Royal Devon University Healthcare NHS Foundation Trust

Emergency Reversal of the DOAC Drugs

Reference Number: RDF1979-23
Date of Response: 01/11/23

Further to your Freedom of Information Act request, please find the Trust's response(s) below:

Please be aware that the Royal Devon University Healthcare NHS Foundation Trust (Royal Devon) has existed since 1st April 2022 following the integration of the Northern Devon Healthcare NHS Trust (known as Northern Services) and the Royal Devon and Exeter NHS Foundation Trust (known as Eastern Services).

Please could you advise if Royal Devon and Exeter Hospital have published guidelines for the use of Adexanet alfa (Ondexxya) or Idarucizumab (Praxbind) for the emergency reversal of the DOAC drugs apixaban, dabigatran and rivaroxaban?

We are aware that such a guideline was published by Northern Devon Healthcare NHS Trust, please find details below.

- *Guideline for the emergency reversal of apixaban, dabigatran and rivaroxaban - https://www.northdevonhealth.nhs.uk/wp-content/uploads/2021/11/DOAC-Reversal-guideline-Final.pdf*

1. *Following the merger of your organisations does this document now cover all parts of Royal Devon University Healthcare NHS Foundation Trust or is the Royal Devon and Exeter Hospital covered by its own guidance. If new guidance exists, please could a copy be supplied,*
   Answer: The Royal Devon is in the process of integrating services and departments including policy governance review. Please find attached the Royal Devon's Eastern Services current 'Anticoagulation and Reversal of Anticoagulation Policy'.

   The Royal Devon's Northern Services 'DOAC Reversal guideline' is still current, as referenced above: https://www.northdevonhealth.nhs.uk/wp-content/uploads/2021/11/DOAC-Reversal-guideline-Final.pdf

Royal Devon and Exeter NHS Foundation Trust

Anticoagulation and Reversal of Anticoagulation Therapy Policy in Adults

Post holder responsible for Procedural Document	[redacted] Medical Director
Author of Policy	[redacted] Consultant Acute Medicine and [redacted] Consultant Haematologist
Division/ Department responsible for Procedural Document	Medicine/Haematology
Contact details	[redacted]
Date of original document	May 2010
Impact Assessment performed	**Yes**/No
Ratifying body and date ratified	Clinical Effectiveness Committee: 7 March 2019
Review date	September 2023 (every 4½ years)
Expiry date	March 2024
Date document becomes live	4 July 2019

Please *specify* standard/criterion numbers and tick ✓ other boxes as appropriate

Monitoring Information		**Strategic Directions – Key Milestones**	
Patient Experience		Maintain Operational Service Delivery	✓
Assurance Framework		Integrated Community Pathways	
Monitor/Finance/Performance		Develop Acute services	
CQC Fundamental Standards - Regulation:		Infection Control	
Other *(please specify)*:			
Note: This document has been assessed for any equality, diversity or human rights implications			

Full History		Status: Final	
Version	Date	Author	Reason
1.0	May 2010	Consultant Physician & Consultant Haematologist	New policy
2.0	September 2018	Consultant Physician & Consultant Haematologist	Complete revision & incorporation of reversal of anticoagulation procedure
2.1	February 2020	Consultant Physician & Consultant Haematologist	Incorporation of Clinical Guideline on Management of patients receiving long-term oral anticoagulants for elective surgery/procedures

Associated Trust Policies/ Procedural documents:	Venous Thromboprophylaxis in Adults Policy Warfarin Therapy Care Plan Clinical Guideline for Hip Fracture **Management of patients receiving long-term oral anticoagulants for elective surgery/procedure**
Key Words	Anticoag, Warfarin, DOAC, AF, DVT, VTE, PE, PTE, Apixaban, Rivaroxaban, Edoxaban, Dabigatran, Dalteparin, Reversal, Bridging
In consultation with and date: [redacted] (Stroke): 20.02.19 [redacted] (Oncology): 22.02.19 [redacted] (Respiratory): 26.02.19 [redacted] (Cardiology): 27.02.19 [redacted] (AMD Primary care): 25.02.19 [redacted] (Renal and CD Planned Care): 18.02.19 [redacted] (Orthopaedics): 26.02.19 [redacted] (Radiology): 27.02.19 [redacted] (Renal): 25.02.19 [redacted] (Anaesthetics/ preop) – 27.02.19 [redacted] (Orthopaedics) 12/04/19 [redacted] (HFOP) 12/4/19 Quality Assurance: 17 April 2019 & 14 February 2020 Clinical Effectiveness Committee: 7 March 2019 [redacted] (CEC sub-group chairs and members): 12 June 2019 [redacted] 14 February 2020	
Contact for Review:	[redacted]

Executive Lead Signature: *(Applicable only to Trust Strategies & Policies)*	[redacted] **Medical Director**

CONTENTS

KEY POINTS OF THIS POLICY:
Atrial Fibrillation

Assessment of Stroke and Bleeding Risks
NICE Guidance CG180[1] states that all patients with atrial fibrillation are assessed for their stroke risk using the CHA_2DS_2-VASC (click here for MDCALC) scoring system if they have[2]:

