Liverpool Heart and Chest Hospital NHS
NHS Foundation Trust

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Subject: Major Haemorrhaging in Hospital Protocols – Update to guidelines

Q1 The guidelines listed below were supplied in your FOI response FOI2021/442 received on the 4/20/2022.

LIVERPOOL HEART & CHEST - Anticoagulation Policy

Please could you confirm whether or not these guidelines are still in use and if they have been updated since the initial request. If they have been updated please could an updated copy be supplied.

If any new protocols for the management of major haemorrhage, the rapid identification of patients taking anticoagulants and the reversal of anticoagulation agents have been published since our initial request please could a copy be supplied.

- If Yes, please could an updated version of the document be supplied.

A1 Please see the attached policy document, which is the latest version – Anticoagulation v9.0

Anticoagulation Policy

For completion by Author			
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Document Statement

This Anticoagulation Policy is designed to ensure that the initiation and maintenance of anticoagulation therapy is conducted in a safe and efficacious manner. The policy covers the initiation of therapy within LHCH and the onward dissemination of information concerning the anticoagulation therapy of our patients to their base hospital, General Practitioner or anticoagulation clinic.

1. Roles and Responsibilities

The Medical Director is responsible for implementation of this policy.

The Drug and Therapeutics Committee is responsible for development and approval of this policy.

Liverpool Heart and Chest Hospital NHS Trust Staff are responsible for co-operating with the development and implementation of corporate policies as part of their normal duties and responsibilities.

Temporary or Agency Staff, Contractors, Students or Others will be expected to comply with the requirements of all Trust policies applicable to their area of operation.

Prescribers will be responsible for the prescribing of anticoagulation therapy, both parenteral and oral, using the LHCH in-patient or out-patient prescriptions appropriately (the Electronic Prescribing System should be used for all in-patient prescribing including intravenous continuous therapy).

Nursing staff will be responsible for administration of anticoagulation therapy in accordance with the Medicines Policy. Nursing staff will also be responsible for the onward communication of anticoagulation information regarding their patients and for ensuring that a monitoring appointment is arranged prior to discharge for patients on Vitamin K antagonists. If transport is required for the patient to achieve their first monitoring appointment this should be arranged before the patient leaves the ward or clinic area.

Pharmacists will be responsible for ensuring that all patients starting long-term anticoagulation therapy are counselled appropriately and that this is documented in their EPR record.

2. Controlled Document Standards

All staff involved with anticoagulation will be expected to comply with current legislation e.g. Medicines Act 1968 and the trust's Medicines Policy, together with their code of professional practice always ensuring safety of patients and other staff.

3. Procedure

Liverpool Heart and Chest hospital NHS Trust aims to ensure that all patients for whom anticoagulation therapy is deemed appropriate will be effectively managed while in the Trust and that their clinical details and supervision of their oral maintenance therapy will be transferred to an appropriate organisation. This policy covers both parenteral and oral anticoagulation.

3.1 Definitions

ACT - Activated clotting time. A measure of heparin activity that can be performed as a near-patient test.

APTT –Activated Partial Thromboplastin Time. A performance indicator measuring the efficacy of both the "intrinsic" (now referred to as the contact activation) pathway and the common coagulation pathways. The APTT is used to detect abnormalities in blood clotting and a ratio of patient's APTT against a laboratory APTT range is used to monitor the treatment effects with heparin, a major anticoagulant.

INR – International Normalised Ratio. A system established by the World Health Organisation (WHO) and the International Committee on Thrombosis and Haemostasis for reporting the results of blood coagulation (clotting) tests. All results are standardised using the international sensitivity index for the particular thromboplastin reagent and instrument combination utilized to perform the test. For example, a person taking the anticoagulant warfarin might optimally maintain a prothrombin time (pro time, or, PT) of 2 to 3 INR. No matter which laboratory checks the prothrombin time the result should be the same.

DOACs – Direct Oral Anticoagulants. Non-vitamin K oral anticoagulation agents which differ in many ways from warfarin, including rapid onset of action, shorter half-life, fewer drug-drug or drug-food interactions, lack of a need for monitoring or dose titration / adjustment. These drugs have limited licensed indications.

PCC – Prothrombin complex concentrate (Octaplex) contains all four vitamin K-dependent coagulation factors (II, VII, IX and X) and the thrombo-inhibitor proteins C and S. It is used to rapidly replenish deficient levels of circulating clotting factors more effectively than fresh frozen plasma in life-threatening bleeding situations.

3.2 Clinical conditions which may require anticoagulation

The following is a list of conditions which may occur within LHCH practice and require anticoagulation; however, this list is not exhaustive. The anticoagulation of some of these conditions may not be within the scope of this policy, however, other policies within the Trust exist for their treatment.

For LHCH the following patients may require oral and / or parenteral anticoagulation therapy:

- Prevention of thrombo-embolism for patients with atrial fibrillation (see below)
- Treatment of deep vein thrombosis or pulmonary embolism (see below)
- Following coronary endarterectomy (refer to consultant or SPR)

- Patients with a left ventricular aneurysm / thrombus (refer to consultant or SPR)
- Following valve surgery (dependent upon the patient, whether mechanical or tissue valve and the position of the valve – refer to consultant)
- Following pulmonary vein isolation (PVI) (see below)
- DC cardioversion for atrial fibrillation/flutter
- Acute Coronary Syndrome (see below)
- Prophylaxis of deep vein thrombosis in surgical patients (see VTE Policy)
- Prophylaxis of deep vein thrombosis in medical patients (see VTE Policy)

Other clinical conditions may require anticoagulation therapy; for example:
Cardiopulmonary bypass patients – see procedure from perfusion department
Off-pump bypass patients
Anticoagulation therapy for renal replacement therapy – see policy within Critical care
Lupus anticoagulant, anticardiolipin antibodies, pregnancy, liver disease and deficiencies of clotting factors – refer to haematologist for advice.
Other electrophysiological procedures – refer to Trust policy "Guidelines for anticoagulation before, during and after EP procedures"

Women with mechanical heart valves considering or planning pregnancy should be referred to a consultant with a specialist interest to plan anticoagulation during pregnancy.

3.3 Heparin (unfractionated) or low molecular weight heparin (LMWH) therapy

3.3.1 Treatment of Pulmonary Embolism or Deep Vein Thrombosis

Unfractionated Heparin Infusion Guidelines
See Appendix 3. These guidelines should be applicable whether the patient has been previously anticoagulated or not.

Low Molecular Weight Heparin

The LMWH of choice for treatment of VTE is Enoxaparin. Enoxaparin can be administered SC either as 1.5 mg/kg once daily or 1mg/kg twice daily. The dose regimen of 1.5 mg/kg once daily should be used in uncomplicated patients with low risk of VTE recurrence. The dose regimen of 1mg/kg twice daily should be used in all other patients such as those with obesity, with symptomatic PE, cancer, recurrent VTE or proximal (vena iliac) thrombosis. The patient's weight must be measured prior to commencement of therapy and rechecked at regular intervals during treatment. Creatinine clearance should also be monitored and the dose of LMWH adjusted accordingly – see Appendix 9. Doses are rounded to the nearest 3mg representing the graduation marks on 120mg or the 150mg syringes to ensure ease of administration.

3.3.2 Treatment of Acute Coronary Syndrome (ACS)
The LMWH of choice for treatment of ACS is Enoxaparin at a dose of 1mg/kg twice a day. Enoxaparin is usually stopped 12 hours before percutaneous coronary intervention (PCI). Creatinine clearance should be monitored while on LMWH and the dose adjusted accordingly – see Appendix 9. Fondaparinux is also licensed for the treatment of unstable angina (UA) or non-ST segment elevation myocardial infarction (NSTEMI). It is administered by subcutaneous injection at a dose of 2.5mg once daily, regardless of body weight. Renal function should be

monitored, and the drug should be avoided if the eGFR is less than 20 ml / minute. Fondaparinux is usually stopped 24 hours before PCI. It is not currently initiated at LHCH.

3.3.3 Prevention of thrombo-embolism for patients with atrial fibrillation

The LMWH of choice for prevention of thromboembolism in patients with AF is Enoxaparin at a dose of 1.5mg/kg once daily. Creatinine clearance should be monitored while on LMWH and the dose reduced to 1mg/kg once daily if creatinine clearance is less than 30ml/min. Enoxaparin may be used whilst concurrent oral anticoagulation with warfarin is commenced and until INR is above 2.0 (see below). New oral anticoagulation agents do not require bridging with enoxaparin because their onset of action is within 4 hours (see later in policy).

3.3.4 Prophylaxis of venous thromboembolism

see Venous Thromboembolism (VTE) Policy

3.3.5 Further monitoring and communication for treatment doses of LMWH

Nursing staff administering LMWH must ensure they check the dose against the relevant dosing table prior to administration.

Prescribers should be vigilant of the need for continual review of the LMWH dose with respect to a patient's renal function

When a patient is transferred to another Trust or discharged on prolonged treatment (i.e. more than a few days), the patient's renal function and weight should be included in the transfer letter/TTO.

3.3.6 Management of patients on oral anticoagulants requiring surgery or invasive procedures

Prophylactic dalteparin should be held at least 12 hrs prior to surgery. Therapeutic doses of enoxaparin should be held a minimum of 24hrs prior to surgery. Patients requiring bridging with LMWH prior to admission should not be asked to administer part syringes of enoxaparin – See Appendix 9c.

3.4 Warfarin therapy (vitamin K antagonist therapy including other coumarins and phenindione)

Warfarin is the most commonly used Vitamin K Antagonist (VKA) agent. Occasionally patients are intolerant of warfarin and may require treatment with other agents such as acenocoumarol (nicoumalone) or phenindione (or new oral anticoagulation agents –see Section 3.5). The dosing schedules for these agents differ from warfarin and haematological advice should be sought for acenocoumarol or phenindione. The principles of treatment are however the same as for warfarin.

Oral anticoagulants antagonise the effects of vitamin K. It takes 72 to 96 hours for the anticoagulant effect to develop. If an immediate effect is required, unfractionated or low molecular weight heparin must be given concomitantly. When changing from heparin to warfarin, heparin should be continued until therapeutic efficacy of warfarin has been confirmed by an INR greater

than 2 on two consecutive days. Heparin should be discontinued if the measured INR exceeds the target range. The dose of warfarin should be titrated according to the measured INR.

Following cardiac surgery, the target INR level and duration of warfarin therapy must be decided by the consultant responsible for the patient, due to the increased complexity of the LHCH case mix (if pacing wires are still in-situ a revised initial target may be required – see Appendix 1). Both the target level and range for the INR, together with the duration, should be entered within the EPR documentation and the target INR entered into the "anticoagulation reminder prescription" (within the anticoagulation order set) which will place this information into the EPR patient banner. If the patient was already taking warfarin, their pre-operation dose should be documented within EPR.

There are several clinical scenarios when patients may be prescribed warfarin which will be reviewed in the following sections:

- Starting warfarin in patients not previously anticoagulated (see section 3.4.1).
- Starting warfarin in patients already anticoagulated with heparin (see section 3.4.1).
- Restarting warfarin in patients whose anticoagulation has been interrupted for more than 3 days e.g. to allow for major cardiac surgery, (see section 3.4.2.1).
- Temporary discontinuation of warfarin to allow for cardiac procedures such as catheterization or pacemaker implantation, (see section 3.4.2.2).

