Reference Number: FOI2021/341
From: Private Individual

Date: 06 October 2021

Subject: Local DOAC (Direct Oral Anticoagulants) guidelines within the NHS

Q1 I am undertaking a project looking at local DOAC (Direct Oral Anticoagulants) guidelines within the NHS. Would you be able to send any:

- guidelines your organisation has available relating to the use of Direct Oral Anticoagulants within your area along with,
- any guidelines referring to the reversal/ antidote of DOAC treatment.

I would be grateful for any information you have to aid my research as I was unable to find the information on your website. If you don't have any local guideline, do you follow NICE?

A1 Please see attached documents:

- Anticoagulation v6.4
- Anticoagulation EP procedures v7.0
- Anticoagulation of critical care patients with confirmed Covid v2.1

Anticoagulation Policy

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Scope: This policy applies to all clinical staff (including temporary staff) working within LHCH who are involved in the prescribing, dispensing and administration of anticoagulants, whether parenteral or oral. This policy also applies to staff involved in the discharge of patients to ensure that sufficient information is sent with the patient to enable the safe continuation of their anticoagulation therapy.	***Classification:*** **Clinical**
Replaces: v6.3	
To be read in conjunction with the following documents: The Medicines Policy, Medicines Administration Procedure, HITT Policy, Prevention of VTE Policy, Use of Enoxaparin in PCI, Guidelines for anticoagulation before, during and after EP Procedures.	
Document for public display? Yes	

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Has the document undergone Equality Analysis?	**No**
Has Endorsement been completed?	**No**

Table of Contents

Policy 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

Medical Director
The above Director is responsible for implementation of this policy.

The Drug and Therapeutics Committee
The above 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.

Medical staff 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. 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 ensuring safety of patients and other staff at all times.

3. Protocol

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

APTT – The partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT or APTT) is 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 – non-vitamin K oral anticoagulation agents – four newer 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. Dabigatran is the only agent which currently has a reversal agent.. 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 (dependant 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 below)
- Prophylaxis of deep vein thrombosis in medical patients (see below)

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* THERAPY

3.3.1 Treatment of Pulmonary Embolism or Deep Vein Thrombosis

- **Unfractionated Heparin Infusion Guidelines**

These are contained within LHCH Drug Formulary; however, they are shown in Appendix 3 for completeness. 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 1 mg/kg twice daily should be used in all other patients such as those with obesity, with symptomatic PE, cancer, recurrent VTE or proximal (vena iliaca) thrombosis. The patient's weight must be measured prior to commencement of therapy and rechecked at regular intervals during their treatment e.g. alternate days. The patient's creatinine clearance should also be monitored daily while on LMWH and the dose adjusted accordingly (for example, for patients with creatinine clearance less than 30ml/min, the dose should be adjusted to 1mg/kg/day). Appendix eight contains guidance tables for prescribing enoxaparin. It is recommended that the prescriber should choose between using the 120mg or the 150mg syringe, where the graduation marks represent 3mg each.

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). The patient's creatinine clearance should also be monitored daily while on LMWH and the dose adjusted accordingly (for example, for patients with creatinine clearance less than 30ml/min, the dose should be adjusted to 1mg/kg ONCE daily). 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. Patient's renal function should be monitored, however, 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. The patient's creatinine clearance should be monitored daily 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 deep vein thrombosis in surgical patients

The LMWH of choice for prophylaxis of DVT in surgical patients is Dalteparin (see table below for dosing and monitoring).

Or

Unfractionated heparin 5000 units subcutaneously 8 hourly

Owing to an increased risk of developing spinal haematoma, dalteparin **must not** be used for patients with an epidural catheter in situ, nor should it be administered within 12 hours to those patients who are to have an epidural catheter inserted. In these cases unfractionated heparin should be used, at a dose of 5000 units subcutaneously 8 hourly.

3.3.5 Prophylaxis of deep vein thrombosis in medical patients

The LMWH of choice for prophylaxis of DVT in medical patients is Dalteparin (see table below for dosing and monitoring).

3.3.6 Dalteparin dosing and monitoring for DVT prophylaxis

Weight	Dalteparin dose	
	Creatinine clearance ≥30ml/min	Creatinine clearance <30ml/min*
≤ 49 kg	2500 units once daily	2500 units once daily*
50 – 100 kg	5000 units once daily	5000 units once daily*
101-149 kg	5000 units twice daily*	5000 units once daily*
≥ 150 kg	7500 units twice daily*	5000 units once daily*

*For patients >100kg or with a creatinine clearance is <30mls/min it is advisable to monitor anti-factor Xa levels. Blood samples should be taken before and 4 hours after the 3rd dalteparin dose has been given. If resultant levels are out of range, haematology should be consulted for dosing advice. Anti-Xa levels should be repeated once weekly to monitor for accumulation.

3.3.7 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 administering the drug

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.

3.4 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 (International Normalised Ratio).

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 one). 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.

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 an individual; 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 cardiac surgery and four days prior to thoracic surgery (see medicines during the peri-operative period policy http://nww.staffintranet.lhch.nhs.uk/media/2796/medicines-during-the-peri-operative-period-v10.pdf)
However, 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 7a.

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 device implants and 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.

N.B. 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 Two 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 faxing the completed referral form.

This form should then be placed in the patient's purple folder and subsequently scanned into EPR.

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 Non-Vitamin K 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 limited 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. Therefore the trust will not initiate their use in patients with artificial valves.

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 Five). Patients with a CHA_2DS_2VASc score greater than or equal to 1 should normally be considered for initiation of oral anti-coagulation therapy.

Assessing the bleeding risk, by using the HASBLED risk score, aids balancing the risk of stroke versus bleeding, shown in appendix six. 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. General caution is advised if HASBLED is greater than two.
Patients with previous intracranial bleed should be reviewed by a specialist stroke physician or neurologist.

Warfarin is traditionally the first line option for the prevention of stroke and systemic embolism in AF. Patients stable on warfarin therapy should not normally be considered for a switch to DOACs. DOACs should be considered as an alternative to warfarin for stroke prevention in AF in people with non-valvular atrial fibrillation with one or more of the following risk factors:

- Previous stroke, transient ischaemic attack or systemic embolism
- Left ventricular ejection fraction below 40%
- Symptomatic heart failure of New York Heart Association (NYHA) class 2 or above
- Age 75 years or older
- Age 65 years or older with one of the following: diabetes mellitus, coronary artery disease or hypertension

Priority patients for initiation of DOACs

These include:

- those currently taking warfarin with poor INR control, indicated by 2 or more unexplained INR values above 5.0 or below 1.7 during a twelve month period. Reasons for poor control should be explored (in particular poor compliance, interacting co-prescribed medication and diet) before treatment is changed.
- those with significant problems associated with the monitoring or taking of warfarin (either actual in those currently taking warfarin or likely in those considered appropriate for warfarin)
- those who clearly express the desire not to take warfarin following an informed discussion of the risks and benefits of each agent.

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 and a CHA_2DS_2VASc score greater than or equal to 1, 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.

Initiation of DOACS in PVI patients See EP protocol

3.5.1.1 DABIGATRAN (SEE DATASHEET FOR FURTHER DETAILS)

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.

Further advice, is shown within Appendix 10.

Please refer to the Pan Mersey statement for the use in AF:

http://www.panmerseyapc.nhs.uk/recommendations/documents/PS101.pdf?UNLID=47453081820159241051115

3.5.1.2 RIVAROXABAN (SEE DATA SHEET FOR FURTHER DETAILS)

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.

Further advice is shown within appendix 10.

Please refer to the Pan Mersey statement for the use in AF:

http://www.panmerseyapc.nhs.uk/recommendations/documents/PS101.pdf?UNLID=47453081820159241051115

3.5.1.3 APIXABAN (SEE DATA SHEET FOR FURTHER DETAILS)

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 gastritis, oesophagitis or gastro-oesophageal reflux, gastro-protection may also be needed.