- symptomatic or asymptomatic paroxysmal, persistent or permanent atrial fibrillation
- atrial flutter
- a continuing risk of arrhythmia recurrence after cardioversion back to sinus rhythm

SCORE	***0***	***1***	***≥2***
MEN	*No Anticoagulation*	*Consider Anticoagulation*	*Offer Anticoagulation*
WOMEN	*No Anticoagulation*	*No Anticoagulation*	*Offer Anticoagulation*

Bleeding Risk
The HAS-BLED (click here for MDCalc) score should be calculated for all people being considered for anticoagulation.
Review and *actively manage* the following:

- Uncontrolled Hypertension
- Poor control of INRs
- Concurrent medication for example concomitant use of aspirin or NSAIDS
- Harmful Alcohol Consumption

DO NOT withhold anticoagulation solely because the person is at risk of falls.

For people with an increased risk of bleeding the benefit of anticoagulation in *primary* prevention may not always outweigh the bleeding risk, and careful monitoring of bleeding risk is important. In *secondary* prevention the risk of stroke always outweighs bleeding risk except in very specific circumstances in which a Consultant should be contacted.

Patients should be regularly re-assessed (yearly and after a major clinical event) to determine if risks have changed and whether they still require anticoagulation.

Anticoagulation

The Royal Devon and Exeter NHS trust recommends the decision of anticoagulant be based on clinical features and patient preference. We recommend based on current evidence a choice between Warfarin or DOAC (preference of Apixaban).

An online tool to aid discussions around risk and choice of therapy can be found here

ONLY Warfarin is indicated in Valvular and Prosthetic Heart Valves AF

Patient likely to benefit most from warfarin see here

Warfarin initiation can be found here

Apixaban	Standard Dose	5mg bd
	Two of following: AGE ≥ 80 years; WEIGHT ≤ 60kg; Creatinine ≥ 133 mmol/L *OR CrCL 15-29ml/min*	2.5mg bd
	GFR < 15 mls/min	Contra-indicated

Anticoagulation Post Stroke

Initiation or management of anticoagulation during the acute stroke phase should be discussed with a senior doctor or the on-call Stroke physician. The following are important to safe anticoagulation in Stroke[3]:

- ⇒ People with disabling ischaemic stroke who are in atrial fibrillation should be treated with aspirin 300 mg for the first 2 weeks before considering anticoagulation treatment.
- ⇒ In people with prosthetic valves who have disabling cerebral infarction and who are at significant risk of haemorrhagic transformation, anticoagulation treatment should be stopped for 1 week and aspirin 300 mg substituted.
- ⇒ People with ischaemic stroke and symptomatic proximal deep vein thrombosis or pulmonary embolism should receive anticoagulation treatment in preference to treatment with aspirin unless there are other contraindications to anticoagulation.
- ⇒ People with haemorrhagic stroke and symptomatic deep vein thrombosis or pulmonary embolism should have treatment to prevent the development of further pulmonary emboli using either anticoagulation or a IVC filter.

Recommended choice of anticoagulation in AF after Stroke is Warfarin or Apixaban

Warfarin may be the preferred option for those people with AF:	**Apixaban or Dabigatran may be the preferred option for those people with AF:**
Who are currently well controlled on warfarin **Who have never taken an anticoagulant (after discussing risks and benefits with the patient)** **Who are at risk of drug interactions with a novel oral anticoagulant** **Who have a CrCl (eGFR) <30 ml/min/1.73m^2**	Who are not taking warfarin because of allergy or intolerance, or in circumstances where routine INR monitoring may be impractical (provided that monitoring of renal and liver function is still practicable) Who are currently taking warfarin but, despite evidence of good compliance with medication and monitoring, have poor anticoagulant control Who are at risk of drug interactions with warfarin Who have never taken an anticoagulant (after discussing risks and benefits with the patient)

Warfarin initiation can be found here

Apixaban	Standard Dose	5mg bd
	Two of following: AGE ≥ 80 years; WEIGHT ≤ 60kg; Creatinine ≥ 133 mmol/L OR CrCl 15-29ml/min	2.5mg bd
	CrCl < 15 mls/min	Contra-indicated

Second line choice of anticoagulation in AF after stroke is Dabigatran 110mg BD

Dabigatran	'Reduced Dose' regime to be used in all patients	Dabigatran 110mg bd
	CrCl < 30 mls/min	Contra-indicated

Further Information on the choice of anticoagulants in Stroke and their recommended clinical practice can be found here:

http://www.swscn.org.uk/wp/wp-content/uploads/2016/06/SW-CV-Network-Guidance-on-4-Non-vit-K-Anticoagulants-2016.pdf

Anticoagulation and Acute Coronary Syndrome (ACS)

Fondaparinux should be administered to patients diagnosed with ACS who do not have a high bleeding risk or will not be receiving urgent same day invasive management (PCI). Duration should 3 days and then the patient should receive prophylactic low dose LMWH [4]. This replaces Dalteparin in ACS.

Dosing:
Fondaparinux 2.5mg SC ONCE DAILY (withhold on day of angiogram) **for 3 Days**

Dosing: renal impairment
CrCl < 20mL/min: Fondaparinux 2.5mg alternate days (up to 2 doses)
NB: Fondaparinux accumulates in patients with severe renal impairment.