3.4.1 Management of patients requiring initiation of oral anticoagulation therapy with warfarin.

Guidelines for the initiation of warfarin therapy are shown in Appendix 1. When starting anticoagulation therapy as an in-patient, patients must have their INR checked every day until their INR is stable. Prescribers must be aware that the dose administered is not reflected in the patient's INR for approximately three days. Lower doses than usual may be required in patients who are small (e.g. body weight less than 45kg), older patients, females and those with right sided heart pathology (e.g. after mitral valve surgery or with heart failure).

Patients being concurrently anticoagulated with heparin (either unfractionated or low molecular weight) should have warfarin therapy initiated in the same way as above, however, the heparin therapy should be discontinued once the INR is greater than 2.0, for two consecutive days. Heparin may be discontinued earlier if the patient is at higher than average risk of bleeding.

Warfarin for mechanical valves:

Mechanical heart valves require lifelong anticoagulation with a vitamin K antagonist (usually warfarin). Warfarin should be initiated on the first post-operative day, bridging therapy with therapeutic enoxaparin should be initiated and continued until the INR is therapeutic. In patients with pacing wires bridging therapy should not be initiated until the pacing wires have been removed (see separate policy: 'Removal of Temporary Epicardial Pacing Wires Post Cardiac Surgery').

Following insertion of a mechanical aortic valve the usual target INR is 2.5 (range 2 -3). The target for mechanical mitral or tricuspid valves is usually 3 (range 2.5-3.5). This target INR may differ depending on different patient factors (see table below from ESC) or based on the discretion of the consultant.

Prosthesis Thrombogenicity	*Patient related risk factors*	
	None	***1 or more risk factor***
Low	*2.5*	*3.0*
Medium	*3.0*	*3.5*
High	*3.5*	*4.0*
Patient related risk factors: *Mitral or tricuspid valve replacement, previous thromboembolism, atrial fibrillation, mitral stenosis (any degree) or LVEF<35%* ***Prosthesis thrombogencity depends on type of valve used:*** *Low risk – Carbomedics, Medtronic Hall, ATS, Medtronic Open-Pivot, St Jude Medical, On-X, Sorin Bicarbon* *Medium – Other Bileaflet valves(mitral)* *High – Lillehei-Kaster, Omniscience, Starr-Edwards(ball-cage), Bkork-Shiley, Tilting-disc valves*		

ON-X Valves:

ON-X valves are a newer generation of mechanical heart valves. Following the PROACT trial it was found that a lower INR range could be used after 3 months of insertion of an aortic ON-X valve. **The target INR range is 2 -3 for the first 3 months and then can be reduced to 1.5 – 2**. There was a >60% reduction in bleeding events and no increase in thromboembolism compared to patients with an INR of 2.0–3.0. Patients with an On-X valve in the mitral valve position (or multiple positions) should have a target INR range of 2.5 – 3.5 after surgery. Aspirin 75mg OD should be continued lifelong in addition to warfarin for patients with ON-X valves.

3.4.1.1 Concomitant use of antiplatelet agents

For patients taking single antiplatelet agents in stable coronary artery disease, consideration should be made to stopping the antiplatelet whilst anticoagulated. For patients being treated with dual antiplatelet therapy and / or in the context of acute coronary syndrome, the decision on duration and dosage of triple therapy should be made by the senior doctor with respect to the patient's bleeding risk versus embolic risk. Consideration should be made to stopping other drugs known to increase bleeding e.g. NSAIDs and to giving adequate gastro-protective agents.

3.4.2 Management of patients on oral anticoagulants requiring surgery or invasive procedures

Patients on oral anticoagulation should have the drug prescribed and suspended so that it is visible on EPR for review post procedure.

3.4.2.1 Surgical patients.

Warfarin is usually discontinued for five days prior to surgery (see Medicines during the peri-operative period policy).

If surgery is delayed resulting in a gap of more than three days or if the patient has a mechanical valve, then bridging anticoagulation with heparin should be discussed with the consultant in charge of the case. For dosing of heparin, see Appendix 3. Guidance on the management of patients on oral anticoagulation therapy requiring urgent surgery is shown in Appendix 8.

3.4.2.2 Medical patients – temporary discontinuation of warfarin therapy for the peri- and intra- procedural management.

There are now extensive data that performance of EP procedures on continuous Warfarin is superior to the strategy of stopping warfarin and bridging with heparin for certain groups. Although occasionally management will need to be individually tailored, in general the approach will be to assign the patient into one of two risk groups as shown in Appendix 4.

For electrophysiological procedures (EP) see separate Trust guidelines- "Guidelines for anticoagulation before, during and after EP procedures"

3.4.3 Prescribing of anticoagulation therapy

Prescribing within LHCH must comply with the Trust's Medicines Policy. The prescriber is legally responsible for their anticoagulation prescription and telephone orders should not be utilized. All anticoagulation therapy must be prescribed on the electronic prescribing system. For in-patients, the drug (for example, warfarin) together with the "anticoagulation therapy reminder prescription", contained within the anticoagulation order set, must be prescribed at the same time.

3.4.4 Dosage and Administration

LHCH currently issues a combination of 1mg and 3mg Warfarin tablets (however, if a higher dose is required pharmacy, following discussion with the patient, may dispense 5mg tablets), each is labelled as follows:

"Take daily at 6.00 p.m. as directed by the anticoagulation clinic".

For in-patients, nursing staff will administer warfarin at 2pm. according to the Trust's administration procedure. Subcutaneous administration of heparin, intravenous heparin or low molecular weight heparin should be administered according to the Trust's administration procedure.

3.4.5 Communication with the anticoagulation clinic

Communication with the anticoagulation clinic taking over the patient's care is essential. Appendix 2 shows the communication sheet (available on each ward printed in triplicate – top copy for the GP to be sent with the discharge summary, second copy for the anticoagulation clinic and third copy for the patient's case notes which can be scanned into EPR following discharge) to be used for onward communication with the patient's GP, anticoagulation clinic or hospital. An appointment must be made by telephone prior to the patient's discharge; however, the appointment must be confirmed by emailing or faxing the completed referral form. This form should then be filed appropriately on the ward.

Anticoagulation clinic appointments should be documented on EPR using the 'warfarin appointment note'.

All new patients (and any existing patients who need one) will receive an anticoagulation booklet at discharge containing details of their first anticoagulant outpatient appointment and details of the dose they will need to take initially. The details of the patient's first dose will be confirmed by pharmacy when dispensing the discharge prescription.

All new patients will be counselled on warfarin by either a pharmacist or a trained technician. A document to this effect will be completed within EPR.

3.4.6 Training of staff involved with anticoagulation therapy.

All staff involved with the prescribing, administration, dispensing and communication process for patients requiring anticoagulation therapy with warfarin will be trained to do so. This training will be appropriate to their role. Induction and mandatory training on medicines management within the Trust will be co-ordinated and managed by the training department, records of training will be held centrally within Human Resources. Specific training for doctors, nurses and pharmacists concerning their roles within this document and clinical aspects of anticoagulation therapy will be co-ordinated by the training pharmacist and clinical nurse trainers, this will be conducted at ward level or during specified training sessions. Records of this training will be held by the nurse trainers or the training pharmacist.

3.5 Direct Oral Anticoagulants (DOACS)

There are currently four DOAC agents, dabigatran, rivaroxaban, edoxaban and apixaban in use within the trust.

DOACs differ in many ways from warfarin, including rapid onset of action, shorter half-life, fewer drug-drug interactions, lack of need for monitoring and no need for titration or dose adjustments. In the absence of a specific clinical reason to select a particular DOAC, Edoxaban is the first line choice due to its simple dosing schedule (can be taken once daily and not affected by food) and lower acquisition cost.

3.5.1 USE IN ATRIAL FIBRILLATION (ALSO SEE 3.5.3)

All four agents are licensed for stroke prevention in atrial fibrillation. There is also experience with their use for pulmonary vein isolation procedures and for cardioversion procedures.

Dabigatran, Rivaroxaban, Edoxaban and Apixaban have been approved by NICE for use for stroke prevention in the UK, DOACs have not been evaluated in patients with heart valve prostheses. Their safety and efficacy profiles in such patients cannot be determined and at present all such patients should remain on warfarin. Following bioprosthetic valve insertion patients may be started on a DOAC for post operative AF, this is usually started if patients have been in AF for 48 hours or have had 2 episodes of AF. Due to the licensing of DOACs LHCH need to supply the initial 3 months of therapy prior to the GP taking over.

Use of new agents in management of AF.

The focus of AF management should be to identify patients with AF and undertake a stroke risk assessment using the CHA_2DS_2VASc risk assessment tool (Appendix 6).

Assessing the bleeding risk, by using the HASBLED or Orbit risk score aids balancing the risk of stroke versus bleeding (see Appendix 7). However, unless there is a significantly larger bleeding risk, anticoagulation is generally indicated as the clinical outcome from a bleeding episode is preferable to a stroke.

Patients with previous intracranial bleed should be reviewed by a specialist stroke physician or neurologist.

DOACs are **not** a suitable alternative to warfarin in patients with bleeding complications associated with warfarin treatment, contraindications to warfarin therapy due to a high bleeding risk, poor compliance with warfarin therapy, a history of alcohol abuse or drug overdose or trivial side effects related to warfarin. Dabigatran is also contraindicated in moderate to severe renal impairment (creatinine clearance less than 30ml/min).

Aspirin (with or without clopidogrel) is not a suitable alternative to warfarin or DOACs in patients with atrial fibrillation as it offers significantly less protection against stroke. Aspirin (with or without clopidogrel) should only be considered for such patients where warfarin and DOACs cannot be used due to allergy or contraindications.

Initiation of DOACs in AF.

DOACs should only be undertaken by clinicians with expertise in initiating anticoagulant therapy for stroke prevention in AF. The initiating clinician is responsible for the safe prescribing of DOACs including:

- Ensuring the patient meets the defined criteria for use
- Ensuring adequate follow up during the initiation phase including providing adherence counselling, dealing with side effects, and addressing any patient concerns regarding therapy.

For further information refer to:

- Manufacturer's summary of product characteristics (SPC) at https://www.medicines.org.uk/emc
- Appendix 12 for Cheshire and Mersey Cardiac Network DOAC Decision Aid
- Pan Mersey statement for the use DOACs in AF
- Guidelines: 'Anticoagulation Before, During and After Electrophysiological Procedures' for Initiation of DOACS in PVI patients

3.5.1.1 Dabigatran

- For the prevention of stroke and systemic embolism in atrial fibrillation, the standard dose is 150mg twice daily
- Patients aged 80 years or above should be treated with 110mg twice daily.
- Patients who receive dabigatran concomitantly with verapamil should have their dose reduced to 110mg twice daily.
- Patients with gastritis, oesophagitis, or gastro-oesophageal reflux, should also have their dose reduced to 110mg twice daily.

3.5.1.2 Rivaroxaban

For prevention of stroke and systemic embolism in atrial fibrillation, the standard dose is 20 mg once daily. For patients with a creatinine clearance of 15 to 49 mL/min, the dose should be

reduced to 15mg once daily. For patients with gastritis, oesophagitis or gastro-oesophageal reflux, gastro-protection may also be needed.