Further advice, is shown within appendix 10.

Please refer to the Pan Mersey statement for the use in AF:

http://www.panmerseyapc.nhs.uk/recommendations/documents/PS101.pdf?UNLID=47453081820159241051115

3.5.1.4 EDOXABAN (SEE DATA SHEET FOR FURTHER DETAILS)

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 gastro-oesophageal reflux, gastro-protection may also be needed

Further advice, is shown within appendix 10

Please refer to the Pan Mersey statement for the use in AF:

http://www.panmerseyapc.nhs.uk/recommendations/documents/PS101.pdf?UNLID=47453081820159241051115

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

3.5.2.1 Dabigatran (SEE DATA SHEET FOR FURTHER DETAILS)

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

Please refer to the Pan Mersey statements for the use in PE and DVT:

http://www.panmerseyapc.nhs.uk/recommendations/documents/PS159.pdf

3.5.2.2 Apixaban-(SEE DATA SHEET FOR FURTHER DETAILS)

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.

Please refer to the Pan Mersey statements for the use in PE and DVT:

http://www.panmerseyapc.nhs.uk/recommendations/documents/PS159.pdf

3.5.2.3 Rivaroxaban (SEE DATA SHEET FOR FURTHER DETAILS),

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

Please refer to the Pan Mersey statements for the use in PE and DVT

http://www.panmerseyapc.nhs.uk/recommendations/documents/PS159.pdf

3.5.2.4 Edoxaban (SEE DATA SHEET FOR FURTHER DETAILS)

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.

Please refer to the Pan Mersey statements for the use in PE and DVT:

http://www.panmerseyapc.nhs.uk/recommendations/documents/PS159.pdf

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 individual patients 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 4 (see separate policy for EP procedures)

Procedures with a low (standard) risk of bleeding, where an INR of 1.5 for patients on warfarin would be acceptable include cardiac catheterisation, diagnostic endoscopy, and minor orthopaedic surgery. Procedures with a high risk of bleeding include device implant procedures (pacemaker/ICD/Box change)

For surgical patients see Appendix 10 and medicines during the peri-operative period policy http://nww.staffintranet.lhch.nhs.uk/media/2796/medicines-during-the-peri-operative-period-v10.pdf

The table in Appendix 10 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 4
For surgical patients consult senior members of team
Note that DOACs have a rapid onset of action.

3.6 ANTICOAGULATION PROBLEMS OR COMPLICATIONS

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

- See HITT Policy.

3.6.2 Management of hemorrhage

3.6.2.1 Warfarin

- Inform Consultant
- Major bleed – stop warfarin, give phytomenadione (vitamin K_1) 5 mg by slow intravenous injection, or prothrombin complex concentrate (factors II, VII, IX and X) 50 units/kg
- INR greater than 8, no bleeding or minor bleeding – stop warfarin, restart when INR less than 5, if there are other risk factors for bleeding give phytomenadione (vitamin K_1) 0.5mg by slow intravenous injection or 5mg by mouth, for partial reversal of anticoagulation give smaller oral doses of phytomenadione e.g. 0.5 to 2.5 mg (using the paediatric intravenous preparation orally), repeat dose of phytomenadione if INR still too high after 24 hours.
- INR 6 – 8, no bleeding or minor bleeding – stop warfarin, restart when INR less than 5.
- INR 5 - 6 , reduce dose or stop warfarin, restart when INR less than 5
- Unexpected bleeding at therapeutic levels – always investigate possibility of underlying cause e.g. unsuspected renal or gastrointestinal tract pathology.

3.6.2.2 DOACs

Emergency testing of haemostatic function for DOACs

Dabigatran
If the thrombin clotting time TCT is normal, the level of dabigatran is very low. (PT) is insensitive to dabigatran and not useful. Point of care testing INR values may be inaccurate in patients receiving dabigatran and should not be used to judge drug effect. At high dabigatran concentrations the aPTT becomes incoagulable but interpretation of the results is difficult and haematology advice should be sought. A normal aPTT would suggest that haemostatic function is not impaired.

Rivaroxaban and Apixaban
The PT is prolonged but the PT response to both drugs is assay dependant and haematology advice should be sought. A normal PT would suggest that haemostatic function is not impaired.

Managing overdose- see appendices 7b, 7c and 9

Dabigatran
If detected soon after ingestion the absorption of dabigatran may be reduced by gastric lavage and/or administration of charcoal. Prothrombin complex concentrate (PCC, Octaplex) may improve haemostasis by providing small amounts of thrombin. Haemodialysis may be useful since only 35% of dabigatran is bound to plasma proteins. In emergency situations – for example

a patient on Dabigatran requiring emergency surgery – the antidote for dabigatran – idarucizumab – may be used.

Rivaroxaban
Due to a high degree of albumin binding in plasma (92-95%), rivaroxaban dialysis would not be useful. Prothrombin complex concentrate (PCC, Octaplex) should be administered in a dose of 50 IU/kg in case of life-threatening bleeding.

Apixaban
Administration of activated charcoal may be useful in the management of apixaban overdose or accidental ingestion.
If life-threatening bleeding cannot be controlled by conservative measures, administration of recombinant factor VIIa may be considered. Re-dosing of recombinant factor VIIa could be considered and titrated depending on improvement of bleeding.

Edoxaban
For life-threatening bleeding that cannot be controlled with the measures such as transfusion or haemostasis, the administration of a 4-factor prothrombin complex concentrate (PCC) at 50 IU/kg has been shown to reverse the effects of edoxaban 30 minutes after completing the infusion.
Recombinant factor VIIa (r-FVIIa) can also be considered. However, there is limited clinical experience with the use of this product in individuals receiving edoxaban.

Managing bleeding complications
When bleeding occurs the event should be risk stratified: Minor bleeding (such as epistaxis, ecchymosis, or menorrhagia) should be managed with simple withdrawal of the anticoagulant for one or more days allowing definitive interventions to be applied. The drug could then be restarted. Moderate bleeding (such as upper or lower gastrointestinal bleeding) should be managed with withdrawal of the anticoagulant, careful clinical monitoring, interventions to identify and definitively treat the bleeding source and consideration of an extended period of withdrawal of the oral anticoagulant to allow healing.

Major and life-threatening bleeding should be treated as follows:
For Dabigatran the antidote idarucizimab should be administered at a dose of 5g. A second dose may be given if there is recurrence of severe bleeding with a prolongation of the clotting time or a second surgery is required. For all other DOACs treatment is supportive with resuscitation measures, immediate anticoagulant withdrawal, aggressive clinical monitoring, transfusion of packed red blood cells and interventions to identify and treat the bleeding source (requiring endoscopy, interventional radiology or surgery). Prothrombin complex concentrate (PCC, Octaplex) may improve haemostasis by providing small amounts of thrombin. Prothrombin complex concentrate (PCC) should be administered in a dose of 50 IU/kg in case of life-threatening bleeding. Haemodialysis may be useful for dabigatran but not for rivaroxaban or apixaban, and should be used if bleeding continues despite administration of idarucizimab.

Dabigatran treatment can be re-initiated 24 hours after administration of Praxbind, if the patient is clinically stable and adequate haemostasis has been achieved.

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 and Review

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

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

8. Appendices

(Appendices start on the next page)

APPENDIX 1

WARFARIN INITIATION SCHEDULE

The information contained in this appendix is divided into three sections:
A, Post Cardiac surgery dosing,
B, Dosing for the prevention of complications for atrial fibrillation patients (in the out-patient setting)
C, Warfarin initiation schedule for guidance in all other in-patients.