Patients who are already on anticoagulation or have an indication for anticoagulation who now present with ACS

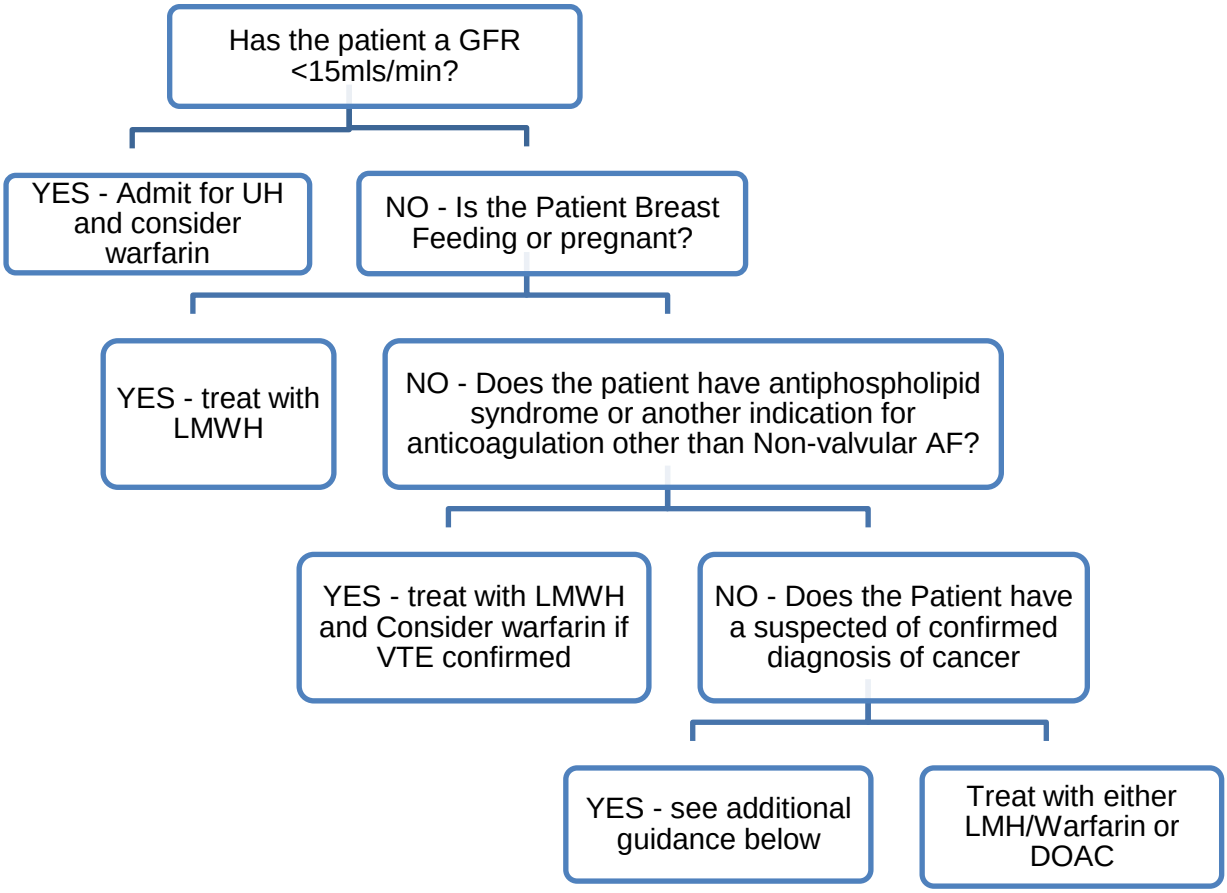
Initiation or management of anticoagulation once ACS confirmed should be discussed with a Consultant or Cardiologist

Take into account all of the following when thinking about treatment for people who have had an MI and who have an indication for anticoagulation:

- bleeding risk
- thromboembolic risk
- Cardiovascular risk.

If anticoagulation is to continue, consider using warfarin or Rivaroxaban and discontinuing treatment with other oral anticoagulants (Apixaban, Edoxaban or Dabigatran).

Treatment of Deep Vein Thrombosis and Pulmonary Embolism



First choice anticoagulation in haemodynamically stable VTE is Warfarin or Apixaban[6,7].

In making a decision to prescribe a DOAC in VTE a discussion with the patient should be performed explaining the benefits vs risks.

There may be more benefit in using a DOAC in uncomplicated VTE given the short period of time required for anticoagulation therefore avoiding potential long term side effects. It is also worth noting that the highest risk of bleeding on warfarin is in the first three months and that is when monitoring is most intense.

