CKD):	In all body weights: Enoxaparin 20mg SC OD or Unfractionated Heparin 5000 units SC twice daily.
Stage 5 CKD-D (chronic kidney disease on dialysis):	In all body weights: Enoxaparin 20mg SC OD or Unfractionated Heparin 5000 units SC twice daily can be considered (in addition to routine anticoagulation for prevention of clotting in extracorporeal circuit.)

In very overweight patients **>150kg and with eGFR or CrCl <15ml/min**, our recommendation would be to give unfractionated heparin rather than enoxaparin to avoid accumulation

3. Therapeutic Anticoagulation

The remainder of this guideline refers to situations when there is an indication for anticoagulation including thrombosis or atrial fibrillation (AF). Please note that there may be an uncertain clinical benefit in patients anticoagulated for AF due to a high thrombotic as well as a

high bleeding risk. In end stage renal failure (ESRF), it may be that offering anticoagulation for AF does not lead to improved clinical outcomes.

Although scoring systems to predict bleeding risk can be used, these generally do not take ESRF into consideration. If a bleeding risk score is being used, the **'ORBIT' score** has shown best discrimination in those with ESRF. It is important in addition to consider prior anticoagulation when considering a patient's risk of bleeding with anticoagulation.

Specific scenarios when **warfarin** is indicated:

- Please note that where anticoagulation is needed, warfarin is recommended in specific scenarios regardless of renal function. This includes patients with: metallic heart valves (where DOACs are contraindicated); antiphospholipid syndrome especially where there has been an arterial thrombosis, and they are triple positive (persistently positive lupus anticoagulant, anticardiolipin antibodies and anti Beta 2 glycoprotein 1 antibodies); and valvular AF.

- Patients with nephrotic syndrome have an 8 times increased risk of thrombosis due to loss of antithrombin III and increased hepatic synthesis of fibrinogen, FVIII, FV and Von Willebrand Factor. Warfarin is advised in nephrotic syndrome.

a. Dosing

RENAL FUNCTION	THERAPEUTIC ANTICOAGULATION – ORAL OPTIONS	THERAPEUTIC ANTICOAGULATION – PARENTERAL OPTIONS
Stage 4 CKD (eGFR or CrCl 15-29ml/min) **Use CrCl for DOACs** (not eGFR)	• Warfarin – consider initiation with a lower dose such as 3mg (rather than 5mg) **AF** • Apixaban 2.5mg BD • Edoxaban and rivaroxaban are licensed (see SPC for dosing) however apixaban is favoured • (Dabigatran is **not** licensed in CrCl < 30ml/min) **Acute VTE** • Apixaban – 10mg BD for 7 days, then 5mg BD - do not dose reduce, monitor for bleeding • Rivaroxaban can be used (see SPC for dosing) however apixaban is favoured	• Consider enoxaparin 1mg/kg SC OD – with anti-Xa monitoring (see below)
Stage 5 CKD/ Stage 5 CKD-D (eGFR<15ml/min)	• Warfarin – consider initiation with a lower dose such as 3mg (rather than 5mg) • All DOACs are currently unlicensed in CrCl <15ml/min (although studies	• Consider enoxaparin 0.7mg/kg SC OD with anti-Xa monitoring (see below) • Unfractionated heparin infusion (UFH) – please see

	are looking into the use of apixaban)	heparin guideline. Speak to haematology if wanting to use UFH outside of ICU or ICU equivalent areas

b. Further information

• Warfarin

Can be used for all indications for long term therapeutic anticoagulation with frequent INR monitoring.
Patients with CKD often require lower daily doses to achieve therapeutic levels due to down regulation of CYP450.

Long term warfarin use is associated with accelerated vascular calcification as well as calciphylaxis in extreme cases which has a mortality of 80% at 2 years. Warfarin is also a risk factor for anticoagulation associated nephropathy characterized by tubular obstruction by red cell casts following glomerular haemorrhage.