3.5.1.3 Apixaban

For prevention of stroke and systemic embolism in atrial fibrillation, the standard dose is 5 mg twice daily. A lower dose of 2.5 mg twice a day should be used for patients with at least two of the following characteristics: age greater than or equal to 80 years, body weight less than or equal to 60 kg, or serum creatinine greater than or equal to 133 micromol/L. For patients with a creatinine clearance of 15 to 29 mL/min the dose should also be reduced to of 2.5mg twice daily. For patients with gastritis, oesophagitis or gastro-oesophageal reflux, gastro-protection may also be needed.

3.5.1.4 Edoxaban

For prevention of stroke and systemic embolism in atrial fibrillation, the standard dose is 60 mg once daily. A lower dose of 30 mg once daily should be used for patients with at least with one or more of the following clinical factors:

Moderate or severe renal impairment (creatinine clearance (CrCL) 15 - 50 ml/min), low body weight ≤ 60 kg, concomitant use of the following P-glycoprotein (P-gp) inhibitors: ciclosporin, dronedarone, erythromycin, or ketoconazole. For patients with gastritis, oesophagitis or gastrooesophageal reflux, gastro-protection may also be needed.

3.5.2 USE IN TREATMENT AND PREVENTION OF DEEP VEIN THROMBOSIS (DVT) AND PULMONARY EMBOLISM (PE) (ALSO SEE 3.5.3)

- Manufacturer's summary of product characteristics (SPC) at https://www.medicines.org.uk/emc
- Pan Mersey statement for the use of DOACs in PE and DVT

3.5.2.1 Dabigatran

The recommended starting dose of dabigatran for the treatment or prevention of VTE in patients less than 80 years is 150mg twice daily. In patients 80 years or older or in those also taking verapamil, the dose should be reduced to 110mg twice daily.

Patients should receive at least 5 days treatment with a parenteral anticoagulant before starting dabigatran

3.5.2.2 Apixaban

The recommended starting dose of apixaban for the acute treatment of VTE is 10mg twice daily for 7 days followed by 5mg twice daily for 6 months. If treatment is to be continued beyond 6 months for the prevention of recurrent VTE, apixaban should be reduced to 2.5 mg twice daily.

3.5.2.3 Rivaroxaban

The recommended starting dose of rivaroxaban is 15 mg twice daily for 21 days then either 20mg or 15mg daily depending on renal function.

3.5.2.4 Edoxaban

The recommended dose is 60 mg edoxaban once daily following initial use of parenteral anticoagulant for at least 5 days. Edoxaban and initial parenteral anticoagulant should not be administered simultaneously.

3.5.3 OTHER CONSIDERATIONS IN DOAC USE

As the new agents are not subject to INR monitoring, there is no ready means to determine if a patient is concordant with their medication; prescribers should therefore also take into consideration whether the patient is likely/able to comply with their medication.

Concomitant use of antiplatelet agents

Studies with dabigatran, rivaroxaban, edoxaban and apixaban in patients with acute coronary syndromes, receiving combined antiplatelet therapy with aspirin and clopidogrel have generally shown a dose-dependent increase in the risk of major bleeding and any bleeding

For patients taking single antiplatelet agents in stable coronary artery disease, consideration should be made to stopping the antiplatelet whilst on anticoagulation.

For patients being treated with dual antiplatelets and/or in the context of acute coronary syndrome, the decision on duration and dosage of triple therapy should be made by the senior doctor with respect to an patient's bleeding risk versus embolic risk. Consideration should be made to stopping other drugs known to increase bleeding e.g. NSAIDs and to giving adequate gastroprotective agents

3.5.4 Timing of interruption of DOACS before surgery or invasive procedures.

Patients on oral anticoagulation should have the drug prescribed and suspended so that it is visible on EPR for review post procedure

For medical patients see Appendix 5 (see separate policy for EP procedures). Advice for device procedures has been updated taking account of current EHRA and ACC guidance.

For surgical patients see Appendix 5 and Medicines during the peri-operative period policy

The table in Appendix 5 summarises discontinuation advice before invasive or surgical procedures.

Any surgery/intervention should be delayed if possible until at least 12 hours after the last dose. If surgery cannot be delayed, there may be an increase in the risk of bleeding. This risk of bleeding should be weighed against the urgency of intervention.

3.5.5 Postoperative management

For medical patients refer to Appendix 5

For surgical patients consult senior members of team. Ideally DOACs should be held until pacing wires have been removed (see Policy: Removal of Temporary Epicardial Pacing Wires Post Cardiac Surgery).

Note that DOACs have a rapid onset of action.

Advice for device procedures has been updated taking account of current EHRA and ACC guidance. If normal haemostasis is achieved and the operator has no concerns, DOACs can usually be restarted the day after (12-24 hours) post procedure.

3.6 Anticoagulation problems or complications

3.6.1 Heparin Immune (Induced) Thrombotic Thrombocytopenia (HIT).

See HIT Policy.

3.6.2 Management of haemorrhage

3.6.2.1 General Measures

- Inform Consultant

In many cases, simple non-pharmacological measures and stabilization of the patient whilst the antithrombotic is eliminated are sufficient to treat or prevent bleeding. The general non-pharmacological measures that should be taken include:

- Stop the antithrombotic drug
- Document the time and amount of last drug dose and presence of hepatic or renal impairment
- Assess the source of bleeding
- Request FBC, coagulation screen, fibrinogen, renal function & liver function
- If available, request a specific laboratory test to measure the effect of the drug. (i.e. INR for warfarin, anti-Xa for LMWH, DOAC levels if available)
- Correct haemodynamic compromise with intravenous fluids/blood products
- Apply mechanical pressure, if appropriate
- Use endoscopic, radiological or surgical measures to arrest haemorrhage Pharmacological measures are specific to the antithrombotic, see tables/sections below.

3.6.2.2 Heparin

Given the short plasma half-life of unfractionated heparin (UFH), treatment or prevention of bleeding can often be achieved by stopping UFH and the use of general measures. UFH can be rapidly reversed with protamine sulphate, which is derived from fish sperm and forms a stable, inactive salt with heparin.

Antithrombotic Agent	Unfractionated Heparin
Half Life	Short
Initial Management	Stop Heparin Infusion
Reversal Agent	Protamine Sulphate
Dose of Reversal Agent	• Calculated from the quantity of UFH administered in the 2 hours prior to reversal • 1mg protamine reverses 80-100 units of UFH. • This should be given no faster than 5mg/min to minimize the risk of adverse reactions • The maximum recommended dose of 50mg protamine is sufficient to reverse UHF in most settings. • If heparin has been stopped >15 minutes, discuss with haematology and refer to protamine summary of product characteristics (SPC) as a lower dose may be required.
Reversal Agent location	Pharmacy/emergency medicines store/ward stock
Monitoring	APTT Ratio Note- APTT ratio of 0.8-1.2 suggests no heparin effect In the context of continued life-threatening bleeding discuss other haemostatic measures with the on-call haematologist.
Cautions	Protamine can cause severe allergic reactions including anaphylaxis, hypotension, bronchospasm and skin reactions in up to 10% of patients.

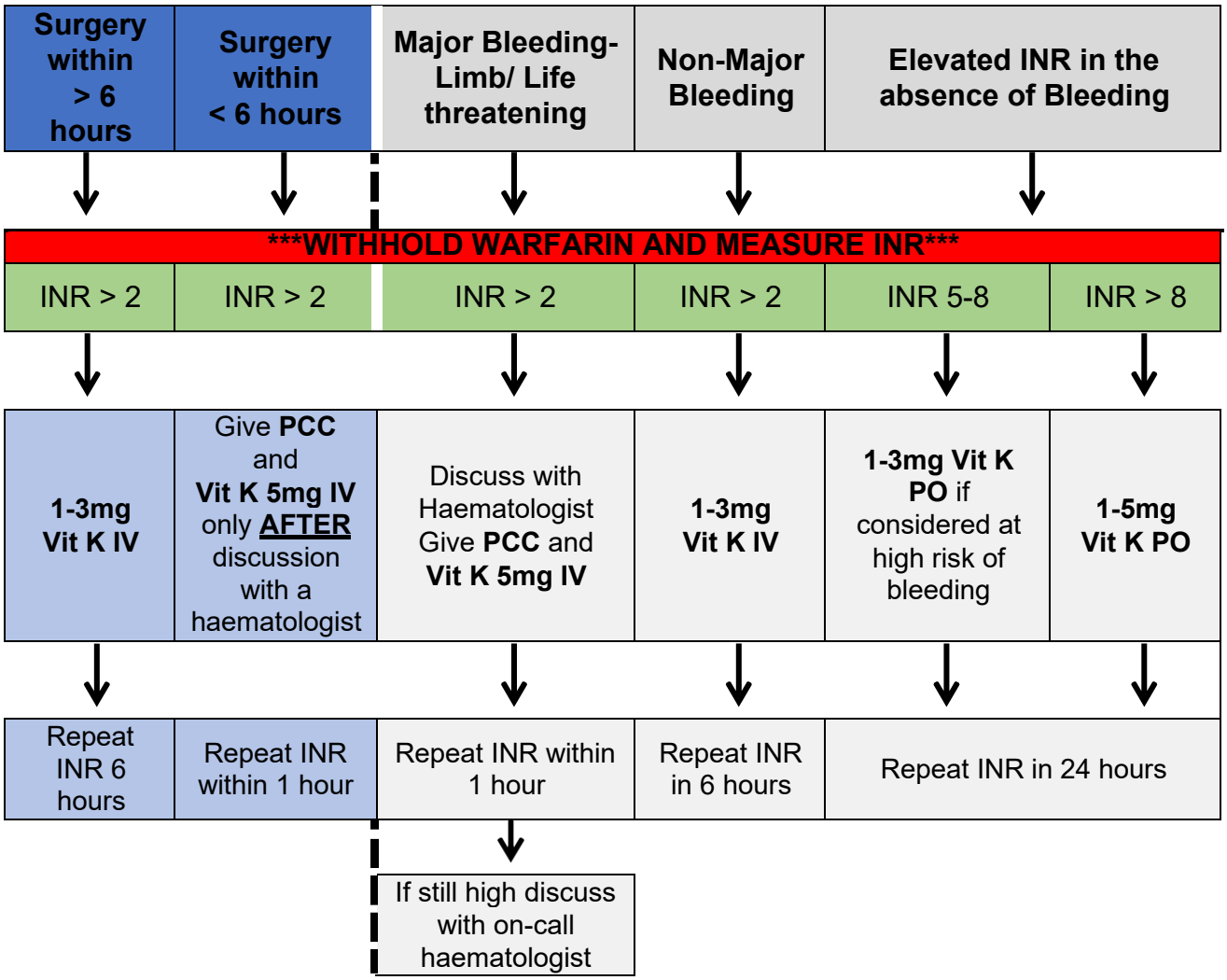
3.6.2.3 Warfarin

The management of bleeding and reversal of anticoagulation with vitamin K antagonists such as warfarin depends on the urgency of which reversal of anticoagulation is required, which is dictated by the clinical situation.