Warfarin initiation can be found here

Apixaban	Standard Dose	10mg bd for 7 days then 5mg bd for a total duration of 3 months in provoked VTE and up to 6 months in unprovoked VTE
	CrCl 15-29	Use with caution no dose adjustment
	CrCl < 15 mls/min	Contra-indicated

Anticoagulation of Acute VTE in patients suspected of or having confirmed Cancer

In patients presenting with VTE due to start SACT (Systemic Anti-Cancer Treatment), LMWH should be used. Otherwise patients with active cancer presenting with VTE can be treated with Dalteparin, Rivaroxaban or Edoxaban [8-10].
Active cancer is defined as a diagnosis of cancer (excludes basal-cell or squamous-cell carcinoma of skin) within 6 months, undergoing cancer treatment within the previous six months, or recurrent or metastatic cancer, or cancer not in complete remission including haematological malignancy.
It is important to engage in a discussion with the patient emphasising the benefits vs risks of each treatment. Rivaroxaban and Edoxaban have demonstrated in recent trials to be non-inferior to Dalteparin however, they are associated with an increased Major and Clinically Relevant Non-Major Bleed risk (Hazard ratio: 2).

The recommended period of anticoagulation therapy is 3 to 6 months however; anticoagulant therapy beyond 6 months should be assessed on the patient's active cancer status, plans for cancer treatment, individual risk assessment for bleeding and recurrent thrombosis.

Considerations when deciding choice of anticoagulation:

- Suggest LMWH in patients with high risk of gastrointestinal or urogenital bleeding (GI or urothelial malignancy, or pre-existing GI ulcers)
- LMWH is preferable in patients with hepatic dysfunction
- LMWH is preferable if there is absorption, anorexia or issues around vomiting
- Concomitant medications can interact with DOAC[2] including chemotherapeutic agents for further information click here.
- The presence of thrombocytopenia demands reassessment of risk-benefit balance of anticoagulation[28,29]
  - Where Plt > 50,000/mm^3 anticoagulation is relatively safe
  - If the platelet count is < 50 x 10^9 /L platelet support should be given to elevate the count to > 50 x 10^9 /L to allow full dose anticoagulation, especially in the immediate period following thrombosis development
  - If the platelet cannot be elevated to > 50 x 10^9 /L then 50% dose LMWH can be given with a platelet count of 25 – 50 x 10^9 /L

Dalteparin[8]	GFR ≥20	40-45kg	7500 units once daily for 30 days 6 months
		46-56kg	10 000 units once daily for 30 days, then 7500 units OD for a further 5 months
		57-68kg	12 500 units once daily for 30 days, then 10 000 units OD for a further 5 months
		69-82kg	15 000 units once daily for 30 days, then 12 500 units OD for a further 5 months
		83-98kg	18 000 units once daily for 30 days, then 15 000 units OD for a further 5 months
		≥ 99kg	18 000 units once daily for 6 months
	GFR <20	Use with caution, refer to Renal Drug Database. Discuss with Renal physician and consider monitoring with anti-Factor Xa levels.	
Rivaroxaban[9]	GFR ≥50	15mg PO twice daily for first 3 weeks, followed by 20mg PO once daily for a total of 6 months	
	GFR 15-49	Following the initial 3 weeks treatment, consider reducing to 15mg once daily and the risk of bleeding outweighs the risk of recurrent DVT or PE	

	GFR <15	Contra-indicated
Edoxaban[10]	GFR ≥50 or	60mg once a day for at least 6 months following initial use of therapeutic-dose LMWH for at least 5 days
	>61kg	
	GFR 30-50 or	30mg once a day for at least 6 months following initial use of therapeutic-dose LMWH for at least 5 days
	≤60kg or	
	P-gp inhibitors	
	GFR <30	Contra-indicated

Perioperative Management of Oral Anticoagulants in Elective Surgery

Important principles:

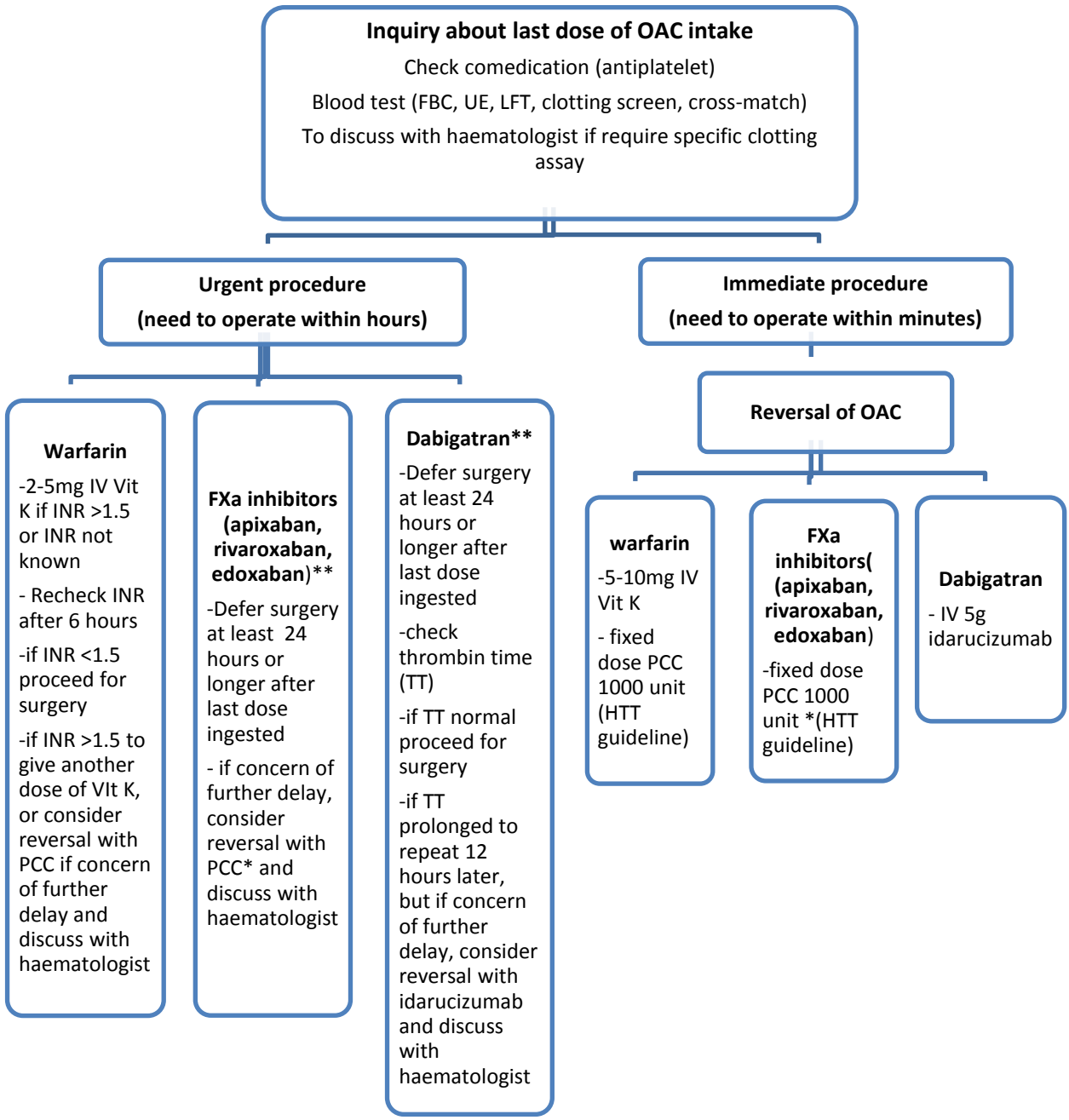
- Risk stratification
- Patient-related and procedure-related risk of thrombosis and bleeding

1. Necessity of anticoagulant interruption
2. Timing of anticoagulant discontinuation and re-initiation
    - Informed by pharmacokinetic – half-life & time to achieve efficacy
    - Laboratory test
3. Determine the need for perioperative bridging therapy with LMWH
    - DOACs do not need bridging

Please refer to the clinical guideline **Management of patients receiving long-term oral anticoagulants for elective surgery/procedure**

A step by step interactive decision-making tool can be found here
http://mappp.ipro.org/www/index.html#drugs

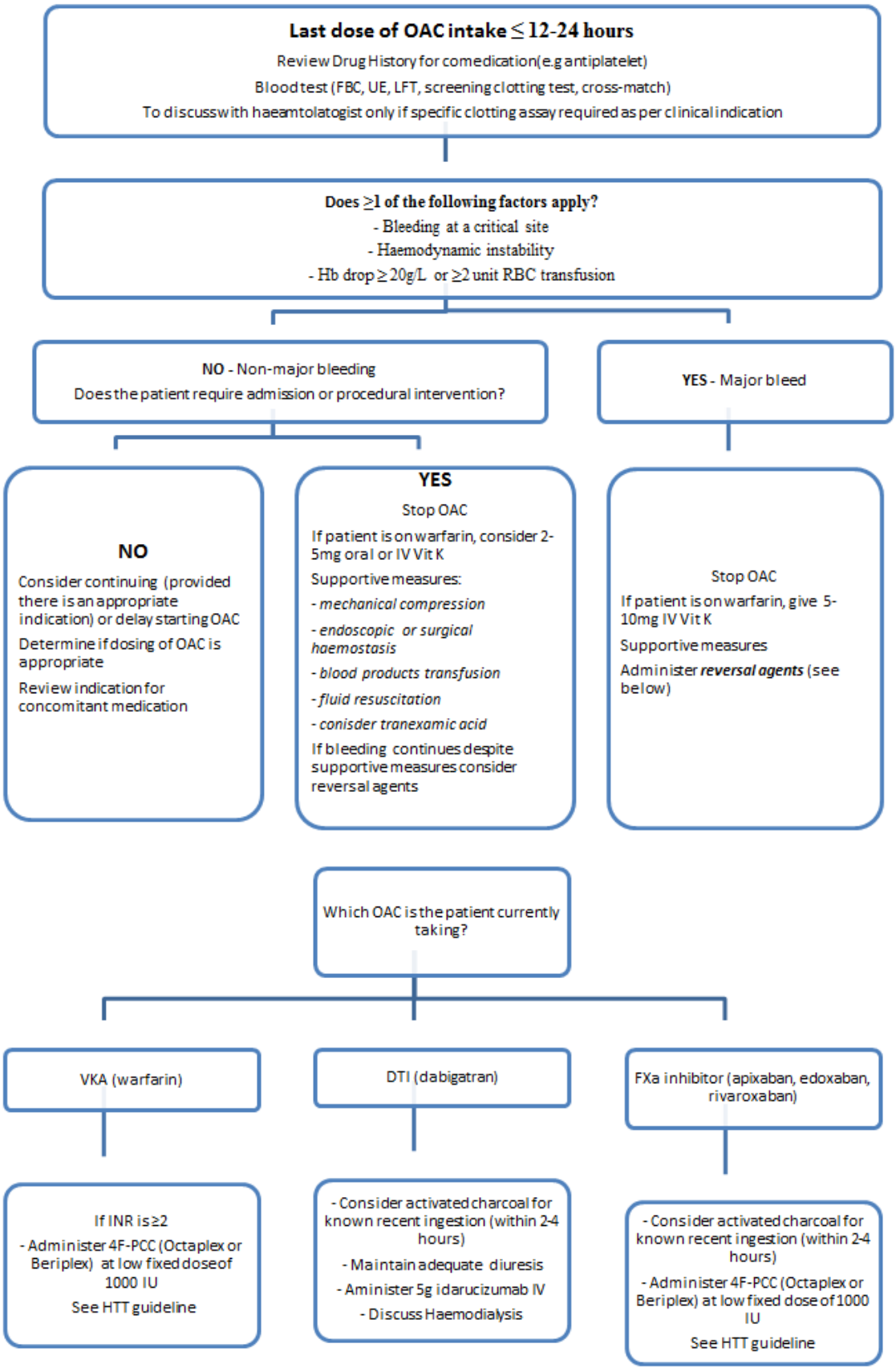
Perioperative Management of Oral Anticoagulants in Unplanned Surgery