A. Post Cardiac surgery:

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

An initial dose of 0.5 to 1mg/10Kg body weight is given unless any of the following conditions apply:

- Day one post-operative INR greater than 1.4
- 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 in-patients 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

Communication Sheet - **Request for Outpatient Anticoagulant Control**

****For Arrowe Park Hospital see separate form below****

Surname	**Forename**	**Unit Number**	**Date of Birth**
Patients Address **Postal code** **Phone No.**		**General Practitioner Name** **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**

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

How to Use Intravenous Heparin in Adults*

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

   Patients less than 70Kg should receive approximately 70 units/Kg as a loading dose.

2. Establish an infusion of heparin 1000units/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.

For patients less than 50kg or patients known to be sensitive to heparin, discuss with the consultant or hematology department.

APPENDIX 4

PROTOCOL FOR THE PERI-PROCEDURAL MANAGEMENT OF MEDICAL PATIENTS RECEIVING REGULAR ORAL ANTICOAGULANTS

THE FOLLOWING TABLE APPLIES TO PATIENTS ON WARFARIN, ACENOUMAROL AND PHENINDIONE:

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

THE FOLLOWING TABLE APPLIES TO PATIENTS ON DOACs

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***
	48 hours	48 hours

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

*__Note dabigatran treatment is contraindicated in these patients__

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

__*** Examples include device implant procedures (Pacemaker/ ICD/ Box Changes)__

APPENDIX 5

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 6

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)

HAS-BLED Major Bleeding Risk Score	Clinical Characteristic	Points	HAS-BLED score total points
H	Hypertension	1	0
A	Abnormal renal & liver function	1 or 2	1
S	Stroke	1	2
B	Bleeding diatheses	1	3
L	Labile INR	1	4
E	Elderly	1	5 to 9
D	Drugs/ Alcohol	1 or 2	

Pisters R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010; 138: 1093–1100.

APPENDIX 7(a)

COUMARINS (E.G. WARFARIN)
MANAGEMENT OF ANTICOAGULATED PATIENTS 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 prothrombin complex concentrate (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 12 hours before the operation (e.g. 18.00 the day before)
- Start bridging anticoagulation 12 – 24 h after the operation when considered safe with respect to surgical bleeding.

Step 4 (Post-operative management)

- Check INR and FBC next morning
- Restart warfarin as soon as the patient is eating and drinking normally
- Continue enoxaparin 1.0mg/kg twice daily as above or unfractionated heparin on the 2nd or 3rd postoperative day when the risk of bleeding is considered lower
- 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 (2.0mg) 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 7(b)
DABIGATRAN

Toolkit for the Management of Massive Haemorrhage

Algorithm for management of bleeding (and urgent reversal in case of need for emergency surgery) in patients on dabigatran

Dabigatran is a direct thrombin inhibitor with a half life of 14-17hours.
Dabigatran is renally excreted and the half life is prolonged in renal impairment.
There is a licensed reversal agent for Dabigatran which should be administered in the case of life threatening bleeding..

Dabigatran-related bleeding
Or requirement for urgent reversal in case of need for emergency surgery

↓

STOP dabigatran

↓

- **Assess clinical bleeding [1,2] and resuscitate patient as appropriate. May need to act before lab results are available in emergency.**
- **Take samples for: FBC, G&S, U&E and Clotting screen for PT, APTT (APTT is qualitative only), TT, and Fibrinogen.**
- **If TT is normal, this effectively excludes dabigatran activity as TT is very sensitive to dabigatran.**
- **Consider dabigatran plasma level **** (** Dabigatran plasma level may not be available in all Hospitals, follow local policy)
- **Indicate time of last dabigatran dose when requesting test and considering management options.**

↓

Mild bleeding → **Delay next dose or discontinue treatment as appropriate**

Moderate-Severe bleeding → **Discuss with haematologist on call**

Life-threatening or site critical bleeding → **Discuss with haematologist on call**

Activate massive haemorrhage pathway as appropriate
CONSIDER GIVING IDARUCIZUMAB 5g

- **Symptomatic treatment**
- **Tranexamic acid**
- **Mechanical compression**
- **Surgical intervention**
- **Fluid replacement, good diuresis haemodynamic support**
- **Activated charcoal (if dabigatran ingestion < 2 hours before or overdose)**
- **Consider need for haemodialysis**
- **Consider Blood product support transfusion if :**
  - **Hb < 8g/dL (80 g/L)**
  - **Platelet count <75 x 10^9/L**
  - **Fibrinogen <1.5g/L**

ADMINISTER IDARUCIZUMAB 5g

Prothrombin complex concentrate (PCC) (50 u/Kg) for less severe bleeding / high thrombotic risk

(consider recombinant VIIa depending on context)

↓

Reassess clinically
Repeat FBC, U&E, Clotting (esp APTT and dabigatran level if available)

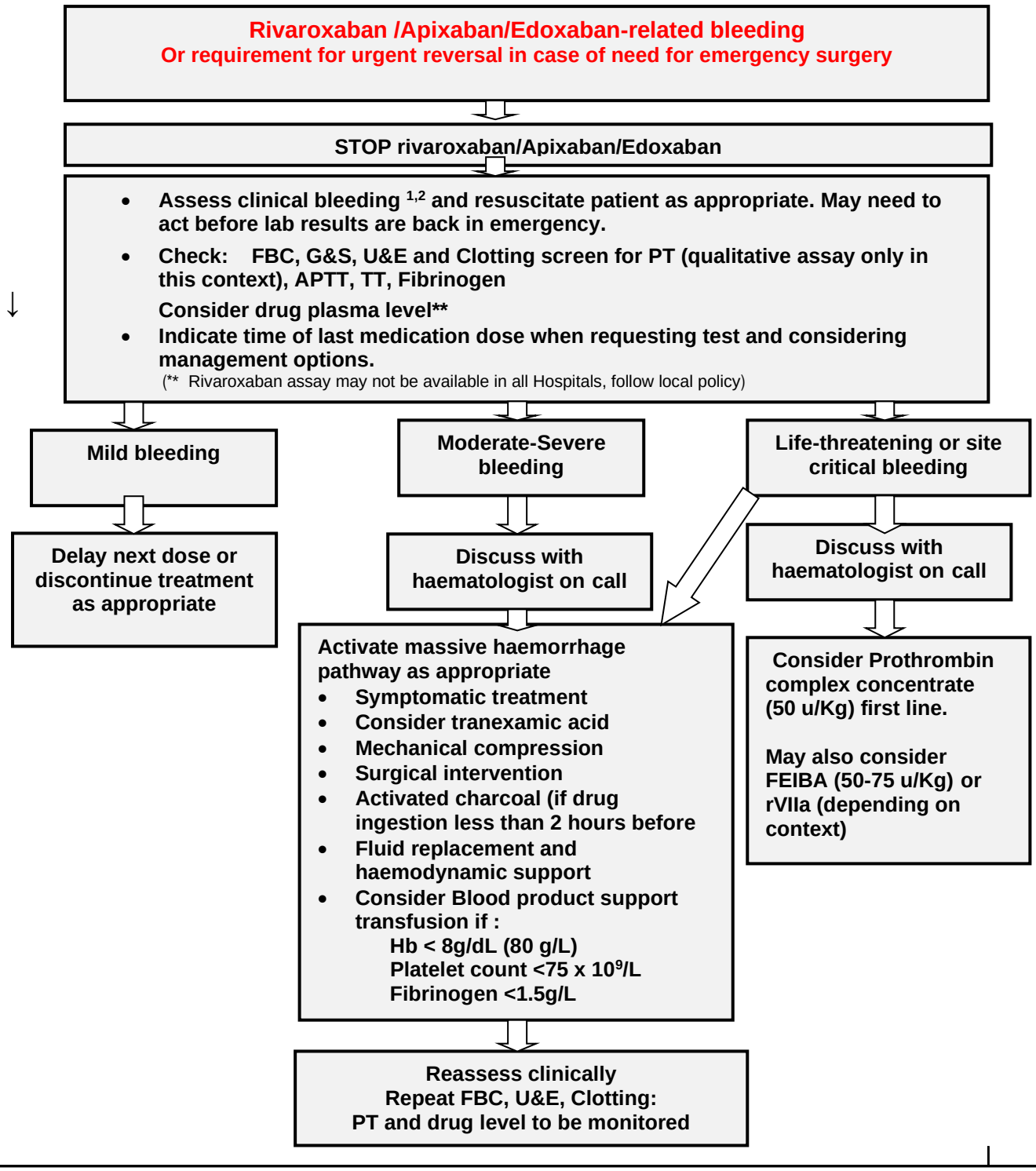
[1]**Moderate to Severe bleeding: -** reduction in Hb ≥ 2gd/L, transfusion of ≥ 2 units of red cells or symptomatic bleeding in critical area (i.e. intraocular, intracranial, intraspinal, intramuscular with compartment syndrome, retroperitoneal, intraarticular or pericardial bleeding).
[2]**Life-threatening bleeding:** – symptomatic intracranial bleed, reduction in Hb ≥ 5gd/L, transfusion of ≥ 4 units of red cells, hypotension requiring inotropic agents or bleeding requiring surgical intervention.