Calciphylaxis is a very rare but serious condition that causes vascular calcification and cutaneous necrosis. Long term warfarin use, in patients with renal impairment, is associated with accelerated vascular calcification as well as calciphylaxis in extreme cases which has a mortality of 80% at 2 years. Warfarin is also a risk factor for anticoagulation associated nephropathy characterized by tubular obstruction by red cell casts following glomerular haemorrhage.
An individual risk assessment should be undertaken for patients eligible for long term anticoagulation. In particular the risks of warfarin for prevention of thromboembolism may outweigh the benefits in this population.

• Apixaban

Please note it is advised that creatinine clearance (CrCl) is calculated rather than eGFR, as this is likely to be more accurate, particularly at extremes of body weight and age.
In patients with a **BMI > 30 kg/m^2**, please use **adjusted body weight** to calculate CrCl. Calculator here

- For patients with AF, Apixaban 2.5mg BD is the advised dose if CrCl 15-29ml/ minute.
- If using for treatment of VTE, current opinion supports no dose reduction.

• Unfractionated heparin continuous intravenous infusion

For consideration in stage 5 CKD/stage 5 CKD-D (eGFR<15ml/min)

Refer to Heparin Guideline – **please discuss with haematology** if wanting to start anyone on unfractionated heparin outside of cardiac surgical ward, ICU or equivalent wards

c. LMWH and anti-Xa monitoring

Enoxaparin is not licensed with a CrCl <15ml/ minute, however there is increasing experience of its safe use in these patients especially in the short term due to ease of once daily administration

Anti Xa monitoring is advised 3-4 hours post dose on day 3 of LMWH as this is when enoxaparin reaches steady state and the peak serum concentration is reached.

Requesting levels at BRI sites

UHBW ICE: LMW Heparin (Anti Xa)

Requesting levels at Weston

Weston ICE: Anti Xa Low Molecular Weight Heparin - ward to send sample urgently to BRI lab

- The target therapeutic range for once daily dosing is 0.8-1.6 U/ml.

If the anti Xa is in therapeutic range this only needs to be repeated if there are concerns regarding bleeding or changes in renal function have been observed.

If the anti Xa is not in range and the timing of the blood sample is correct, please consider discussion with the haematology team regarding whether a change of dose is required.

If the dose is changed following anti-Xa results, further anti-Xa levels can be taken after the 3rd new dose.

4. Managing anticoagulation around procedures/surgery

The following section of the guideline is relevant to those having:

- Renal biopsies
- Renal transplants
- General surgical procedures

A pre and post- operative plan for anticoagulation needs to be made in advance. . This will depend on factors such as the anticoagulation the patient is on and the indication for anticoagulation, as well as the bleeding and thrombotic risk of the procedure. Understanding the indication for anticoagulation will influence a patient's thrombotic risk. A guide to an individual's thrombotic risk group can be found below.

Please note that bridging is generally not required when considering patients on anticoagulants other than warfarin.

Please see information for specific anticoagulants below

a. Management of procedures for patient on Apixaban:

PRE- PROCEDURE MANAGEMENT - APIXABAN

Licensed in those with creatinine clearance 15-29ml/minute:

High bleeding risk procedure – the last dose of anticoagulation should be given 72 hours before.

Low bleeding risk procedure – the last dose of anticoagulation should be given 48 hours before.

(If felt to be at very high thrombotic risk (i.e. patients with a VTE within the last 3 months and particularly within the last 6 weeks, patients with a stroke/ TIA in the last 3 months or patients with a previous stroke/ TIA and 3 or more of the following risk factors: congestive cardiac failure, hypertension with BP of >140/90mmHg or on medication; age >75 years or diabetes mellitus) consideration should be given to giving a dose of prophylactic LMWH on the day before surgery.)

POST- PROCEDURE MANAGEMENT - APIXABAN

More harm can be caused by restarting therapeutic anticoagulation too early after procedures with moderate or high bleeding risk. This is because bleeding is associated with both a higher overall thrombotic risk and will require an even longer period off anticoagulation.