* use of a PCC in DOAC can be considered *but has no evidence base* therefore patients or their families should be informed that it may increase the risk of stroke/MI/PE without proven benefit.

** **In patients with hip fracture on DOAC, refer to the specific management plan in** **Appendix 7 (Page 40/41)**

Managing Bleeding in patients on OAC



Use of a PCC in DOACs can be considered *but has no evidence base* therefore patients or their families should be informed that it may increase the risk of stroke/MI/PE without proven benefit.

HTT guideline available here

1. INTRODUCTION

1.1 The clinical benefits of anticoagulation for many conditions are well documented. The risks inherent in anticoagulation are just as well known. 500,000 people are on anticoagulants in the U.K. at present, and a high proportion of them will experience significant morbidity and mortality because of haemorrhage. 600 cases of harm or near harm resulting from anticoagulant use were reported to the NHS Litigation Authority in 2005 and 20% of these were fatal[11].

1.2 The safe initiation of oral anticoagulation is a skilled procedure, and there is considerable evidence that it is done badly, exposing patients to unnecessary risk. All staff involved in the prescription, monitoring and administration of anticoagulants should demonstrate competency and undergo training.

1.3 The process of initiating oral anticoagulation therapy should be broken down into the following areas, and each should be carefully documented in the patient's records.

- Risk assessment of anticoagulation therapy Indication and goals of anticoagulation therapy Baseline monitoring
- Verbal and written communication of information to patient regarding prescription of anticoagulation and relevant monitoring of anticoagulation therapy
- Plan for discharge and subsequent monitoring

1.4 **Failure to comply with this policy could result in disciplinary action.**

2. PURPOSE

2.1 The Policy exists to provide guidance for healthcare staff on best practice approach to anticoagulation of different conditions. The policy provides healthcare staff with background information and links to outside resources to aid decision making and explanation to patients. It is not exhaustive and may be superseded by specific guidance in individual specialist conditions or under supervision by the patients named consultant.

3. DEFINITIONS

3.1 **BSH -** British Society of Haematology

3.2 **e-GFR –** Electronic Glomerular Filtration Rate (ie Creatinine Clearance CrCl) - a calculated estimation of renal function

3.3 **INR** - International Normalised Ratio – the test used to assess degree of anticoagulation with warfarin

3.4 **LMWH -** Low-molecular weight heparin – e.g. dalteparin

3.5 **NSTEMI -** Non ST-elevation Myocardial Infarction

3.6 **PCC -** Prothrombin complex concentrate – e.g. Octaplex – used in the emergency reversal of over anticoagulation. Now referred to as Dried Prothrombin Complex

3.7 **STEMI -** ST-elevation Myocardial Infarction

3.8 **VTE -** Venous thrombo-embolism

3.9 **DOAC** – Direct Oral Anticoagulant

3.10 **OAC** – Oral Anticoagulant

3.11 **ACS** – Acute Coronary Syndrome

4. DUTIES AND RESPONSIBILITIES OF STAFF

4.1 The **Medical Director** is responsible for oversight of the implementation and governance of the policy.

4.2 The **Clinical Effectiveness Committee** is responsible for the ratification of this policy

4.3 The **Patient Blood Management Group (PBMG)** is responsible for ensuring the safe, secure and economic use of blood transfusions and blood products and compliance with legislation and best practice. This group includes clinical and medical representatives from key areas of the Trust. The PBMG reports to the Clinical Effectiveness Committee.

4.4 **All staff involved in the prescription, monitoring and administration of anticoagulants** should demonstrate competency and undergo training.

5. RISK ASSESSMENT OF ANTICOAGULATION THERAPY

5.1 Before the decision to anticoagulate a patient is taken, the prescriber or a competent deputy should review the patient's medical record and other medications to perform a full risk – benefit analysis.