APPENDIX 7(C)
RIVAROXABAN / APIXABAN / EDOXABAN

Toolkit for the Management of Massive Haemorrhage

Algorithm for management of bleeding (and urgent reversal in case of need for emergency surgery) in patients on rivaroxaban / apixaban/edoxaban

Rivaroxaban,Edoxaban and Apixaban are factor Xa inhibitors. Rivaroxaban, Edoxaban and Apixaban have half lives of 7-11hours, 10-14hours and 12hours respectively
There is no licensed reversal agent for these drugs.



[1]**Moderate to Severe bleeding: -** reduction in Hb ≥ 2gd/L, transfusion of ≥ 2 units of red cells or symptomatic bleeding in critical area (i.e. intraocular, intracranial, intraspinal, intramuscular with compartment syndrome, retroperitoneal, intraarticular or pericardial bleeding).
[2]**Life-threatening bleeding:** – symptomatic intracranial bleed, reduction in Hb ≥ 5gd/L, transfusion of ≥ 4 units of red cells, hypotension requiring inotropic agents or bleeding requiring surgical intervention.

APPENDIX 8

Enoxaparin 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**		

Enoxaparin 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 severe renal impairment (Creatinine Clearance less than 30ml/minute) 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 9

Reconstitution of Octaplex
Maintain aseptic technique throughout. The product reconstitutes quickly at room temperature to a clear or slightly opalescent solution. Use immediately after reconstitution.

Allow the solvent (water for injection) and the concentrate to warm to room temperature. Remove the caps from both vials and wipe with an alcohol swab.	
Remove the protective cover from the short end of the double-ended needle, making sure not to touch the exposed tip of the needle. Perforate the centre of the solvent vial with the needle held vertically. In order to withdraw the solvent completely, the needle must be introduced in such a way that it just penetrates the stopper and is visible in the vial.	
Remove the protective cover from the other long end of the double-ended needle, making sure not to touch the exposed end of the needle. Hold the solvent (water for injection) vial upside down above the upright concentrate vial and quickly perforate the centre of the rubber stopper. The vacuum inside the concentrate vial will draw in the water.	
Remove the double-ended needle with the empty solvent vial from the concentrate vial (place sharps in sharps container) and slowly rotate the vial until the concentrate is completely dissolved. Inspect the vial: Octaplex® dissolves quickly at room temperature to a colourless or slightly blue solution. Do not use if cloudy, has deposits or fails to dissolve completely.	
After reconstitution, remove the protective cover from the filter needle (filter needle is single use only) and perforate the rubber stopper of the concentrate vial. Remove the cap of the filter needle and attach a 20ml syringe. Turn the vial with the attached syringe upside down and draw the solution into the syringe. Label the syringe (as per hospital Standard Operating Procedures regarding Preparation and Administration of an Injectable Medicine).	

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 I.V. 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 10

Management during invasive or surgical procedures

Table (below) summarises discontinuation advice before invasive or surgical procedures.

Calculated creatinine clearance (ml/min)	Timing of last dose before surgery	
	Standard risk of bleeding*	High risk of bleeding**
Dabigatran		
>50m	24 hours	2 days
30-50m	2 days	4 days
<30m	Contraindicated	
Rivaroxaban/Apixaban/Edoxaban		
>30	24 hours	2 days
15-30	2 days	4 days
<15	Contraindicated	

*Examples are cardiac catheterisation, , colonoscopy without removal of large polyps, uncomplicated laparoscopic procedures such as cholecystectomy.

**Examples are major cardiac surgery, insertion of pacemakers or defibrillators (due to the risk for pocket haematoma), neurosurgery, large hernia surgery, major cancer/urologic/vascular surgery.

General DOAC considerations

Conversion from Vitamin K antagonist to DOAC or vice-versa or conversion from parenteral anticoagulant to DOAC or vice-versa- refer to relevant Data Sheets

Concomitant use of antiplatelet agents-Studies with dabigatran, rivaroxaban 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.

MONITORING
Baseline: Renal function, LFTs, FBC
On-going: Renal function at least once per year, more frequently if renal function is expected to decline.
Changes in renal function may require dose adjustments or cessation of therapy

DOACs are intensively monitored drugs (black triangle drug), as such any possible adverse effects (including any considered not to be serious) relating to treatment should be reported via the yellow card scheme (www.yellowcard.gov.uk).

Contraindications, Cautions and Adverse Effects**-SEE DATA SHEETS FOR FURTHER DETAILS**

INFORMATION TO PATIENT

Patients should be advised of benefits and risks of treatment, including signs of bleeding and of need to inform health care staff that they are taking a DOAC before any surgery is scheduled, and before taking any new medicine.

Other considerations
Dabigatran capsules are hygroscopic and should thus not be removed from their original packaging. Individual capsules should not be placed into blister packs because they will lose potency.

8. Endorsed By:-

Name of Lead Clinician/ Manager or Committee Chair	Position of Endorser or Name of Endorsing Committee	Date

10. Record of Changes

Section Number	Version Number	Date of Change	Description of Amendment	Description of Deletion	Description of Addition	Reason
3.3.4		15/07/2020	LMWH of choice for prophylaxis changed from enoxaparin to dalteparin			
3.3.6		20/07/2020	Dalteparin dosing table according to weight and renal function			

Anticoagulation Before, During and After Electrophysiological Procedures

Guideline

Authors Name & Title: Dr Dhiraj Gupta		
Scope: All Clinical Areas	**Classification: Clinical**	
Replaces: Anticoagulation Before, During and After Electrophysiological Procedures v6.0		
To be read in conjunction with the following documents: Anticoagulation Policy (however this document represents the specific guidance on this patient group)		
Document for public display? Yes		
Unique Identifier: TD07(10)	**Review Date: 27/10/2021**	
Issue Status: Approved	**Version No: 7.0**	**Issue Date: 17th January 2018**
Authorised By: Drug & Therapeutics Committee	**Authorisation Date: 17th January 2018**	
After this document is withdrawn from use it must be kept in archive for *the lifetime of the Trust, plus 6 years*		
Archive: Document Control	**Date added to Archive:**	
Officer responsible for archive: Document Control Co-ordinator		

Has the document undergone Equality Analysis?	**No**
Has Endorsement been completed?	**No**

Table of Contents

Guideline Statement

These guidelines on the pre- peri- and post-procedural anticoagulant management of patients undergoing EP Lab procedures should be adhered to unless a specific decision is made by senior staff to deviate from standard practice on clinical grounds. The guidelines represent specific advice on a selected subgroup of patients under the Trust Anticoagulation Policy and represents the definitive advice on this patient subgroup.