There are two agents which can be used for the reversal of Vitamin K Antagonists –

- Vitamin K (phytomenadione): Available as IV and oral preparations from pharmacy, most ward areas and the emergency drug cupboard out of hours.
- Prothrombin Complex Concentrate (PCC) - Octaplex. This is issued by the Hospital Transfusion Service.

The management of warfarin associated bleeding is summarised in Figure 1, further information can be found in Table 3.



Major Bleeding with Warfarin: Life threatening bleeding
• Resuscitate and non-pharmacological measures to manage bleeding as necessary • Withhold Warfarin • Send samples for INR, FBC, group and save/ plasma cross match • Discuss with haematologist • Administer **Vitamin K (Phytomenadione- Konakion MM) 5mg by slow IV injection over 2 minutes.** Alternatively Vitamin K can be diluted in 50ml Glucose 5% and administered over 10 minutes. • Administer **PCC (Octaplex) 25-50 units/kg (maximum dose 3000 units).** Instructions for the reconstitution of PCC are found with the issued product. The infusion should start at a speed of 1 mL per minute, followed by 2-3 mL per minute, using an aseptic technique. Batch number must be recorded. • Recheck INR within 1 hour of administering PCC • If repeat INR remains elevated – discuss with on-call Haematologist • Consider activating the massive haemorrhage protocol.
Non-Major Bleeding with Warfarin- Less Severe Haemorrhage- Haematuria, Epistaxis or headache
• Withhold Warfarin and check INR • Non-pharmacological measures to manage bleeding • Discuss with a clinical haematologist • If INR >3.0, administer **Vitamin K 1-3mg via slow IV injection** • Recheck INR 6 hours after administration of Vitamin K
Elevated INR due to Warfarin in absence of bleeding
• Check INR • INR 5-8 – administer **Vitamin K 1-3mg PO** (paediatric injection to administered orally) - if considered to be at high risk of bleeding • INR >8 – administer **Vitamin K 1-5mg PO** (paediatric injection to administered orally) • Repeat INR in 24 hours.
Unexpected bleeding or headache at therapeutic levels of INR
• Cause of bleeding should be investigated as for patients who are not taking warfarin • Modify warfarin dose as appropriate • If cerebral haemorrhage is suspected INR should be reversed as soon as possible as in major bleeding

3.6.2.4 Direct Oral Anticoagulants (DOACs) - Dabigatran, Rivaroxaban, Apixaban, Edoxaban

The management of bleeding in the presence of these drugs is largely through cessation of treatment and general haemostatic measures.

In the context of major bleeding the use of pro-haemostatic and reversal agents **must be guided by a haematologist**.

The use of andexanet alfa **must be discussed with a haematologist**. Andexanet may increase the risk of thrombosis particularly when administered with other bloods products including PCC.

For patients who are likely to require urgent surgery with intra-operative anticoagulation, administration of andexanet will make anticoagulation difficult and reversal with PCC should be considered instead.

Note: Vitamin K and protamine administration will be ineffective in the reversal of these agents and have no role in reversal of bleeding under DOACs

<table>
<tr><td rowspan="3">Antithrombotic Agent</td><td colspan="4">Direct Oral Anticoagulants</td></tr>
<tr><td colspan="3">Factor Xa Inhibitor</td><td>Direct Thrombin Inhibitors</td></tr>
<tr><td>Apixaban</td><td>Rivaroxaban</td><td>Edoxaban</td><td>Dabigatran</td></tr>
<tr><td>Half Life</td><td>12 hours</td><td>5-13 hours</td><td>10-14 hours</td><td rowspan="2">12-18hours. Normalisation of plasma levels depends on CrCl
Normal Function- 12-24 hours
CrCl 50-80ml/min- 24-36hours
CrCl 30-50ml/min- 36-48hours
CrCl <300ml/min- >48hours</td></tr>
<tr><td colspan="3">Normalisation of plasma levels within 12-24 hours</td></tr>
<tr><td>Initial Management</td><td colspan="4">• Cessation of treatment- Confirm prescribed regime and timing of last dose
• General haemostatic measures
• Fluid replacement
• Consider stopping antiplatelet therapy and other factors which may influence plasma concentration
• Request FBC, Group & Save, eGFR, APTT, PT, fibrinogen
• Request drug levels
• Consider activated charcoal if ingested within 2 hours</td></tr>
<tr><td rowspan="2">Reversal Agent</td><td colspan="3">Andexanet Alfa
(off label for edoxaban)</td><td rowspan="2">Idarucizamab
(Praxbind©)</td></tr>
<tr><td colspan="3">Only for life threatening or uncontrolled GI bleeding</td></tr>
<tr><td>Dose of Reversal Agent</td><td colspan="3">See dosing tables below</td><td>5g IV over two consecutive infusions of 2.5g no more than 15 minutes apart</td></tr>
<tr><td>Monitoring</td><td colspan="4">Routine coagulation tests for these agents are difficult to interpret, and often do not reflect the bleeding tendency. Interpretation should be guided by a Haematologist.</td></tr>
</table>

	The haematology laboratory has the ability to assay Rivaroxaban, Apixaban, Edoxaban and Dabigatran levels – these should be discussed with a clinical Haematologist.
Cautions	In the context of continued life-threatening bleeding discuss other haemostatic measures with the on-call haematologist.

The management of DOAC associated bleeding is summarised below:

Life threatening

- Call consultant Haematologist
- Initiate Trust Massive Haemorrhage policy (Appendix 2 of Transfusion Policy)
- Discuss the use of haemostatic agents
- Consider haemodialysis
- Consider reversal agent

** Even after direct reversal significant DOAC concentrations may reappear in some patients and contribute to recurrent or continued bleeding **

Non life-threatening Major Bleeding

- Supportive measures
  - Mechanical compression
  - Endoscopic Haemostasis if gastrointestinal bleed
  - Surgical Haemostasis
  - Fluid replacement
  - RBC Substitution aiming for Hb >7g/dl
  - Platelet transfusion aiming for platelets >50 x 10^9 or >100 x 10^9 if CNS bleeding
  - Maintain BP and urine output
- Consider Tranexamic acid 1g IV bolus over 10mins
- For Dabigatran-Consider idarucizumab or haemodialysis
-

Minor Bleeding

- Mechanical Compression
- Delay next dose or discontinue drug
- Reconsider choice of DOAC
- Reconsider concomitant medication aimed at treating the cause of bleeding e.g.- PPI for gastric ulcers

Dabigatran Reversal

Idarucizumab (Praxbind©) is a licensed humanised monoclonal antibody which binds specifically to dabigatran to block its anticoagulant affects and its metabolites. It neutralises anticoagulant activity by forming a stable complex which is then excreted.

It is licensed for use in adults treated with dabigatran etexilate (Pradaxa), when rapid reversal of anticoagulation is required, such as for:-

- Emergency surgery or urgent procedures
  - Stop dabigatran
  - Consider deferring surgery for > 12 hours
  - Optimise Hb and platelets
  - Inform anaesthetist
- Life threatening, uncontrolled bleeding
  - Stop dabigatran and anti-platelets
  - Initiate local/ supportive measures
  - Follow trust major haemorrhage protocol (See Transfusion Policy / Resus Trolley)

IMPORTANT
Idarucizumab will NOT reverse the action of other anticoagulants. Its action is specific to dabigatran. It must NOT be given unless the patient has taken dabigatran.

Dose: 5 grams IV as two consecutive infusions of 2.5grams in 50ml over 5 – 10 minutes each or as two 2.5gram bolus injections.

Supply: Idarucizumab is available from the transfusion laboratory. If a dose is given, the pharmacy department should be informed immediately to ensure replacement stock is ordered.

Administration of a second 5 gram dose may be considered in the following situations only when approved by a haematologist:-

- Recurrence of clinically relevant bleeding together with a prolonged APTT
- If potential re-bleeding would be life threatening or a prolonged APTT is observed
- Patients require a second emergency surgery or urgent procedure and have a prolong APTT

Absence of antithrombotic therapy exposes patients to the thrombotic risk of their underlying disease or condition.

<u>Apixaban, rivaroxaban and edoxaban reversal</u>

Andexanet Alfa (Ondexxya) is a recombinant form of human factor Xa which binds specifically to apixaban, rivaroxaban and edoxaban thereby reversing their anticoagulant effects.

It is licensed for reversal of apixaban or rivaroxaban in life-threatening or uncontrolled bleeding. However, it is only commissioned for use in with life-threatening or uncontrolled bleeding if the bleed is in the gastrointestinal tract. Andexanet alfa is recommended only in research for reversing anticoagulation from apixaban or rivaroxaban in adults with life-threatening or uncontrolled bleeding in the skull (intracranial haemorrhage; ICH), in the form of an ongoing

randomised trial mandated by the regulator. If a patient taking a DOAC presents with another source of life-threatening bleeding this should be discussed urgently with the on-call haematology consultant and a decision may be made to administer andexanet alfa in exceptional circumstances.

The ANNEXA-4 study show that andexanet alfa significantly decreased anti-factor Xa activity and excellent or good haemostasis at 12 hours was observed in 79% of patients. It is also important to note that concerns have been raised regarding high thrombosis rates after andexanet administration. The procoagulant effect of andexanet is debated due to the nature of the populations being studied and administration of other bloods products including PCC but may be attributed to reduced TFPI activity.

For patients who are likely to require intra-operative anticoagulation (and the procedure cannot be postponed), consideration should be given to anticoagulation reversal with PCC instead of andexanet alfa.

The use of andexanet alfa for reversal of edoxaban is off-label however there is evidence to support its use. See Pan Mersey Statement for further information.

Andexanet has a shorter duration of action than anti-Xa inhibitors and has been not evaluated in patients with renal impairment in whom anti-Xa inhibitors may have accumulated.

See appendix 10 for details of reconstitution, administration and dosing information.

Dose

The dose of andexanet alfa should be calculated using the patient's regular dose of apixaban, rivaroxaban or edoxaban.

Andexanet alfa dosing regimens

	Initial intravenous bolus	**Continuous intravenous infusion**	**Total number of 200mg vials needed**
Low dose	400mg at a target rate of 30mg/min	4mg/min for 120mg minutes (480mg)	5
High dose	800mg at a target rate of 30mg/min	8mg/min for 120mg minutes (960mg)	9

Reversal of apixaban

The recommended dose regimen of andexanet alfa is based on the dose of apixaban the patient is taking at the time of anticoagulation reversal, as well as on the time since the patient's last dose of apixaban.

FXa inhibitor	**Last dose**	**Timing of last dose before andexanet alfa initiation**	
		< 8 hours or unknown	**≥ 8 hours**
Apixaban	≤ 5 mg	Low dose	Low dose
	> 5 mg/ Unknown	High dose	

Reversal of rivaroxaban

The recommended dose regimen of andexanet alfa is based on the dose of rivaroxaban the patient is taking at the time of anticoagulation reversal, as well as on the time since the patient's last dose of rivaroxaban (see table 8).

FXa inhibitor	Last dose	Timing of last dose before andexanet alfa initiation	
		< 8 hours or unknown	≥ 8 hours
Rivaroxaban	≤ 10 mg	Low dose	Low dose
	> 10 mg/ Unknown	High dose	

Reversal of Edoxaban

The recommended dose regimen of andexanet alfa is based on the dose of edoxaban the patient is taking at the time of anticoagulation reversal, as well as on the time since the patient's last dose of rivaroxaban.