Prescribers should be aware of the British Committee for Safety in Haematology's "Guidelines for Oral Anticoagulation with warfarin – Fourth Edition" and the updates to warfarin's **Summary of Product Characteristics** (SPC) by the MHRA in December 2009.

American College of Chest Physician (ACCP), European Society of Cardiology, International Society of Thrombosis and Haemostais[15] also contain extensive and current information about evidence based anticoagulation

5.2 The appropriateness of anticoagulation should be considered in light of the patient's current health, social status, co-morbidity, concomitant treatment and preferences. These include, but are not limited to:

- Ability to comply with the treatment.
- Risk of haemorrhagic complications (e.g. frequent falls, occupation etc). Co-morbidity (e.g. previous haemorrhagic disease, liver disease, renal dysfunction, peptic ulcer disease).
- Other prescription or over-the-counter (OTC) medication:
  - Enzyme Inducers (e.g. anticonvulsants – phenytoin, St. John's Wort)
  - Enzyme Inhibitors (e.g. macrolide antibiotics)
  - Other drugs likely to augment anticoagulant effect
  - Please see British National Formulary Appendix 1 for full details
- Access to clinical facilities for monitoring.

- Consumption of alcohol.
- Likelihood of current or intended pregnancy / breast feeding.
- Abnormal baseline blood tests (see Section 7)

5.3 In using Warfarin the preferred loading regime should be considered based on the indication and co-morbidity (see Section 9).

5.4 **Pregnancy and Warfarin**. Warfarin is contraindicated in pregnancy (first and third trimesters) and is highly teratogenic. Pregnancy should be excluded prior to starting warfarin therapy. Women of child-bearing potential who are starting warfarin should be counselled against falling pregnant whilst on treatment and asked to take appropriate contraception.

5.5 **Pregnancy and Direct Oral Anticoagulants**. DOACs are currently contraindicated in pregnancy and breastfeeding due to insufficient research data.

5.5 **Active Malignancy:** Please see Anticoagulation of Acute VTE in patients suspected of or having confirmed Cancer

5.6 **Protein C & S Deficiency:** Patients with protein C deficiency are at particular risk of developing skin necrosis during initiation of warfarin therapy. These patients must have heparin cover and rapid loading doses of warfarin should not be given. Protein S deficiency also carries some risk of this and slow introduction of warfarin should also occur in these patients[13]. There is no concern, case reports support the use of DOACs in this population without adverse outcomes[17].

5.7 **Ischaemic Stroke**: Anticoagulation following ischaemic stroke may increase the risk of secondary haemorrhage into the infarcted area. Please see Anticoagulation Post Stroke.

5.8 **Perioperative Anticoagulation:** please see perioperative anticoagulation.

5.9 **Acute Coronary Syndrome**: patients who have already been anticoagulated or have an indication for anticoagulation who then are diagnosed with ACS should be discussed with a Cardiologist. Warfarin and Rivaroxaban are currently the only oral anticoagulants recommended and careful risk stratification is required.

6. INDICATION AND GOALS OF ANTICOAGULATION THERAPY

6.1 The reason(s) for anticoagulation should be clearly documented in the medical notes and discharge letter.

6.2 Patients likely to benefit most from warfarin:

- Indication not covered by DOAC e.g. valvular AF
- Severe renal failure or high chance of significant deterioration
- Hepatic dysfunction
- Prosthetic (metal or tissue) heart valves
- Arterial grafts
- Patient concerns over long term safety data
- Taking other drugs where DOACs are contra-indicated
- Other medical conditions where data on the use of DOACs is limited such as antiphospholipid syndrome
- Use of unusual drugs where experience of them alongside DOACs is limited

- Target INR other than 2.5 (2.0-3.0) as DOACs designed to give equivalent anticoagulation to INR 2.5

6.3 If using a DOAC a discussion with the patient providing evidence of patient preference should be documented where appropriate along with current renal function and follow up plans for monitoring renal and liver function.

6.4 If using Warfarin the duration of therapy and the target INR should also be written clearly. This information should also be written in full on the prescription, and transcribed to the patient's 'Yellow Book' at the time of prescription. Target INRs for common indications for warfarin therapy are summarised on page 3 of the prescription chart - see Appendix 3 Oral Anticoagulant Prescription Chart.

6.5 This information should also be made clear to the practitioner accepting long-term monitoring of the treatment (usually the GP) before discharge.

7. BASELINE MONITORING

7.1 If not already performed, all patients should have routine laboratory testing prior to commencing anticoagulation therapy to exclude any significant haematological or hepato- renal dysfunction that might influence the risk-benefit analysis. This should include:

- Haemoglobin and platelet count.
- Basic liver function tests
- Urea and electrolytes
- A baseline INR
- A baseline APTT if unfractionated heparin use is indicated. Full clotting testing if clinically relevant

To avoid spuriously high INRs, please ensure the INR bottles are not under filled.

7.2 These results should be reviewed before the administration of the first dose. If the baseline INR is greater than 1.4, the patient should be screened for inherited or acquired coagulopathies.