The general principle of post procedural anticoagulation management is to start with prophylactic doses and gradually increase to therapeutic doses where required. This is most easily done with LMWH.

In all cases the ongoing bleeding/ thrombotic risk should be reviewed at a minimum every 24 hours

The exact schedule of resuming anticoagulation should depend on an assessments of an

individual's bleeding/ thrombotic risk but the following schedule should be considered:

- Prophylactic anticoagulation advised on the evening of surgery (Minimum of 4 hours post-surgery) – usually LMWH
- Dependent on bleeding/ thrombotic risk continue prophylactic heparin 24-48 hours (see section on prophylactic anticoagulation)
- Then dependent on bleeding/ thrombosis risk escalate to intermediate dose Enoxaparin 0.5mg/kg SC OD for 24-48hrs. Escalated to therapeutic Enoxaparin 0.7mg/kg SC OD for 24-48hrs dependent on bleeding/ thrombotic risk. (For patients with CKD 5/ CKD 5-D this is full therapeutic dose, for patients with CKD Stage 4 they can then be escalated to Enoxaparin 1mg/kg SC OD which is full therapeutic dose)
- For patients with CKD Stage 4 it is appropriate to consider restarting apixaban when haemostasis has been achieved, the patient has been on prophylactic anticoagulation for a minimum of 24-48 hours with consideration of dose escalation as above and there has been no bleeding complications. Therefore it may be appropriate to substitute the therapeutic enoxaparin step with therapeutic apixaban. However depending on the procedure and bleeding risk many teams prefer the familiarity of LMWH and will switch to therapeutic apixaban once they are confident that the is not bleeding on therapeutic enoxaparin

- Peak levels of apixaban are achieved 2-3 hours after an oral dose i.e. the patient will be therapeutically anticoagulated.

b. Management of procedures for patient on warfarin:

PRE- PROCEDURE MANAGEMENT – WARFARIN

The following table provides guidance on risk stratification into thrombotic risk groups

Thrombotic risk group	Indication for anticoagulation	Action to take pre- procedure/ surgery
Low Thrombotic Risk	• Atrial fibrillation (with no history of stroke / Transient Ischaemic Attack (TIA) • Venous thrombosis > 3 months • Tissue heart valve	Do not need to give to give routine thromboprophylaxis Stop warfarin day -5
Moderate thrombotic risk	Atrial fibrillation with severe mitral stenosis Atrial fibrillation with a history of stroke/TIA > 3 months previously	Stop warfarin day -5 eGFR: 20-30mls 20mg enoxaparin SC OD Day -2 and Day -1 Last dose 18.00 day before surgery eGFR less than 20mls: 5000 units heparin SC BD last dose 18.00 day prior to surgery
High thrombotic risk	Patients with a VTE within previous 3 months. Very high risk patients such as patients with a previous VTE whilst on therapeutic anticoagulation who now have a target INR of 3·5. Patients with a previous stroke/TIA in last 3 months. • Patients with a previous stroke/TIA and three or more of the following risk factors: o Congestive cardiac failure o Hypertension (>140/90 mmHg or on medication) o Age >75 years o Diabetes mellitus MHV patients other than those with a bileaflet aortic valve and no other risk factors	Stop warfarin day -5 pre op Check INR on day -3 pre-op: When INR less than 2: Stage 4 CKD consider 1mg/kg enoxaparin SC OD Day -3 Day -2 Day -1 Last dose to be given at 8am on day prior to procedure Stage 5 CKD/ CKD-D: Consider enoxaparin 0.7mg/kg SC OD Day -3 Day -2 Day -1 Last dose to be given at 8am on day prior to procedure

POST- PROCEDURE MANAGEMENT - WARFARIN

More harm can be caused by restarting therapeutic anticoagulation too early after procedures with moderate or high bleeding risk. This is because bleeding is associated with both a higher overall thrombotic risk and will require an even longer period off anticoagulation.