FXa inhibitor	Last dose	Timing of last dose before andexanet alfa initiation	
		< 8 hours or unknown	≥ 8 hours
Edoxaban	30 mg	Low dose	Low dose
	60 mg/ Unknown	High dose	

Supply- Andexanet alfa is available from the transfusion laboratory. If a dose is given, the pharmacy department should be informed immediately to ensure replacement stock is ordered.

Administration- Andexanet alfa is administered as an intravenous bolus at a target rate of approximately 30 mg/min over 15 minutes (low dose) or 30 minutes (high dose), followed by administration of a continuous infusion of 4 mg/min (low dose) or 8 mg/min (high dose) for 120 minutes.

3.6.2.5 Other anticoagulants

There is no specific reversal agent for fondaparinux, danaparoid or argatroban. If bleeding occurs whilst prescribed one of these agents, treatment should be stopped and general haemostatic measures taken. Contact the on-call clinical haematologist for further advice.

3.6.2.6 Restarting anticoagulation after bleeding

The reintroduction of anticoagulation following bleeding is clinically guided re-anticoagulation should be considered to prevent thrombotic events due to the patient's underlying medical condition. Medical judgement should balance the benefits of anticoagulation with the risks of re-bleeding

Dabigatran etexilate treatment can be re-initiated 24 hours after administration of idarucizumab, if the patient is clinically stable and adequate haemostasis has been achieved. Other anticoagulants may be re-introduced once clinically indicated/appropriate. Haematology advice can be sought for alternative anticoagulants and interventions (e.g IVC filter).

4. Policy Implementation Plan

This policy will be disseminated via the Drug and Therapeutics Committee. All ward managers received an information pack via their ward pharmacist during implementation of the first version of this policy, however, further training sessions will be arranged at ward level by ward pharmacists to ensure nurses are aware of this policy. The policy will be explained to all medical staff during their induction training and during their medicines management training sessions.

The policy will become part of a check list for all clinical staff to read during induction, records of this training will be held within the Human Resources Department.

Managers have a responsibility to ensure staff have read and understood the policy and a record of this should be kept. Pharmacy will carry out an annual audit of anticoagulation practice within the Trust which will be reported to Drug and Therapeutics Committee. Audit results demonstrating (lack of) adherence may require the author to develop local strategies for further dissemination. The policy will be updated following feedback from audit results.

With the introduction of the first version of this policy the new anticoagulation booklet was introduced to the Trust following recommendation by the National Patient Safety Agency. A new communication sheet was also introduced for use by the wards for the onward dissemination of anticoagulation information to referring hospitals, anticoagulation clinics and GP surgeries. The booklet and communication sheet will continue to be used.

5. Monitoring of Compliance

Audit of the policy will be conducted annually by the audit department via incident reports and via audit of the communication sheet to ensure onward communication of patient's anticoagulation therapy has been undertaken. Pharmacy will conduct an annual audit of clinical issues in line with NPSA guidance.

6. Expert Advice

Advice on the development of this policy has been obtained from the haematology department at the RLBUHT and Wirral NHS Trust.

7. References

1. Fennerty et al. British Medical Journal 1988;297:1285-8
2. Jan Steffel, Peter Verhamme, Tatjana S Potpara, Pierre Albaladejo, Matthias Antz, Lien Desteghe, Karl Georg Haeusler, Jonas Oldgren, Holger Reinecke, Vanessa Roldan-Schilling, Nigel Rowell, Peter Sinnaeve, Ronan Collins, A John Camm, Hein Heidbüchel, The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation, *European Heart Journal*,

Volume 39, Issue 16, 21 April 2018, Pages 1330–1393, https://doi.org/10.1093/eurheartj/ehy136
3. Essebag V, Healey JS, Joza J, Nery PB, Kalfon E, Leiria TLL, Verma A, Ayala-Paredes F, Coutu B, Sumner GL, Becker G, Philippon F, Eikelboom J, Sandhu RK, Sapp J, Leather R, Yung D, Thibault B, Simpson CS, Ahmad K, Toal S, Sturmer M, Kavanagh K, Crystal E, Wells GA, Krahn AD, Birnie DH. Effect of Direct Oral Anticoagulants, Warfarin, and Antiplatelet Agents on Risk of Device Pocket Hematoma: Combined Analysis of BRUISE CONTROL 1 and 2. Circ Arrhythm Electrophysiol. 2019 Oct;12(10):e007545. doi: 10.1161/CIRCEP.119.007545. Epub 2019 Oct 15. PMID: 31610718.
4. Doherty JU., Gluckman TJ., Hucker WJ., Januzzi JL., , Ortel TL., Saxonhouse SJ., Spinler SA. (2017) ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients with Nonvalvular Atrial Fibrillation: A Report of the American College of Cardiology Clinical Expert Consensus Document Task Force, *Journal of the American College of Cardiology* Volume 69, Issue 7, 2017, Pages 871-898.
5. Makris, M., Van Veen, J. J., Tait, C. R., Mumford, A. D., Laffan, M. (2013), Guideline on the management of bleeding in patients on antithrombotic agents. *British Journal of Haematology*, 160: 35–46
6. Keeling, D., Baglin, T., Tait, C., Watson, H., Perry, D., Baglin, C., Kitchen, S., Makris, M. and British Committee for Standards in Haematology (2011), Guidelines on oral anticoagulation with warfarin – fourth edition. British Journal of Haematology, 154: 311–324
7. Birnie DH, Healey JS, Wells GA, Verma A, Tang AS, Krahn AD, Simpson CS, Ayala-Paredes F, Coutu B, Leiria TL, Essebag V; BRUISE CONTROL Investigators. Pacemaker or defibrillator surgery without interruption of anticoagulation. *N Engl J Med*. 2013;368:2084–2093. doi: 10.1056/NEJMoa1302946
8. Birnie DH, Healey JS, Wells GA, Ayala-Paredes F, Coutu B, Sumner GL, Becker G, Verma A, Philippon F, Kalfon E, Eikelboom J, Sandhu RK, Nery PB, Lellouche N, Connolly SJ, Sapp J, Essebag V. Continued vs. interrupted direct oral anticoagulants at the time of device surgery, in patients with moderate to high risk of arterial thrombo-embolic events (BRUISE CONTROL-2). *Eur Heart J*. 2018;39:3973–3979. doi: 10.1093/eurheartj/ehy413
9. Electronic Medicines Compendium (eMC). Praxbind 2.5 g/50 mL solution for injection/infusion. 2019. https://www.medicines.org.uk/emc/product/5073
10. Electronic Medicines Compendium (eMC). Ondexxya 200mg powder for solution for infusion 2021 https://www.medicines.org.uk/emc/product/10933
11. Andexanet alfa for reversing anticoagulation from apixaban or rivaroxaban. Technology appraisal guidance [TA697]. 2021 https://www.nice.org.uk/guidance/ta697/chapter/1-Recommendations
12. Andexanet Alfa for Acute Bleeding During Treatment With Edoxaban. https://www.ahajournals.org/doi/10.1161/str.52.suppl_1.P3

8. Appendices

Appendix 1: Warfarin initiation schedule

A. Post Cardiac surgery:

Schedules for oral anticoagulant therapy after cardiac surgery are different to all other LHCH **inpatients.**

An initial dose of 5mg is usually given unless any of the following conditions apply:

Day one post-operative INR greater than 1.4
For patients already taking warfarin, consider their usual dose
Weight less than 55Kg or more than 100Kg
Abnormal liver function
Right heart failure
Antibiotic therapy or other concomitant drug(s) that may interact with warfarin (if in doubt contact pharmacy for information).

The dose schedule of warfarin should be discussed with the registrar or consultant of the team involved should any of the above criteria exist. The above regimen should be used in all inpatients to achieve the desired target INR. It may be necessary to aim initially for an INR of 2.0 to 2.5 in patients where pacing wires are still in-situ. Once the pacing wires have been removed the interim INR can be crossed through on the prescription chart and the desired INR (as determined by the consultant) can be prescribed.

Subsequently daily warfarin doses should be determined by review of the patient's INR and by discussion with the consultant in charge of the case.

B. Prevention of complications for atrial fibrillation patients (in the out-patient setting):

Warfarin may be commenced in the out-patient setting. Patients may be commenced using a dose that is deemed to be an appropriate maintenance dose for that patient, however, it is important to ensure that all patients commenced in this manner have access to an anticoagulation clinic 72 hours after starting their anticoagulation.

C. All other LHCH in-patients

The following table refers to initiation of warfarin therapy ONLY and SHOULD NOT be used as a guide to maintenance dose adjustment.

Day	INR	Warfarin dose (mg)
Day 1 (*)	Less than 1.4 before treatment	10 (1st dose)
Day 2	Less than 1.8	10
	1.8	1
	Greater than 1.8	0.5
Day 3	Less than 2	10
	2 – 2.1	5
	2.2 – 2.3	4.5
	2.4 – 2.5	4
	2.6 – 2.7	3.5
	2.8 – 2.9	3
	3 – 3.1	2.5
	3.2 – 3.3	2
	3.4	1.5
	3.5	1
	3.6 – 4	0.5
	4	0
		Predicted maintenance dose
Day 4	Less than 1.4	More than 8
	1.4	8
	1.5	7.5
	1.6 – 1.7	7
	1.8	6.5
	1.9	6
	2 – 2.1	5.5
	2.2 – 2.3	5
	2.4 – 2.6	4.5
	2.7 – 3	4
	3.1 – 3.5	3.5
	3.6 – 4	3
	4.1 – 4.5	Miss out next day's dose then give 2mg
	Greater than 4.5	Miss out 2 day's doses then give 1mg
**** Day 1 INR greater than 1.4 – seek specialist haematology advice*** ***Other induction regimens to be used at the discretion of the consultant***		

Appendix 2: Anticoagulant clinic communication sheet (use for all except Arrowe Park)

Surname	Forename	Unit Number	Date of Birth

Patients Address	General Practitioner Name
Postal code Phone No.	GP Address GP Phone No.

Ward / Clinic	Consultant	Date of next Consultant appt.