1. Objectives

The following outlines the standard approach to anticoagulation before, during and after electrophysiological procedures. These are designed to balance the competing goals of avoiding thromboembolic events whilst minimising haemorrhagic complications.

The approach is highly standardised, and limited numbers of alternative strategies are available at each stage. However it is stressed that in clinical medicine there will never be absolute uniformity between cases – an individual patient may have features such that they are at high risk of thromboembolism and thus an active decision may be made to utilise a more aggressive anticoagulation regime than is usual for that type of case. Conversely the opposite may be appropriate if the patient is at high risk of haemorrhagic complications.

The standard approach should be utilised unless a Consultant or Registrar makes a decision on clinical grounds to deviate. This decision will be indicated: -
Pre procedure - in the letter at which the decision to list was made or on the listing pages of the ICP (currently p4-5).
During procedure - verbally.
Post procedure - in the written notes/ EPR.

2. Roles and Responsibilities

These guidelines are updated guidance prepared by Dr Dhiraj Gupta on behalf of and in consultation with Doctors: Hall, Hobbs, Snowdon, Todd and Waktare.

The EP department is responsible for the overall implementation of this policy.

At all times the EP consultant or EP SPR is responsible for determining individualisation of antiplatelet and/or anticoagulation therapy for a particular patient.

Heart Rhythm Nurse Specialists (HRNS), Clinical Nurse Practitioners (CNPs), Ward Nurses, Cath Lab Nurses and junior (SHO) and middle grade (SpR / Fellow) doctors involved in the care of EP patients should be fully conversant with these guidelines.

HRNS are required to facilitate post-procedure anticoagulation care (where indicated).

The Medical Staffing and Education Manager to facilitate dissemination to SHOs.

3. Guideline

3.1 Pre-procedural care

Patients not on anticoagulation

No change in treatment.

Patients on antiplatelet therapy

No change in treatment.

Patients on oral anticoagulant therapy with Warfarin

Principles

Many EPS procedures entail only femoral venous puncture, and thus may be performed safely with INR values up to 4 on the day of the procedure. Although subclavian venous access is used in some cases, femoral access is nearly always an acceptable alternative and thus may be used if the patient is anticoagulated. Conversely a therapeutic INR level (greater than 2) is clinically indicated for some patients, for example those who are in persistent atrial flutter or fibrillation. However in some situations, principally where femoral arterial access or transeptal puncture is planned, INR levels should ideally be less than 3.5 (individualised by clinical situation).

Regimes

1. ***Continue Warfarin as usual***

Applicable to: most patients who come in for EP procedures and who are already on warfarin for their arrhythmia or another reason. This will include majority of patients coming in for left atrial ablation for persistent AF and a proportion of patients coming in for ablation for paroxysmal AF. .
Protocol: Patients should be instructed to continue normal warfarin until the their procedure, and ask their anticoagulant monitoring clinic or hospital to ensure their INR is 2.0 to 3.0 in the pre-EPS period. They should have a final INR check performed 4 to 7 days pre-EPS to ensure this and the dose adjusted to achieve an INR of 2.0 to 2.5 on the day. If INR less than 2.0 at any stage in 4/52 pre-EPS for patients having ablation then contact Consultant for advice.

2. ***Use bridging LMWH***

Applicable to: This applies to clearly pre-identified patients who require arterial access or are expected to have difficult transeptal access. Examples may include patients coming in for ischemic VT ablation who also have persistent atrial fibrillation/ documented LA clot.
Protocol: Pre-procedural care is identical to the previous group, but warfarin is stopped 5 days before the day of the procedure. Patients receive 1.5mg per kg subcutaneous enoxaparin daily for three days prior to their procedure, either by self-administration or nursing/medical staff unless otherwise instructed. They should not have LMWH on the day of their procedure.

3. ***Discontinue Warfarin***

Applicable to: Patients who require arterial access or transeptal puncture and have a low thromboembolic risk. Most patients in this category are accounted for by those having ablation for ischemic VT, but multiple other assorted examples exist.
Protocol: Continue anticoagulation as usual but stop pre-procedure. Typically this will be 5 days pre-procedure, but this may be varied according to instruction in ICP or clinic letter.

Patients on oral anticoagulant therapy using Newer Oral Anticoagulants (NOACs)

There is increasing published experience with use of Dabigatran Rivaroxaban, Edoxaban and Apixaban around AF ablation procedures. The published experience suggests that the use of these drugs is safe in this setting, including if the last dose is taken on the morning of the procedure. As such, these drugs should not be discontinued prior to the EP procedure.

3.2 Intra-procedural care

Principles

In order to standardise care, the Consultants undertaking EP procedures at LHCH have agreed to operate to one of three heparin regimes for patients. There is also broad consensus on which heparin regime is applicable to different case types (see below). However the decision on the appropriate risk/benefit calculation will remain individualised and it should not be automatically assumed that a case will be managed in a particular way. Additional factors such as prior haemorrhagic complications or a raised INR will appropriately lead to tailored approaches for a minority of cases. However failure to follow the "standard" approach is something that should be appropriately questioned to ensure that it is a deliberate decision rather than an oversight

Regimes

1. No anticoagulation

No heparin is administered but this decision is reconfirmed hourly by operator.
Applies to: Brief procedures (expected to take less than 1 hour, e.g. diagnostic EPS) **or** where a high risk of haemorrhagic complications exists **or** where the patient already has a therapeutic INR (hourly review not needed in the latter two cases).

2. Standard anticoagulation

Heparin at a dose of 70 units per kg is administered as a bolus via a central cannula once full vascular access has been obtained (i.e. delayed until after transeptal puncture has been performed or it is confirmed on diagnostic EP study that this is not needed). Typically no further boluses or monitoring of ACT is required but this decision is reconfirmed hourly by operator. Target ACT greater than 200 seconds (if tested).
Applies to: All EP procedures not covered specifically by regimes 1 or 3.

3. Intense anticoagulation

Heparin at a dose of 100 units per kg is administered as a bolus via a central cannula once full vascular access has been obtained (i.e. delayed until after transeptal puncture has been

performed if applicable). ACT check performed after 10 minutes (target ACT over 250). Operator will specify further boluses and the time delay until next ACT check (typically either 30 minutes or 1 hour), and these may be administered either via a central or a large bore cannula. Patients with therapeutic INR levels may require a lower dose of Heparin (50-70 units per kg) to achieve target ACT level and this is to be confirmed by the operator.

This intense anticoagulation may be reversed with a bolus of intravenous protamine (maximum 10 mg for every 1000 IU, adjusted downward for time since heparin) just prior to sheath removal to facilitate local hemostasis. This decision would be taken by the operator after the left atrium has been exited.
Applies to: Curative AF ablation procedures ("PVI", etc.) ablation for ischemic VT, procedures involving potentially thrombogenic catheters (e.g. ESI Array) and other cases identified as being high risk of thromboembolism.

3.3 Post-procedural care

Principles

Most patients will not require heparin therapy post-procedure. This now includes patients coming in for AF ablation procedures who on warfarin before ablation. AF ablation patients have extensive ablation of the atrial wall and literature data suggest peri-procedure thromboembolic rates of 1-2%. Our routine use of aggressive peri-procedure anticoagulation is felt to be one important factor contributing to an observed rate lower than this. However, it is equally true that most groin complications are felt to be due to a combination of administration of Low Molecular Weight Heparin and concurrent loading with Warfarin. Our revised approach of maintaining patients on therapeutic levels of Warfarin aims to avoid these two aggravating influences.

While most patients will either be managed with no anticoagulation or our standard regime, the precise regime or even decision to anticoagulate may not be the "standard" one. Thus if ward staff detect deviation from usual care then the rationale for this should be sought in the notes and if necessary, re-confirmed with the operator. However it is inappropriate to alter the prescribed treatment to restore "standard" care without confirming the intention of the operator.

