Anticoagulation in patients with severe renal impairment and end stage renal failure

Division: Trust-Wide

Document No:CG-25

Specific staff groups to whom this policy directly applies	Likely frequency of use	Other staff who may need to be familiar with policy
Renal Multidisciplinary Team including renal clinicians. Non Renal Doctors/ Nurses.	Daily	Pharmacy team.

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Summary of changes since the previous version	This is a new document.

1. Executive summary

Summary of key points:

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

1.2 The aim is to unify guidance for patients with stage 4 and 5 renal impairment with regards to prophylactic and treatment dose anticoagulation. The guideline also provides advice on the management of anticoagulation around procedures.

Contents

2. Purpose of the policy

2.1 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.

2.2 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.

2.3 The purpose of this guideline is to provide guidance on anticoagulation in patients with a creatinine clearance of 29 ml/minute or less including dialysis patients where anticoagulation is felt to be appropriate.

2. The document will discuss:

- Prophylactic anticoagulation
- Therapeutic anticoagulation
- Management of anticoagulation around a procedure and bridging where this is appropriate

3. Scope of the Policy

3.1 This is a trust wide policy.

4. 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
DOAC's:	Direct oral anticoagulants
AF:	Atrial fibrillation
LMWH:	Low molecular weight heparin
UFH:	Unfractionated Heparin

5. Roles and responsibilities

5.1 This policy relates to the renal team as well as medical staff throughout the trust.

6. Procedures

6.1 Prophylactic anticoagulation

6.1.1 Stage 4 CKD (chronic kidney disease): Enoxaparin 20mg SC OD

6.1.2 Stage 5 CKD: Enoxaparin 20mg SC OD or Unfractionated Heparin 5000 units SC twice daily.

6.1.3 Stage 5 CKD-D (chronic kidney disease on dialysis): 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.)

6.2 Therapeutic anticoagulation

6.2.1 The remainder of this guideline refers to situations when there is an indication for anticoagulation including thrombosis or atrial fibrillation. Please note that there may be an uncertain clinical benefit in patients anticoagulated for Atrial Fibrillation (AF) due to a high thrombotic as well as a high bleeding risk. In end stage renal failure, it may be that offering anticoagulation for AF does not lead to improved clinical outcomes.

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

6.3 Specific scenarios

- 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 (direct oral anticoagulants) 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.

6.4 Stage 4 CKD (eGFR 15-29ml/min)

6.4.1 Note dabigatran is not licensed in Stage 4 CKD and 5 CKD, edoxaban and rivaroxaban are not licensed in Stage 5 CKD.

6.4.2 Options where anticoagulation is required in stage 4 CKD:

- Warfarin
- Apixaban
- LMWH.

6.5 Warfarin

6.5.1 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.

6.5.2 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.

6.6 Apixaban

6.6.1 Please note it is advised that creatinine clearance is calculated rather than eGFR, as this is likely to be more accurate, particularly at extremes of body weight and age.

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

6.7 LMWH (Low molecular weight heparin)

6.7.1 Consider dose of Enoxaparin 1mg/kg SC OD

6.7.2 Anti Xa monitoring advised 3-4 hours post dose on day 3 of LMWH to ensure anti- Xa levels are in therapeutic range.

- On the NBT ICE system anti- Xa levels for enoxaparin can be requested by typing ‘Enoxaparin’ into the search function on ICE. Full clinical details including time of last dose should be given.
- The target therapeutic range for Once Daily dosing is 0.8-1.6 U/ml.

6.7.3 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.

6.7.4 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.

6.8 Stage 5 CKD/ Stage 5 CKD-D (eGFR<15ml/min)

6.8.1 All DOACs (direct oral anticoagulants) are currently unlicensed in stage 5 CKD although studies are ongoing looking at reduced dose of apixaban at 2.5mg BD.

6.8.2 Note dabigatran is not licensed in Stage 4 and 5 CKD, edoxaban and rivaroxaban are not licensed in Stage 5 CKD.

6.8.3 Options where anticoagulation is required in stage 5 CKD/ Stage 5 CKD-D:

- Warfarin
- Heparin: LMWH, UFH
- Warfarin

6.8.4 Can be used for all indications for long term therapeutic anticoagulation with frequent INR monitoring.

6.8.5 Patients with CKD often require lower daily doses to achieve therapeutic levels due to down regulation of CYP450.

6.8.6 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.

6.8.7 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.

6.9 Heparin

LMWH (Low molecular weight heparin):

6.9.1 Enoxaparin is not licensed with a creatinine clearance of less than 15ml/ minute, however there is increasing experience of its safe use in these patients especially in the short term If to be used due to ease of once daily administration

6.9.2 Consider Enoxaparin 0.7mg/kg SC OD with anti- Xa monitoring.

6.9.3 Anti Xa monitoring advised 3-4 hours post dose on day 3 of LMWH to ensure anti- Xa levels are in therapeutic range.

- On the NBT ICE system anti Xa levels for enoxaparin can be requested by typing 'Enoxaparin' into the search function on ICE. Full clinical details including time of last dose should be given.
- The target therapeutic range for Once Daily dosing is 0.8-1.6 U/ml.

6.9.4 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.

6.9.5 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.

Unfractionated Heparin continuous intravenous infusion

Refer to NBT Adult Unfractionated Heparin Intravenous (IV) Infusion Chart

Managing anticoagulation around procedures/ surgery

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

- Renal biopsies
- Renal transplants
- Non renal surgery including general surgical procedures

6.9.7 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.

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

Please see information for specific anticoagulants below

6.10 Management of procedures for patient on Apixaban:

6.10.1 PRE-PROCEDURE MANAGMENT (Apixaban)

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

6.10.3 For procedure with high bleeding risk the last dose of anticoagulation should be given 72 hours before.

6.10.4 For procedure with low bleeding risk 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.)

6.10.5 POST-PROCEDURE MANAGEMENT (Apixaban)

6.10.6 **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.**

6.10.7 **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.**

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

6.10.9 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.

6.11 Management of procedures for patient on Warfarin:

6.11.1 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: Congestive cardiac failure Hypertension (>140/90 mmHg or on medication) Age >75 years 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

6.11.2 POST PROCEDURE MANAGEMENT: WARFARIN

6.11.3 **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.**

6.11.4 **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.

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

6.11.6 Post operative management: Patients on Warfarin

6.11.7 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

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

No

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

Yes

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.

6.12 Management of procedures for patient on LMWH (Low molecular weight heparin):

6.12.1 PRE- PROCEDURE MANAGEMENT LMWH

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

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

6.12.4 POST-PROCEDURE MANAGEMENT LMWH

6.12.5 **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.**

6.12.6 **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.**

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

6.12.8 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)

7. Monitoring effectiveness

What will be monitored	Monitoring/ Audit method	Monitoring responsibility (individual/group/ committee)	Frequency of monitoring	Reporting arrangements (committee/group the monitoring results are	How will actions be taken to ensure improvements and learning
Compliance with renal anticoagulation guideline	Retrospective review of notes/ audit of consecutive cases	Renal Clinical Governance Lead	Annually	For presentation to Renal Clinical Governance Meeting	Dissemination of results to those involved in prescribing/ checking renal anticoagulation.

8. Associated policies/documents

8.1 NBT Anticoagulation in Nephrotic Syndrome Policy

9. References

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