Indication for Anticoagulation	Relevant Previous Medical History	INR Target Recommended ((with range)	Duration of Treatment

Date Warfarin Started (if not warfarin, indicate drug)	INR on Discharge	Appointment Date for INR Check	Antiplatelet therapy required YES NO

Hospital INR History Date INR Dose	Other Drugs Prescribed

Anticoagulation clinic to be referred to:

Name of clinic / hospital	Address	Telephone Number	Fax Number
Arrowe Park Hospital	See form below		
Countess of Chester	Liverpool Rd, Chester	01244 365373	01244 365122
Halton General Hospital	Runcorn, Cheshire	01928 753213	01928 753922
Ormskirk DGH	Wigan Road	01695 656890	01695 656819
Roald Dahl Centre RLBUHT	Prescott Street L1	0151 706 3393	0151 706 5837
Walton Hospital	Rice Lane, L9	0151 529 4421	0151 529 4626

Signature of Doctor	Date

Appendix 2: Anticoagulant clinic communication sheet – Arrowe Park Only

Diagnostics Division
Directorate of Laboratory Medicine
Department of Haematology

Wirral University Teaching Hospital NHS
NHS Foundation Trust

ANTICOAGULANT OUTPATIENTS CLINIC REFERRAL FORM

Please note that appointments will only be made when all sections are fully completed

REFERRER DETAILS	Referring Unit	Name of Referring Consultant	Contact Name	Contact Tel N°
				Contact Fax N°
If discharged from acute care please state location:			Ward:	Discharge Date

PATIENT DETAILS	Surname	Forename	Date Of Birth
Address			Telephone N°
			MRN
Postcode			NHS number

GP DETAILS	GP Name	GP Address	GP Phone N°

ANTICOAGULATION INFORMATION				
Indication (Please circle)			**Target INR** (Please circle)	**INR Range** (Please circle)	**Duration of treatment** (Please circle)
DVT	**PE**	**AF**	2.5 3.5 Other (please state)	2 to 3 3 to 4 Other (please state)	3 months 6 months Long term Other (Please state)
Other (please state)					
To help with patient counselling : If the indication for anticoagulation is atrial fibrillation please state CHA_2DS_2VASc or CHADS2 score					CHA_2DS_2VASc / CHADS2
If patient is to have DC cardioversion please state date of appointment :					
Has the patient been newly commenced on oral anticoagulant therapy? (Please circle) **Yes or No**			**Name of anticoagulant**		**Please state date anticoagulant started if applicable:**
Is the patient currently prescribed an antiplatelet? (Please circle) **Yes or No**			**Name of antiplatelet** (please circle) Aspirin Dipyridamole Clopidogrel Other:		**Is the antiplatelet to stop when INR reaches therapeutic level?** (Please circle) **Yes or No**

	Date	INR result	Anticoagulant Dose :	
PREVIOUS INR RESULTS				**TO BOOK APPOINTMENT TELEPHONE 0151 604 7393** **CONFIRM REQUEST BY FAXING REFERRAL TO 0151 604 0370**
SIGNATURE OF REFERRING CLINICIAN				**DATE OF REFERRAL**

For anticoagulant clinic clerk use only:			
MRN	Clinic Appointment date	Date actioned	Actioned by (name)

Form produced by Alice Foster WUTH Specialist Anticoagulant Pharmacist
Approved: WHAG October 2012 Review Date: October 2015

Appendix 3: Heparin Infusion Guidelines

1. Give a bolus – loading dose of 5,000 units by intravenous injection (see below):

    a. For patients less than 70Kg give 70 units/Kg.
    b. For patients less than 50kg or patients known to be sensitive to heparin, discuss with the consultant or haematology department.

2. Start an infusion of heparin 1000 units/ml (40ml containing 40,000units). Set infusion to run at 1.3ml per hour (approximately 30,000 units over 24 hours).

3. Check APTT 6 to 8 hours after starting infusion.

4. Change the infusion rate to achieve the therapeutic APTT ratio range of 1.8 to 3.3 (depending on indication and concurrent therapy) by 24 hours (see table).

For Adjusting the Dosage of Intravenous Heparin 1000 units/ml	
APTT Ratio	**Infusion rate change**
Greater than 7.2	Stop for 60 minutes. At restart, reduce rate by 1ml/hr.
5.7 – 7.1	Reduce by 0.3ml/hr.
3.4 – 5.6	Reduce by 0.1ml/hr.
1.8 – 3.3	No change.
1.4 – 1.7	Increase by 0.2ml/hr.
Less than 1.4	Increase by 0.4ml/hr.
Repeat APTT ratio 6-8hours after each alteration in rate, unless APTT ratio is greater than 7.2 when measurements should be made more frequently.	

Modified from Fennerty et al. British Medical Journal 1988:297: 1285-8

5. Replace heparin infusion (syringe) at least every 24 hours and repeat APTT daily, or more frequently if infusion rate is altered (as above).
6. If heparin continues for more than 5 days, check platelet count and serum potassium level daily.

Appendix 4: Protocol for the peri-procedural management of medical patients on warfarin (or other coumarins)

Stratify patients according to risk for thrombo-embolism	
High risk (1 or more of the following) • Mechanical mitral valve • Tilting disc/Caged –ball heart valve • AF:CHADS score >4 • Recent thromboembolism within 3 months	**Low-Medium risk** • Bi-leaflet aortic valve • AF: CHADS score ≤4 • Remote thrombo embolism
Pre-procedural management (NB for non-radial access-discuss with consultant)	
Continue warfarin without dose reduction **AIM FOR INR<3.0**	Stop warfarin for 4 days and aim for INR <2.5
Post-procedural management	
• Continue warfarin post wound check • No low molecular weight heparin unless explicitly requested	• Resume usual dose warfarin on same day post wound check • No low molecular weight heparin unless explicitly requested

Appendix 5: Management of patients on DOACs during invasive procedures or surgery

For all EP and ablation procedures, including PVI refer to Trust policy for anticoagulation during EP procedures

Dabigatran

Preoperative management; Timing of last dose prior to procedure		
Estimated Creatinine Clearance (ml/min)	Standard risk of bleeding**	High Risk of Bleeding***
>50	24 hours	2 days
30-50	2 days	4 days
<30*	4 days	6 days
Postoperative management: Re-initiation post-procedure		
	Standard risk of bleeding**	High Risk of Bleeding***
	24 hours	48 hours

***Note dabigatran treatment is contraindicated in these patients**

Rivaroxaban/Apixaban/Edoxaban

Preoperative management; Timing of last dose prior to procedure		
Estimated Creatinine Clearance (ml/min)	Standard risk of bleeding**	High Risk of Bleeding***
>30	24 hours	2 days
15-30	2 days	4 days
Postoperative management: Re-initiation post-procedure		
	Standard risk of bleeding**	High Risk of Bleeding***
	Consider at least 12hours post procedure after wound check	Consider at least 12hours post procedure after wound check

** **Standard risk procedures include:** cardiac catheterisation, colonoscopy without removal of large polyps, uncomplicated laparoscopic procedures such as cholecystectomy. Device procedures: New pacemaker/ICD/CRT implant (including leadless pacemakers and subcutaneous ICDs), generator changes

*** **High risk procedures include:** major cardiac surgery, neurosurgery, large hernia surgery, major cancer/urologic/vascular surgery. Device procedures: Device upgrades, lead extraction, wound revision, submuscular reburial

Restarting

Device procedures: DOACs can usually be restarted 12-24 hours post procedure if the wound is satisfactory but individualised advice will be documented in the Cardiac Devices post procedure review document

Cardiac surgery: DOACs can usually be restarted 36 hours post cardiac surgery if chest drain losses < 0.25 ml/kg/hr.

Appendix 6: CHA_2DS_2VASc Score

The risk factor-based approach for patients with non-valvular AF can be expressed as an acronym, CHA_2DS_2VASc [congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74, and sex category (female)]. This scheme is based on a point system in which 2 points are assigned for a history of stroke or TIA, or age ≥75; and 1 point each is assigned for age 65–74 years, a history of hypertension, diabetes, recent cardiac failure, vascular disease (myocardial infarction, complex aortic plaque, and PAD, including prior revascularization, amputation due to PAD, or angiographic evidence of PAD, etc.), and female sex.

CHA_2DS_2VASc score and stroke rate

Risk factor-based approach expressed as a point based scoring system, with the acronym CHA_2DS_2VASc
(Note: maximum score is 9 since age may contribute 0, 1, or 2 points)

Congestive heart failure/LV dysfunction	**1**
Hypertension	**1**
Age >75	**2**
Diabetes mellitus	**1**
Stroke/TIA/thrombo-embolism	**2**
Vascular disease	**1**
Age 65–74	**1**
Sex category (i.e. female sex)	**1**

Maximum score 9

Adjusted stroke rate according to CHA_2DS_2-VASc score

Based on data from 7329 patients. Lip GY, Frison L, Halperin JL, Lane DA. Identifying patients at high risk for stroke despite anticoagulation: a comparison of contemporary stroke risk stratification schemes in an anticoagulated atrial fibrillation cohort. Stroke 2010;41 (12):2731–8. 0

0	**0%**
1	**1.3%**
2	**2.2%**
3	**3.2%**
4	**4.0%**
5	**6.7%**
6	**9.8%**
7	**9.6%**
8	**6.7%**
9	**15.2%**

Appendix 7: Bleeding Risk Assessment Tools

Anticoagulant risk / benefit assessment

Risk benefit assessment involves making a clinical assessment in respect of the safety or otherwise of commencing or continuing anticoagulation. Relevant indicators to look out for include:

- Major spontaneous bleeding complications including gastrointestinal, intracranial bleeding etc.
- Deterioration in cognitive function, onset of dementia etc. (e.g. patient unable to remember whether has taken medication or not)
- Recurrent accidental falls with head injury or likely to lead to head injury
- Requirement for new medication likely to potentiate risk of bleeding e.g. aspirin or Clopidogrel
- Significant deterioration in renal or hepatic function (both likely to increase bleeding risk)

Warfarin: Stability of anticoagulation (widely fluctuating INRs with no obvious cause may indicate a higher risk of bleeding, stable INR control is associated with a more favourable bleeding risk profile)

There are 2 bleeding risk scores available to assess risk-benefit of anticoagulation in atrial fibrillation care, HAS-BLED and ORBIT. ORBIT is favoured by NICE FOR as per NG196 as e evidence shows that it has a higher accuracy in predicting absolute bleeding risk than other bleeding risk tools.

ORBIT Bleeding Risk Score for Atrial Fibrillation

HAS-BLED Score for Major Bleeding Risk

Appendix 8: Management of patients on warfarin (or other coumarins) requiring urgent surgery

Step 1

- Send sample for INR
- Give Vitamin K IV 2.0 mg (slow injection or infusion in Glucose 5%) to all patients, if INR > 2.5
- Stop warfarin

Step 2a (Surgery within 6 hours required)

- Give PCC 30 units per kg IV in addition to Vitamin K
- PCC will reverse warfarin / normalize INR within 10 – 15 minutes
- PCC (Octaplex) is available from the Transfusion Laboratory (see appendix 8)
- Round dose to use full vials (500 units per vial)
- Send sample for INR post-PCC
- If necessary proceed with surgery immediately post PCC (without waiting for INR result)

Step 2 b (Surgery can be delayed > 6 hours)

- Check INR 6 hours post Vitamin K. Proceed if INR < 1.6.
  INR between 1.5 and 2.0 may be safe for some procedures.
- If INR still deranged despite Vitamin K give another 2.0 mg of Vitamin K IV and consider PCC (see above)

Step 3 (Bridging anticoagulation)

- Patients with a moderate/high risk of thromboembolism (see below) need bridging anticoagulation
- If bridging anticoagulation is indicated, refer to Appendix 4 high risk patients and section 3.4.2.1
- If surgery is delayed start bridging anticoagulation pre-op (either unfractionated heparin or low molecular weight heparin, discuss with consultant in charge of the case. Start when INR <2.0. Give last dose of enoxaparin 24 hours before the operation (e.g. 18.00 the day before)

Step 4 (Post-operative management)

- Check INR and FBC next morning
- Restart warfarin as soon as the patient is eating and drinking normally, usually on the 1st postoperative day.
- Start enoxaparin 1mg/kg twice daily or unfractionated heparin after the 4th postoperative day if the INR is not therapeutic.
- Stop bridging anticoagulation with enoxaparin or unfractionated heparin when INR in therapeutic range
- Bridging anticoagulation and re-introduction of warfarin can be completed in the community following discharge

For all steps seek advice from haematology

Comments

- The “watch and wait” - approach (stop warfarin and wait until INR comes down) is too slow, results in significant delays and prolongs length of stay. This practice should be abandoned.
- All patients should be given Vitamin K. Oral Vitamin K has a very slow onset and the effect is unreliable. Intravenous Vitamin K should be used instead.
- The dose of intravenous Vitamin K suggested here (2mg) represents a compromise. Lower doses may be insufficient to reverse warfarin, higher doses may make re-anticoagulation difficult.
- FFP should not be used for reversal of warfarin because a) the reversal may be incomplete b) it is slow c) there is a risk of infection and transfusion-related acute lung injury d) it can result in fluid overload.
- The clotting factors (prothrombin complex concentrate) given to reverse warfarin have a short half-life of only 4 – 6 hours (Factor VII). Therefore, surgery should be performed as early as possible after the administration of clotting factors.
- It is essential that intravenous (IV) vitamin K is given in addition to PCC to switch on endogenous synthesis of vitamin K dependent clotting factors.
- Warfarin has a slow onset of action. Therefore, it can safely be restarted at the regular dose on the evening after the operation provided the patient can have oral medication and is resuming a normal diet (if patient still has post-procedural drains in situ, consult with consultant).