Use of Antiplatelet therapy alone is employed in some cases as outlined below.

Regimes

1. No change from pre-procedure anticoagulation

This should now be the default care for many EP cases. Most patients not on Warfarin beforehand do not need to be started on this agent, although they could be given one of the other NOACs post-procedure as per physician instructions (see below). All patients already maintained on Warfarin would receive their maintenance dose starting on the night of the procedure.

2. Oral anticoagulation with bridging LMWH

- Enoxaparin (LMWH) is administered at a dose of 1 mg per kg s/c 4-6 hours post-procedure as a single dose. Enoxaparin 1.5 mg per kg s/c is then administered on the following morning and each morning thereafter until INR greater than 2. Ward nursing staff must ensure that a clear plan exists for ongoing LMWH administration at

discharge (self-administration or by a friend/relative, by district nurse, or by ward attendance).

- Warfarin commenced / re-commenced in the evening post-procedure. Where a stable dose is known (i.e. from previous therapy), re-loading will typically use 2 doses of 2 or 3 times their previous usual dose. For all other patients, please refer to Trust Anticoagulation Policy appendix 1(c). Regimes will also be individualised according to timing of first INR check and INR on admission.
- Heart Rhythm Nurses (ext. 1270, Bleep 2326/2327) are available to facilitate post-procedural anticoagulation care if needed but **must** be notified as soon as the need for their input is identified (and *not* just before discharge).

Applies to: Used in the minority of patients who have undergone curative AF ablation ("PVI", etc.) and selected other cases as identified by the operator either before or during the procedure.

3. Antiplatelet Therapy

Loading dose of aspirin 300mg given post-procedure, and continued at a dose of 75mg for one month. Clopidogrel 75mg daily monotherapy used if aspirin contra-indicated. Clopidogrel may also be used in combination with aspirin in some cases (loading dose 300mg then maintenance of 75mg daily). NB this is an unlicensed use of clopidogrel.
Applies to: Used for selected low risk (or high risk of haemorrhagic complications) patients who have undergone curative AF ablation.

4. Dabigatran Therapy

Dabigatran 150 mg twice a day commenced on the evening of the procedure, followed by 150 mg twice a day. Consideration should be given to use a lower dose of 110 mg if patient has one or more of the following risk factors: Age more than 80 years, Creatinine clearance 30-50 ml/min, Body weight less than 50 kg or concurrent treatment with Verapamil. Treatment should be continued for a minimum of 4 weeks, with decisions on continued anticoagulation treatment (with Dabigatran or Warfarin) being guided by risk stratification and as per local prescribing guidelines.

Applies to: Used for most low risk patients who have undergone curative AF ablation and who are not on oral anticoagulation pre-procedure. Also to those patients who are on Dabigatran pre-procedure.

5. Rivaroxaban therapy

Rivaroxaban 20 mg once a day commenced on the evening of the procedure, followed by 20 mg once a day. A lower dose of 15 mg should be used in patients with estimated Creatinine clearance 30-49 ml/min, Treatment should be continued for a minimum of 4 weeks, with decisions on continued anticoagulation treatment (with NOACs or Warfarin) being guided by risk stratification and as per local prescribing guidelines.

Applies to: Used for most low risk patients who have undergone curative AF ablation and who are not on oral anticoagulation pre-procedure. Also to those patients who are on Rivaroxaban pre-procedure.

6. Apixaban therapy

Apixaban 5 mg twice a day commenced on the evening of the procedure, followed by 5 mg twice a day. 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. Treatment should be continued for a minimum of 4 weeks, with decisions on continued anticoagulation treatment (with NOACs or Warfarin) being guided by risk stratification and as per local prescribing guidelines.

Applies to: Used for most low risk patients who have undergone curative AF ablation and who are not on oral anticoagulation pre-procedure. Also to those patients who are on Rivaroxaban pre-procedure.

7. Edoxaban therapy

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 less than or equal to 60 kg, concomitant use of the following P-glycoprotein (P-gp) inhibitors: ciclosporin, dronedarone, erythromycin, or ketoconazole. Treatment should be continued for a minimum of 4 weeks, with decisions on continued anticoagulation treatment (with NOACs or Warfarin) being guided by risk stratification and as per local prescribing guidelines.

3.4 Special Note on Pre-Procedural INR Checks

Delays awaiting INR results can delay lists, and strategies should be employed by medical and nursing staff to mitigate against this. Measures include:

- Bloods for INR should be sent as early as practical after arrival on all patients who require an INR check. This applies to **all** patients, not just the first case on the list (the list order may need to be changed for other reasons).
- As stated above, most procedures can be safely performed as long as INR is less than 4. Therefore, in most situations patients may be sent to the cath lab while the INR is still outstanding as long as the following criteria are met:
    - INR levels usually stable (values have been 2 to 3.5 recently) **and**
    - Last INR was done less than 7 days ago and was less than 3.5 **and**
    - No other drugs commenced in last 7 days
- The important issue is to liaise with medical staff regarding how to get the patient to the lab on time, and not to automatically assume that the patient must not leave the ward because the INR is not back.

4. Expert Advice

This is always available from the SpR/clinical fellow or the EP consultant involved in the case. Where these individuals are not contactable, enquiries to be directed to the SpR on call for the Heart Rhythm Service (in-hours) or SpR on-call (out of hours), or the Heart Rhythm Consultant on call.

5. Guideline Implementation Plan

The author will write to the relevant nursing team leader / ward managers, and all SpR's to inform them of the issuing of the guideline. Author will disseminate to medical staff. The Medical Staffing and Education Manager to facilitate dissemination to SHOs, and highlight at relevant meetings (e.g. ECG teaching).

HRNS Team Leader will disseminate to all relevant Ward Managers/Team Leaders, except Cath lab, where this will be performed by the Clinical Practice Facilitator. Matrons / Heads of Nursing for Medicine to ascertain that relevant nursing team leaders / ward managers have cascaded to all their staff.

6. Monitoring and Review

Issues arising from this guideline will be detected through audit and incident reporting mechanisms.

Compliance to these guidelines will be audited by a member of the EP team under the direct supervision of one of the EP Consultants, on a annual basis and the results presented to the Drug & Therapeutics Committee.

These guidelines are highly complex and highly individualised. As such there are many nuances. It is not possible to stipulate exactly which areas will be audited. This will be determined on an annual basis by the EP Consultants.

7. Endorsed By:-

Name of Lead Clinician/ Manager or Committee Chair	Position of Endorser or Name of Endorsing Committee	Date

8. Record of Changes

Section Number	Version Number	Date of Change	Description of Amendment	Description of Deletion	Description of Addition	Reason

Anticoagulation of critical care patients with confirmed COVID-19

Policy

For completion by Author			
Author(s) Name and Title:	Dr Clare Quarterman (Consultant Anaesthetist and Intensivist), Marc Vincent (Deputy Chief Pharmacist - Clinical Services)		
Scope:	Critical Care	Classification:	Clinical
Version Number:	2.1	Review Date:	15/01/2022
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Executive Lead	Dr Raph Perry		

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Officer responsible for Archive:		IG and Document Control Facilitator			

Contents

Document Statement

Patients with COVID-19 infection demonstrate a significant acute phase response with elevation of fibrinogen, VWF, factor VIII and other acute phase reactants. Reports from China and Italy suggest that a majority of deaths show signs of coagulation activation mimicking disseminated intravascular coagulopathy (DIC) and thrombotic microangiopathy, and potentially exhibit a higher incidence of venous thromboembolism. Data from a retrospective, observational review of patients with COVID-19 treated in China have shown that D-dimer, prothrombin time (PT) and age are positively associated with mortality.