Warfarin often takes greater than 48 hours to reach therapeutic range. Consideration therefore can be given to starting this the day following surgery. Restart at the dose the patient was on preoperatively and monitor the INR daily from D 2-3

The general principle of post procedural anticoagulation management is to start with prophylactic doses and gradually increase to therapeutic doses where required. This is most easily done with LMWH.

In all cases the ongoing bleeding/ thrombotic risk should be reviewed at a minimum every 24 hours

Consider restarting prophylactic anticoagulation at a minimum of 4 hours post- surgery if haemostasis has been achieved (see section on prophylactic anticoagulation)

Does the patient have one of the following indications for anticoagulation:

1. Metallic heart valves
2. Recent thrombotic episode (in last 4-6 weeks)
3. Patients who have had a thrombotic episode while receiving therapeutic anticoagulation

No

Yes

Continue prophylactic enoxaparin until INR is therapeutic
(This is the majority of patients)

Consider escalating to therapeutic enoxaparin until their INR is therapeutic: Dependent on bleeding/ thrombotic risk consider the following schedule:
Prophylactic LMWH for 24-48 hours
0.5mg/kg LMWH for 24-48 hours
0.7mg/kg LMWH- if the patient has CKD stage 5 this is therapeutic dose. If not they should be escalated to therapeutic to 1mg/kg LMWH after 24-48 hours.

c. Management of procedures for patient on LMWH:

PRE- PROCEDURE MANAGEMENT - LMWH

The last dose of **therapeutic** LMWH should be given a maximum of 24 hours prior to a procedure.

The last dose of **prophylactic** LMWH should be given a maximum of 24 hours prior to a procedure.

POST- PROCEDURE MANAGEMENT - LMWH

More harm can be caused by restarting therapeutic anticoagulation too early after procedures with moderate or high bleeding risk. This is because bleeding is associated with both a higher overall thrombotic risk and will require an even longer period off anticoagulation.

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The exact schedule of resuming anticoagulation should depend on an assessments of an individual's bleeding/ thrombotic risk but the following schedule should be considered:

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- Then dependent on bleeding/ thrombosis risk escalate to intermediate dose Enoxaparin 0.5mg/kg SC OD for 24-48hrs
- Escalated to therapeutic Enoxaparin 0.7mg/kg SC OD for 24-48hrs dependent on bleeding/ thrombotic risk. (For patients with CKD 5/ CKD 5-D this is full therapeutic dose, for patients with CKD Stage 4 they can then be escalated to Enoxaparin 1mg/kg SC OD which is full therapeutic dose)

Table A

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RELATED DOCUMENTS AND PAGES	• Low molecular weight heparin (LMWH) https://uhbw.mystaffapp.org/12200/document_view.pdf • Reversal of anticoagulation - Warfarin Management Of Emergency Surgery https://uhbw.mystaffapp.org/707/document_view.pdf • Risk Assessment And Management Of Warfarin In Adult Patients Undergoing Elective Noncardiac Surgery And Endoscopy https://uhbw.mystaffapp.org/404/document_view.pdf • Perioperative Anticoagulation (Adults) - Low Molecular Weight Heparins Cessation Prior To Surgery https://uhbw.mystaffapp.org/13831/document_view.pdf • (NBT - Anticoagulation in Nephrotic Syndrome Policy)

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Appendix 1 – Evidence of Learning from Incidents

The following table sets out any incidents/ cases which informed either the creation of this document or from which changes to the existing version have been made.

Incidents	Summary of Learning

Document Change Control				
Date of Version	Version Number	Lead for Revisions	Type of Revision	Description of Revision
June 2024	1.0	Anticoagulant Pharmacist	Major	New document, adapted from NBT renal anticoag guideline
Sept 2024	1.1	Anticoagulant Pharmacist	Minor	Added a link to the Orbit score calculator as a handy link for staff to access