Appendix 9a: Enoxaparin dosing table 1.5mg/kg once daily (e.g. PVI, DVT and PE Treatment)

USE ONLY 120mg or 150mg syringes - Each Graduation is 3mg

Weight (Kg)	Syringe Dose (mg)	NB Dose for patients with Creatinine Clearance less than 30ml/minute is 1mg/kg once daily	
		Weight (kg)	Syringe dose (mg)
50	75	50-52	51
51-52	78	53-55	54
53-54	81	56-58	57
55-56	84	59-61	60
57-58	87	62-64	63
59-60	90	65-67	66
61-62	93	68-70	69
63-64	96	71-73	72
65-66	99	74-76	75
67-68	102	77-79	78
69-70	105	80-82	81
71-72	108	83-85	84
73-74	111	86-88	87
75-76	114	89-91	90
77-78	117	92-94	93
79-80	120	95-97	96
81-82	123	98-100	99
83-84	126	101-103	102
85-86	129	104-106	105
87-88	132	107-109	108
89-90	135	110-112	111
91-92	138	113-115	114
93-94	141	116-118	117
95-96	144	119-121	120
97-98	147	122-124	123
99-100	150	125-127	126
101-102	**153 -use 2 SYRINGES 120mg+33mg**	128-130	129
103-104	**156-use 2 SYRINGES 120mg +36mg**		
105-106	**159-use 2 SYRINGES 120mg +39mg**		
107-108	**162-use 2 SYRINGES 120mg+42mg**		
109-110	**165-use 2 SYRINGES 150mg+15mg**		
111-112	**168-use 2 SYRINGES 150mg+18mg**		
113-114	**171-use 2 SYRINGES 150mg+21mg**		
115-116	**174-use 2 SYRINGES 150mg+24mg**		
117-118	**177-use 2 SYRINGES 150mg+27mg**		
119-120	**180-use 2 SYRINGES 150mg+30mg**		
121-122	**183-use 2 SYRINGES 150mg+33mg**		
123-124	**186-use 2 SYRINGES 150mg+36mg**		
125-126	**189-use 2 SYRINGES 150mg+39mg**		

APPENDIX 9b: Enoxaparin dosing table 1mg/kg twice daily (e.g. ACS treatment, patients with prosthetic valves, high-risk DVT/PE)

USE ONLY 120mg or 150mg syringes- Each Graduation is 3mg

The dose for patients with creatinine clearance less than 30ml/min is 1mg/kg once daily

Weight (Kg)	Syringe Dose (mg)
50-52	51
53-55	54
56-58	57
59-61	60
62-64	63
65-67	66
68-70	69
71-73	72
74-76	75
77-79	78
80-82	81
83-85	84
86-88	87
89-91	90
92-94	93
95-97	96
98-100	99
101-103	102
104-106	105
107-109	108
110-112	111
113-115	114
116-118	117
119-121	120
122-124	123
125-127	126
128-130	129
131-133	132
134-136	135
137-139	138
140-143	141

Appendix 9c: Enoxaparin dose banding for outpatients

To minimise the risk of administering an incorrect dose, outpatients requiring enoxaparin should be prescribed the nearest syringe size to the calculated dose so a full syringe can be administered.

Scenarios where outpatient enoxaparin may be required include:

- Bridging patients on Warfarin preoperatively with mechanical valves
- Bridging patients who are on Warfarin post-operatively prior to achieving a therapeutic INR

Pharmacy will confirm with the patient that they know how to administer the subcutaneous injection but it is the responsibility of the CNPs in Outpatients to educate patients on administration.

Calculated dose (mg)	Banded dose and syringe to be supplied
51	60 mg syringes
54	
57	
60	
63	
66	
69	80 mg syringes
72	
75	
78	
81	
84	
87	
90	100mg syringes
93	
96	
99	
102	
105	
108	
111	120 mg syringes
114	
117	
120	
123	
126	
129	
132	
135	150 mg syringes
138	
141	

Appendix 10: Octaplex Reconstitution Instructions

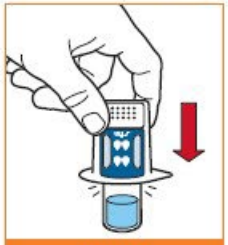
octaplex® Human Prothrombin Complex

Instructions for reconstitution using Nextaro®

Follow the hospital's aseptic procedures at all times. If necessary, allow the solvent (water for injections) and the powder in the closed vials to reach room temperature. This temperature should be maintained during reconstitution. Working on a clean flat surface, remove the vials from the outer packaging and remove the flip top lids. Disinfect the rubber stoppers on the vials appropriately.

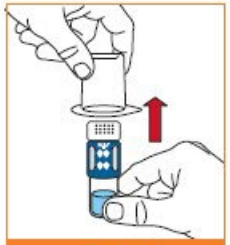
Step 1

Peel away the lid of the outer package of the Nextaro®. Do not remove the device from the package.



Step 2

Place the solvent vial on an even surface and hold it firmly. Without removing the outer package, place the blue part of the Nextaro® on top of the solvent vial and press firmly down until it snaps into place. Do not twist while attaching!

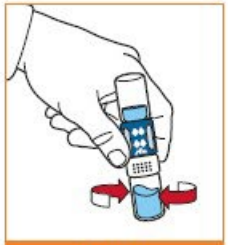


Step 3

While holding onto the solvent vial, carefully remove the outer package from the Nextaro® being careful to leave the Nextaro® attached firmly to the solvent vial.

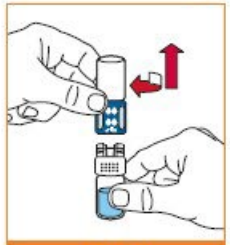
Step 4

Place the powder vial on an even surface and hold it firmly. Take the solvent vial with the attached Nextaro® and turn it upside down. Place the white part of the Nextaro® connector on top of the powder vial and press firmly down until it snaps into place.



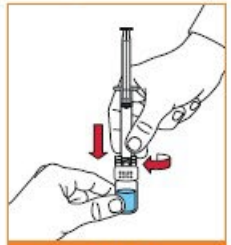
Step 5

The solvent flows automatically into the powder vial. With both vials still attached, gently swirl the powder vial until the product is dissolved. Octaplex® dissolves quickly at room temperature to a colourless to slightly blue solution.



Step 6

Unscrew the Nextaro® into two parts. Dispose of the empty solvent vial with the blue part of the Nextaro®. If the powder fails to dissolve completely or an aggregate is formed, do not use the preparation.



Step 7

Attach a syringe to the luer lock outlet on the white part of the Nextaro®. Turn the vial upside down and draw the solution into the syringe. Dispose of the Nextaro® and the empty vial.

The reconstitution guidelines above have been adapted from octaplex® Summary of Product Characteristics, please read for full prescribing and reconstitution details. Prescribing information (PI) can be found on the reverse of this page. Nextaro® a registered trademark of sfm medical devices GmbH.

May 2022 UK-PLEX-2200007

octapharma

Reconstitution of Octaplex

See diagram above

Administration

Octaplex should only be used by a clinician following discussions with a Consultant Haematologist.

After removing the filter, administer the dose by slow intravenous injection by either IV bolus or via a syringe pump.

The rate of administration is initially 1 ml/minute for the first minute increase to 3ml/minute if tolerated with no significant change in observations.

If there is more than 1 vial reconstituted, the same administration line can be used for each syringe.

The dose can be put into one or more 60ml syringes for ease of use rather than several 20ml syringes (as provided in the box), as long as the infusion pump can accommodate them.

Check INR following administration (within 1 hour). If reversal is incomplete (INR>1.5) contact haematologist to discuss further management.

NB: Rate via a syringe pump: 1ml/minute = 60ml/hr, 3ml/minute = 180ml/hr

Appendix 11: Andexanet alfa dosing recommendations

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited.[4]

Ondexxya® andexanet alfa ▼

▼This medicinal product is subject to additional monitoring.

Ondexxya® reconstitution and administration[1]

1. Preparing the (200 mg Ondexxya®) vials

- Ondexxya® does not need to be brought to room temperature before reconstitution or administration to the patient. Aseptic technique during the reconstitution procedure should be used.
- Remove the flip-top
- Wipe the rubber stopper of each vial with an alcohol swab

2. Reconstituting the lyophilisate in the vials

Per vial

- Using a 20 mL (or larger) syringe and a 20-gauge (or larger) needle, withdraw 20 mL of water for injection
- Insert the syringe needle through the centre of the vial's rubber stopper
- Push the plunger down slowly to inject the water for injections into the vial

IMPORTANT: Carefully direct the stream of water for injection toward the inside wall of the vial to minimise foaming.

Inject all required vials before proceeding to the next step.

3. Dissolve

- Gently swirl each vial until the powder is completely dissolved
- Do NOT shake the vial(s), as this can lead to foaming

IMPORTANT: The powder will have dissolved and the solution will be ready for use after approximately 3–5 minutes.

4. Inspect

- Prior to administration, inspect the reconstituted solution for particulate matter and/or discolouration
- Do not use if the solution contains opaque particles or is discoloured
- Solution after reconstitution: 10 mg/mL

IMPORTANT: The reconstituted solution is clear, colourless or slightly yellow.

5. Transfer

Withdraw the reconstituted solution from each vial into the large-volume (50 mL or larger) syringes (equipped with a 20-gauge or larger needle)

Administration by syringe pump

IMPORTANT

- **Low dose:** 1 infusion syringe intravenous (IV) bolus, 1 infusion syringe continuous IV infusion
- **High dose:** 2 infusion syringes IV bolus, 2 infusion syringes continuous IV infusion
- Hold the syringe needle upright and do not set the syringe down between multiple withdrawals from vials (to prevent air bubbles)

Use of IV bags

- Transfer the reconstituted solution from the syringe into an appropriate IV bag
- It is recommended to split the solution intended for bolus and continuous infusion into two separate bags to ensure the correct administration rate

6. Administration

The IV rate is the same whether using a syringe pump or IV bags.