There is some evidence that patients with sepsis-induced coagulopathy, a precursor of sepsis-associated DIC, benefit from anticoagulant therapy. There has been suggestion also that patients with a more severe derangement of coagulation, in the context of COVID-19, benefitted from heparin treatment with a significantly lower mortality where low molecular weight heparin (LMWH) was used. 28 day mortality in heparin users was lower than non-heparin users in patients with an SIC (sepsis induced coagulopathy) score >/= 4 or D-dimer > 3 mcg/ml (3000ng/ml).

One Italian study utilised standard and viscoelastic tests of anticoagulation to assess the baseline coagulation profile of patients with COVID-19 pneumonia. They identified a highly procoagulant profile, increased clot strength with significantly increased influence of both platelets and fibrinogen, elevated D-dimer and hyperfibrinogenaemia. Through use of thromboprophylaxis – both LMWH and anti-platelet agents – there was evidence of some normalisation of the profile with a fall in fibrinogen levels, D-dimer and clot strength.

There is clear evidence that the coagulation system is part of the immune response to infection, where the laying down of fibrin contributes to the compartmentalisation of pathogens and reduces their dissemination, and therefore the potential benefit of the use of LMWH, particularly in patients without evidence of a coagulation burden must be weighed against the risk of suppression of the patient's own immune response.

Initially there were no randomised controlled trials of anticoagulation of this patient group, and there was uncertainty whether heparin and antiplatelet treatment was associated with a better prognosis in severe COVID-19 disease. Following the review of several available guidelines and information regarding practice from other institutions in the UK (namely Liverpool University Hospitals Trusts and Imperial College Hospital, London), Europe and America, as a department developed guidance for the management of patients admitted to critical care at LHCH. The REMAP-CAP study has since shown no benefit from blanket use of therapeutic anticoagulation (for a limited period of 14 days) in patients with COVID-19 pneumonia. This study also included the critical care population and also demonstrated an increased incidence of bleeding complications in this patient group. NICE guidance on anticoagulation of patients with COVID-19 pneumonia does however continue to state that acutely ill medical patients requiring advanced respiratory support should receive double the standard prophylactic dose of LMWH. The guidance also states that bleeding and VTE risk should be assessed daily, and the dose reviewed accordingly.

NB: NICE define advanced respiratory support as invasive mechanical ventilation, bilevel positive airway pressure (BiPAP) or continuous positive airway pressure (CPAP).

1. Roles and Responsibilities

All clinicians and critical care nurse practitioners working within the critical care setting have a responsibility to review the requirement for anticoagulation as part of the FASTHUG assessment on a daily basis. A review of recent blood results and the requirement for escalation or de-escalation of dose must be considered, in line with the guidance below. It is anticipated that the majority of patients will be ready for dose de-escalation prior to discharge from critical care. Where this is not the case, a clear handover to the ward team must be made with regard to the ongoing requirement for anticoagulation and when the next review of dose is required.

Members of the pharmacy team have a responsibility to ensure that patients are on correct doses and also discharged with an adequate supply of LMWH or appropriate alternative depending upon availability.

Nursing staff must follow the Trust Medicines Administration Policy when administering medicines described in this policy.

2. Controlled Document Standards

All medical staff involved in the management of patients with COVID-19 infection should be aware of this policy and apply it where appropriate.

3. Procedure

For critical care/medical patients with isolated COVID-19 pneumonia that have not undergone recent surgery, refer to section 3.1. For patients that have recently undergone surgery and have subsequently tested positive for COVID-19 and for asymptomatic positive medical patients refer to section 3.9.

3.1 Use of LMWH for prophylactic anticoagulation

Patients admitted to critical care with COVID-19 pneumonia requiring advanced respiratory support should be commenced on enoxaparin at double the standard prophylactic dose, taking into account their body weight and renal function. The starting dose of enoxaparin should be prescribed as per the guidance in Table 1. Dose titration following this should be as per section 3.2.

Pharmacological prophylaxis should be continued as long as the platelet count remains > $30x10^9$/L and there is no evidence of bleeding. Whilst all patients may benefit from the use of intermittent pneumatic compression stockings, where there is a requirement for suspension of anticoagulation due to low platelet count or for a planned procedure, their use is strongly encouraged unless there is a specific contraindication.

Dosing in the critically ill patient is likely to be based upon an estimated body weight. If information on actual body weight can be obtained from the patient's GP or a family member this should be used until an accurate body weight can be safely measured.

Table 1 – Enoxaparin dosing on admission to LHCH

Weight	Creatinine clearance	
	≥ 30 ml/min	< 30 ml/min
≤49kg	40mg once daily	20mg once daily
>50kg	80 mg once daily	40mg once daily

Previous policies involved dose titration based on d-dimer level. This is no longer advocated. D-dimer should still be re-assessed every 3 days or when there is a clinical change as this may be an indicator of underlying venous thromboembolism or pulmonary embolism, and the clinical team may wish to investigate for this. Where there is a suspicion of either, the team should then arrange suitable investigations to confirm the diagnosis or, where the patient is deemed too unstable for transfer, consider whether therapeutic anticoagulation is required.

3.2 Monitoring and dose adjustment for prophylactic anticoagulation

Anti-Xa levels should be measured 4 hours post the third dose, and then every 48-72 hours. The target dose range to ensure that treatment is effective at a prophylactic level is 0.2-0.4IU/mL.

If peak level <0.2IU/mL, increase dose by 10mg (or 10% of the total dose where the patient's estimated weight is either <50kg or >120kg), rounded to the nearest measurable dose (see appendices). Re-check anti-Xa level 4 hours after 3rd increased dose.

If peak level >0.4IU/mL, omit one dose and reduce subsequent dose by 10mg (or 10% of the total dose where the patient's estimated weight is either <50kg or >120kg), rounded to the nearest measurable dose (see appendices). Re-check anti-Xa level 4 hours after 3rd reduced dose.

3.3 Use of LMWH for therapeutic anticoagulation

In addition to the above, teams should maintain a high clinical suspicion for venous thromboembolism (VTE) and pulmonary embolism (PE). Where there is a suspicion of DVT/PE, the therapeutic level of anti-Xa required is higher. Where DVT/PE is confirmed the dose of LMWH should be increased to **therapeutic dose of 1.5mg/kg OD (or 1mg/kg OD for patients with creatinine clearance <30ml/min)**.

Our early experience suggests that patients with more severe disease despite being on large doses of enoxaparin, may still only reach plasma anti-Xa levels consistent with prophylactic dosing. Therefore, anti-Xa levels should be measured after the third dose and if significantly below the therapeutic range of 0.4-0.8 IU/mL, consideration should be given to use of an unfractionated heparin (UFH) infusion with APTTr monitoring as per current policy, until the patient's clinical status has improved.

3.4 Monitoring and dose adjustment for therapeutic anticoagulation

Where LMWH is used for therapeutic anticoagulation the target anti-Xa level is 0.4-0.8IU/mL where twice daily dosing is used.

Where there is normal renal function and a peak level <0.4IU/mL increase dose by 10mg (or 10% of the total dose where the patient's estimated weight is either <50kg or >120kg), rounded to the nearest measurable dose. Re-check anti-Xa level 4 hours after 3rd increased dose.

Where there is normal renal function and a peak level >0.8IU/mL omit one dose and reduce subsequent dose by 10mg (or 10% of the total dose where the patient's estimated weight is either <50kg or >120kg), rounded to the nearest measurable dose. Re-check anti-Xa level 4 hours after 3rd reduced dose.

3.5 Heparin resistance

Where there is failure to achieve Anti-Xa levels or APTTr despite adequate dose increases, this must be discussed with a consultant haematologist. Assessment of anti-thrombin level or use of an alternative agent may be required.

3.6 VTE and bleeding risk assessment

All patients should have their VTE and bleeding risk assessed within 24 and 48 hours of admission to hospital. Where patients are receiving an intermediate dose of LMWH solely for COVID-19 pneumonia, their bleeding and VTE risk should be assessed daily, to ensure that they are on the appropriate dose. Clinicians within the critical care will complete the COVID-19 VTE and bleeding risk assessment document within EPR on a once daily basis, recording assessment of both risks but also the target anti-Xa level that the patient requires.