- **IV bolus rate**
  Low dose: 400 mg, which corresponds to 40 mL, 180 mL/hr, administered over approximately 15 minutes.
  High dose: 800 mg, which corresponds to 80 mL, 180 mL/hr, administered over approximately 30 minutes.
- **Continuous IV infusion rate**
  Low dose: 480 mg, which corresponds to 48 mL, 24 mL/hr, for 120 minutes.
  High dose: 960 mg, which corresponds to 96 mL, 48 mL/hr, for 120 minutes.

The infusion should be administered using 0.2 µm (or 0.22 µm) in-line filters (polyethersulfone [PES] or a similar material with low protein binding).

All used syringes, needles, and vials, including any unused portion of reconstituted solution, should be disposed of in accordance with local requirements.

In-use stability after reconstitution

- In primary packaging/vial: 16 hours at 2–8°C
- Ready-to-use medication: a further 8 hours at room temperature (≤ 25° C)

From a microbiological point of view, once reconstituted, the product should be used immediately. If this is not the case, the user is responsible for the storage times and conditions prior to use.

Appendix 11: Andexanet alfa dosing recommendations

Ondexxya® dosage recommendations[1]

Ondexxya® andexanet alfa

Two dosing regimens, individualised depending on the specific direct factor Xa (FXa) inhibitor, last individual dose of FXa inhibitor and time since last FXa inhibitor dose[1]

FXa inhibitor	Last individual dose	Time since last individual dose		
		< 8 hours	≥ 8 hours	Unknown
Apixaban	≤ 5mg	LOW	LOW	LOW
	> 5mg or unknown	HIGH	LOW	HIGH
Rivaroxaban	≤ 10mg	LOW	LOW	LOW
	> 10mg or unknown	HIGH	LOW	HIGH

	Initial intravenous bolus	Continuous intravenous infusion	Total number of Ondexxya® (200 mg) vials
LOW DOSE	400mg, which corresponds to 40 mL, 180 mL/hr, administered over 15 minutes 	480mg, which corresponds to 48 mL, 24 mL/hr for 120 min 	5 x 
HIGH DOSE	800mg, which corresponds to 80 mL, 180 mL/hr, administered over 30 minutes 	960mg, which corresponds to 96 mL, 48 mL/hr for 120 min 	9 x 

Appendix 12: Initiating DOACs in AF

Cheshire and Merseyside Health and Care Partnership | miaa | Cheshire & Merseyside Cardiac Network | NHS North West Coast Clinical Networks

Initiating a DOAC in Patients with Atrial Fibrillation / Flutter (AF)

Patients to consider

- Newly identified patients with AF or previous diagnosis not on an OAC
- Patients on VKAs with consistently low TTR < 70%, we recommend considering interventions to improve TTR or switching to DOACs

Determine risk of stroke using CHA_2DS_2-VASc score and bleeding risk

- Patients with a CHA2DS2-VASc =1 in men or =2 in women should be considered for an oral anticoagulant (OAC)
- Patients with a CHA2DS2-VASc score ≥2 in men and ≥3 in women: It is recommended that these patients should be prescribed an OAC
- Assess bleeding risk using HAS-BLED score or ORBIT score and address modifiable risk factors for anticoagulation in all AF patients e.g. BP control, use of NSAIDs, alcohol intake, obesity

Assess if suitable for oral anticoagulation

- Consider contraindications, concomitant medicines (e.g. aspirin, SSRIs, NSAIDs, bisphosphonates), alcohol and drug abuse.

Does the patient have a contraindication to a DOAC?

- With a prosthetic mechanical valve
- With moderate to severe mitral stenosis
- With antiphospholipid antibody syndrome (APLS)
- Who are pregnant, breastfeeding or planning a pregnancy
- With severe renal impairment - Creatinine Clearance (CrCl) < 15ml/min (edoxaban, apixaban and rivaroxaban). If CrCl 15-30 mL/min use edoxaban, apixaban and rivaroxaban with caution. Do not prescribe dabigatran if CrCl<30 ml/min.
- Requirement for triple therapy (dual antiplatelet therapy plus OAC) or those requiring a higher INR than the standard INR range of 2.0 – 3.0, without appropriate discussion with an anticoagulant specialist or cardiologist
- With active malignancy/ chemotherapy (unless advised by a specialist)
- Prescribed interacting drugs – check SPCs for full list e.g. HIV antiretrovirals and hepatitis antivirals - check with HIV drug interactions website at https://www.hiv-druginteractions.org/ and some antiepileptics – phenytoin, carbamazepine, phenobarbitone or rifampicin are likely to reduce DOAC levels so should be discussed with an anticoagulation specialist
- If the patient has a lesion or condition considered a significant risk for major bleeding, including current or recent gastrointestinal ulceration, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities – seek specialist advice.
- There is no data to suggest lack of DOAC efficacy in patients with active CA but consider specialist advice before initiation
- There are little data on DOACs for patients with venous thrombosis at unusual sites (e.g. portal vein thrombosis) - discuss with an anticoagulation specialist

If YES to any of the above, consider warfarin if clinically appropriate and discuss with specialist if required

If the answer if NO to all of the above, continue down the flowchart

Appendix 12 - Initiating DOACs in AF

References:

- Lip GYH *et al.* Antithrombotic Therapy for Atrial Fibrillation CHEST Guideline and Expert Panel Report. Chest. 2018 Nov;154(5):1121-1201. doi: 10.1016/j.chest.2018.07.040.
- https://www.medicines.org.uk/emc/ - edoxaban, apixaban, dabigatran and rivaroxaban
- Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014;383(9921):955-962.
- Carmo J, Moscoso Costa F, Ferreira J, Mendes M. Dabigatran in real-world atrial fibrillation. Meta-analysis of observational comparison studies with vitamin K antagonists. Thromb Haemost. 2016;116(4):754-763.
- Bai Y, Deng H, Shantsila A, Lip GY. Rivaroxaban versus dabigatran or warfarin in real-world studies of stroke prevention in atrial fibrillation: systematic review and meta-analysis. Stroke. 2017;48(4): 970-976.
- Hohnloser SH, Basic E, Nabauer M. Comparative risk of major bleeding with new oral anticoagulants (NOACs) and phenprocoumon in patients with atrial fibrillation: a postmarketing surveillance study. Clin Res Cardiol. 2017;106(8):618-628.
- Li XS, Deitelzweig S, Keshishian A, et al. Effectiveness and safety of apixaban versus warfarin in non-valvular atrial fibrillation patients in "real-world" clinical practice. A propensity-matched analysis of 76,940 patients. Thromb Haemost. 2017;117(6):1072-1082.
- Bai Y, Shi XB, Ma CS, Lip GYH. Meta-Analysis of Effectiveness and Safety of Oral Anticoagulants in Atrial Fibrillation With Focus on Apixaban. Am J Cardiol. 2017;120(9):1689-1695.
- Chao TF, Joung B, Takahashi Y, Lim TW, Choi EK, Chan YH, Guo Y, Sriratanasathavorn C, Oh S, Okumura K, Lip GYH. 2021 Focused Update Consensus Guidelines of the Asia Pacific Heart Rhythm Society on Stroke Prevention in Atrial Fibrillation: Executive Summary..Thromb Haemost. 2022 Jan;122(1):20-47. doi: 10.1055/s-0041-1739411. Epub 2021 Nov 13.
- Lee SR, Choi EK, Kwon S, Han KD, Jung JH, Cha MJ, Oh S, Lip GYH. Effectiveness and Safety of Contemporary Oral Anticoagulants Among Asians With Nonvalvular Atrial Fibrillation. Stroke. 2019 Aug;50(8):2245-2249.
- Boriani G *et al.* Relationship between body mass index and outcomes in 21,028 patients with atrial fibrillation treated with edoxaban or warfarin in ENGAGE AF-TIMI 48. European Heart Journal, 2019: 40:1541-1549
- Lixiana European Public Assessment Report (EMA/321083/2015) published 23 Apr 2015 https://www.ema.europa.eu/en/documents/assessment-report/lixiana-epar-public-assessment-report_en.pdf) accessed Mar 2022
- Boriani G *et al.* Edoxaban versus Warfarin in Patients with Atrial Fibrillation at the Extremes of Body Weight: An Analysis from the ENGAGE AF-TIMI 48 Trial. Thromb Haemost 2021; 121:140-149
- Steffel J *et al.* 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation. Europace, 2021; 23(10):1612-1676
- Lee SR, Choi EK, Jung JH, Park SH, Han KD, Oh S, Lip GYH. Body Mass Index and Clinical Outcomes in Asian Patients With Atrial Fibrillation Receiving Oral Anticoagulation. Stroke. 2021 Jan;52(2):521-530. doi: 10.1161/STROKEAHA.120.030356. Epub 2021 Jan 11. PMID: 33423512.
- Gosselin RC, Adcock DM et al. An update on laboratory assessment for direct oral anticoagulants (DOACs). international Journal of Laboratory Haematology. 2019; 41 Suppl 1: 33-9
- Barakat AF, Jain S, Masri A, Alkukhun L, Senussi M, Sezer A, Wang Y, Thoma F, Bhonsale A, Saba S, Mulukutla S. Outcomes of Direct Oral Anticoagulants in Atrial Fibrillation Patients Across Different Body Mass Index Categories. JAC Clin Electrophysiol. 2021 May;7(5):649-658.

Abbreviations:
DOAC = direct-acting oral anticoagulant
AF = atrial fibrillation
VKA = vitamin K antagonist
TTR = time in therapeutic range
BP = blood pressure
NSAIDS = non-steroidal anti-inflammatories
SSRIs = selective serotonin reuptake inhibitors
TIA = transient ischaemic attack
GI = gastrointestinal
BMI = body mass index
PPI = proton pump inhibitor

Version 1 Sept 2022
Review date Sept 2025 or sooner if new information becomes available

9. Endorsed By:

Name of Lead Clinician / Manager or Committee Chair	Position of Endorser or Name of Endorsing Committee	Date
Dr Denis Wat	Drug & Therapeutics	16/11/22

10. Record of Changes

Section No	Version No	Date of Change	Description of Amendment	Description of Deletion	Description of Addition	Reason
3.3.4		November 2022			Removal of VTE section	Separate VTE policy available
3.4.1		November 2022	Updated target INR for mechanical valves including ON-X valves			ESC Guidance according to valve thrombogenicity
3.6.2.1		November 2022			Management of haemorrhage including use of andexanet	National and regional guidance
Appendix 1		November 2022	Initial warfarin loading dose usually 5mg			Reflects current practice
Appendix 5		November 2022	Merge of medical and surgical procedures DOAC advice			duplication
Appendix 7		November 2022	Addition of ORBIT bleeding risk assessment tool			NICE guidance
Appendix 9c		November 2022			Outpatient dose banding of enoxaparin	Safety: to avoid administration of part syringe.
Appendix 10		November 2022	Nextaro presentation of Octaplex			New presentation
Appendix 11		November 2022			Andexanet administration advice	New product
Appendix 12		November 2022			New network guidance for DOAC initiation	New regional guidance