3.7 Treatment post-discharge from critical care

3.7.1 Prophylaxis

When patients are discharged from critical care and ultimately from hospital, the risk of VTE persists until their usual level of activity returns. Patients should therefore have a repeat VTE risk assessment completed and, where appropriate, be discharged with VTE prophylaxis for the duration of this period, anticipated to be a minimum of 7 days (supply 10 days on discharge). The patient should be advised that if their level of activity has returned to normal within this time they can stop treatment. If their level of activity is still significantly below normal at 10 days post-discharge, they should contact their GP for a further assessment.

There are anticipated national pressures on supplies of LMWH. The use of DOAC agents for VTE prophylaxis following orthopaedic surgery (NICE Technology Guidance TA245) and for prevention of recurrent venous thromboembolism following pulmonary embolism (NICE guideline NG158) is already established practice. Where ongoing VTE prophylaxis is required clinicians should consider use of a DOAC post-discharge. Prescribers should note any clinically significant drug interactions (e.g. antiviral, antifungal, antibiotics etc) and whether a DOAC is still appropriate (discuss with pharmacist if required). Following a review of NG158 we recommend the use of apixaban 2.5mg BD, unless there is a contraindication to its use. Calculation of the HAS-BLED score should be performed, and if the score exceeds 4 consider stopping anticoagulation.

The discharge letter to the GP should clearly state that the patient is to receive a DOAC for the purpose of VTE prophylaxis only, and that the treatment should stop as soon as the normal level of activity is resumed.

Where there is a contraindication, the patient should be discharged with LMWH at standard prophylactic dose, appropriate to their weight and renal function. Should the patient refuse or be unsuitable for ongoing treatment with DOAC or LMWH, discharge on aspirin 75mg OD.

3.7.2 Treatment

Where VTE or PE has been confirmed, the patient should receive sufficient treatment in terms of dose and duration in the post-critical care period. The patient should be referred to their local haematology department to confirm the plan for ongoing anticoagulation and ensure appropriate follow-up.

Treatment is expected to be for a minimum of 3 months, with transition from LMWH/UFH to a direct oral anticoagulant (DOAC) post-discharge where there is no contraindication. Intravascular catheter associated thrombosis is also common and where identified patients should also have a review of the prescribed dose of LMWH and receive a more prolonged course of appropriate anticoagulation, likely a DOAC to complete 6 weeks of treatment.

3.8 Patients taking a DOAC or warfarin pre-admission

Critical illness, medications and changes in renal and hepatic function may impact plasma levels and lead to difficulty ensuring a safe level of anticoagulation. Antiviral treatments that may in the future be employed in the management of COVID-19 infection, either as part of a clinical trial or as routine treatment, may interact with oral anticoagulants. Critical illness may lead to difficulty in maintaining a stable INR where warfarin is used. Where patients are admitted to critical care and are already taking either warfarin or a DOAC, consideration should be given to switching to therapeutic LMWH (enoxaparin 1mg/kg BD) or an UFH infusion, depending upon the reason for anticoagulation. Where use of therapeutic LMWH is utilised, anti-Xa levels should continue to be checked as per the policy to ensure an adequate range is achieved. Where this proves challenging, advice should be sought from a Consultant Haematologist.

Where patients are admitted on warfarin, but then transition to LMWH or UFH during their illness, consideration should be given regarding their suitability for treatment with a DOAC long-term post discharge, as per recent NHS England guidance. This avoids the requirement for regular INR monitoring, which may relieve pressure on overwhelmed systems. The guidance should be reviewed on an individual patient basis and can be accessed at: https://www.nice.org.uk/Media/Default/About/COVID-19/Specialty-guides/specialty-guide-anticoagulant-services-and-coronavirus.pdf

Patients taking a DOAC pre-admission should be continued post discharge (if appropriate). Care should be taken to ensure the correct dose is prescribed following acute illness (e.g renal function, concurrent therapy).

3.9 Anticoagulation of surgical patients testing positive for COVID-19 and asymptomatic medical patients testing positive for COVID- 19

Where patients test positive for coronavirus but are showing no symptoms, there is a potential that they will never go on to develop COVID-19 pneumonia/disease with the associated thromboembolic sequalae. Efforts are being made through the use of pre-operative screening to ensure that patients do not undergo elective/urgent surgery if they have coronavirus. If despite this a patient tests positive for coronavirus after they have undergone surgery, this section of guidance should be adhered to.

For surgical patients, routine post-operative use of anti-platelet agents and standard VTE prophylaxis with dalteparin should be as per existing trust policy; DOACs or warfarin should be used according to the requirement of the patient.

For medical patients standard VTE prophylaxis with dalteparin should be used in addition to concurrent therapy according to the requirement of the patient.

Where the patient remains well, VTE prophylaxis should continue as per routine practice. There is no requirement for assessment of effectiveness with anti-Xa level in this cohort, unless there is a respiratory deterioration requiring admission to critical care.

Should the patient begin to show symptoms of COVID-19, the anticoagulation strategy will require review. COVID-19 demonstrates a wide spectrum of severity, with many patients experiencing minor symptoms and only a minority developing more severe symptoms that would require hospital admission. The dose of LMWH should not be increased unless the patient develops a requirement for advanced respiratory support, **and** there is evidence of sub-prophylactic anti-Xa level. For all post-surgical patients requiring advanced respiratory support, adequacy of prophylaxis with dalteparin should be assessed upon transfer to critical care through assessment of anti-Xa level. If the level is within the prophylactic range, continue to treat with standard VTE dose dalteparin. Where the anti-Xa level is sub-prophylactic, transition to enoxaparin as per table 1 and titrate as in section 3.2, as long as the risk of bleeding is deemed to be acceptable and there are no further procedures planned e.g. removal of pacing wires, insertion of pacing device.

Where a DOAC or warfarin is in use, consideration should be given to the severity of symptoms and whether treatment should be stopped and therapeutic enoxaparin commenced as per section 3.7 on an individual patient basis. In more complex patients, advice should be sought from a consultant haematologist.

4. Policy Implementation Plan

This policy will be implemented initially within critical care and will continue when patients are discharged to the ward area. As such, implementation will require dissemination by:

- Medical Director
- Associate Medical Directors
- Clinical Leads
- Ward / Department Managers

5. Monitoring of Compliance

All patients within LHCH with a diagnosis of COVID-19 should receive LMWH, unless there is a specific contraindication. This should be confirmed regularly by the medical and pharmacy teams, and where this is not the case should be rectified. Practice will be audited in the future to ensure that all patients received treatment, appropriate to the departmental policy at that time.

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7. Appendices

APPENDIX 1

Enoxaparin 1.5mg/kg

USE ONLY 120mg or 150mg syringes – each graduation is 3mg

Weight (Kg)	Syringe Dose (mg)
50	75
51-52	78
53-54	81
55-56	84
57-58	87
59-60	90
61-62	93
63-64	96
65-66	99
67-68	102
69-70	105
71-72	108
73-74	111
75-76	114
77-78	117
79-80	120
81-82	123
83-84	126
85-86	129
87-88	132
89-90	135
91-92	138
93-94	141
95-96	144
97-98	147
99-100	150
101-102	153 – use 2 SYRINGES: 120mg+33mg
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 2

Enoxaparin 1mg/kg

USE ONLY 120mg or 150mg syringes – each graduation is 3mg

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

8. Endorsed By:

Name of Lead Clinician / Manager or Committee Chair	Position of Endorser or Name of Endorsing Committee	Date
Dr Scawn	Drug & Therapeutics	20/1/21

9. Record of Changes

Section No	Version No	Date of Change	Description of Amendment	Description of Deletion	Description of Addition	Reason