8. VERBAL AND WRITTEN COMMUNICATION OF INFORMATION TO PATIENT

8.1 Prior to the administration of anticoagulation, patients should receive adequate verbal and written information regarding their therapy. This information should ideally come from the senior prescriber initiating anticoagulation therapy, or if not, a competent delegate. The verbal information should include as a minimum:

- A definition of anticoagulation.
- The indication for and the anticipated duration of treatment.
- Inform patient about the bleeding risk. To report excessive or unusual bleeding event or major trauma.
- Warfarin is contraindicated in first and third trimesters of pregnancy. DOACs are contraindicated in pregnancy and breast feeding. Women of childbearing age should avoid falling pregnant and use appropriate forms of contraception during warfarin or DOACs treatment.
- Information for if doses of anticoagulants are missed and what to do

- Need to inform medical professionals that they are taking an anticoagulant medication i.e. dentists
- If on Warfarin:
    - The need for regular blood test monitoring - the “INR” – to guide the variable dose an individual might take.
    - That doses are made up of different strength (and coloured) tablets.
    - The need to keep the anticoagulation record safe and up to date with dosage and INR results.
    - The potential interactions with drugs, OTC preparations, alcohol and foodstuffs.

- If on DOACs
    - No need for routine blood testing but emphasize the importance of compliance with dosing due to the short half-life.
    - The need for caution when stopping or starting new drugs or OTC medications
    - Explain any specific instructions for each DOAC i.e. Rivaroxaban to be taken with main meal

8.2 If commencing Warfarin the British Society for Haematology Standards Task Force / NPSA designed yellow booklet (comprising the ‘alert card’, general information book and blood test and dosage record) should be provided to the patient and/or carer. They should be encouraged to read this and clarify any areas they do not understand with staff whilst in hospital.

Staff initiating anticoagulation should ensure that the following sections are fully completed by staff in liaison with the patient and/or carer:

- The forms on pages 1-4 of the BSH / NPSA Information Booklet. The forms on pages 1-4 of the Dosage Record Book.
- The Alert Card.

8.3 If commencing a DOAC please provide the relevant patient information leaflet.

8.4 All clinical areas involved in the initiation and maintenance of anticoagulation therapy should either stock or have quick access to these patient documents.

8.5 This information should be repeated at the time of discharge, and the patient given the opportunity to ask questions regarding the treatment.

8.6 Extra care should be taken with patients with cognitive dysfunction, or those who have reduced hearing or sight, as they may receive substandard counselling. This may involve more prolonged conversations, as well as early communication with the patient’s carers, family, and the GP.

9. PRESCRIPTION OF DOACS

- The prescription of DOACS have been associated with multiple errors due to poor understanding of the different dosing regimens and indications.

- When prescribing a DOAC it is imperative to check the indication and any necessary dose alterations as provided by the manufacturers’ guidance.

- Where possible there are recommended doses for the condition in this guideline however further guidance can be found from the BNF or EMC.

- DO NOT REDUCE THE DOSES OF THE DOACs WHEN IT IS NOT INDICATED as this will reduce the efficacy and adversely affect patient outcome.

Information on the evidence surrounding DOAC use is summarised in Appendix 2

10. PRESCRIPTION OF WARFARIN AND CONCOMITANT HEPARIN THERAPY

10.1 There are two key schedules in the prescription of warfarin:

- Slow Induction[17]
- Rapid Anticoagulation (using either an initial 5mg or 10mg loading dose).

10.2 **Slow induction** involves starting a low daily dose of warfarin without heparin cover and with less frequent INR monitoring. It is only appropriate when slow introduction of warfarin over a longer period of time is safe. Advantages include avoidance of the hypercoagulable state seen for the first few days after rapid anticoagulation and the possibility of earlier discharge of patients needing warfarin but who are otherwise fit to leave hospital. Additionally, the risk of excessive anticoagulation should also be less[17].

Slow induction is suitable for patients:

- The short-term thrombo-embolic risk is low; e.g. non-rheumatic atrial fibrillation with no co-morbidities carrying higher or additional risks of thrombo- embolism.
- The risk of bleeding is low
- There are no interacting factors that might cause significant increases in the INR (e.g. liver disease, interacting drugs (see page 4 of drug chart in appendix A), right heart failure)
- Outpatient anticoagulation is possible and imminent
- The GP has agreed to follow the anticoagulation therapy

A suitable schedule has been described[17]. 2mg of warfarin can be given daily, and the INR is measured at week 1 and 2 after commencing treatment.

Whilst the original paper checked INRs initially only after 1 and 2 weeks, **it is recommended that patients have intermittent INR checks** if they remain as an inpatient, especially if their condition or treatment changes. However, unless the INR is higher than wanted, the dose should not be altered during the first two weeks of treatment.

The INR at the end of two weeks of 2mg can be used as approximate guide of an individual patient's daily warfarin requirements. This will generally be assessed in general practice but the guide is shown below. Please note the gender differences in the dose per day.

Male		Female	
INR at week 2	Maintenance Dose (mg)	INR at week 2	Maintenance Dose (mg)
1.0	6	**1.0-1.1**	5
1.1- 1.2	5	**1.2-1.3**	4
1.3-1.5	4	**1.4-1.9**	3
1.6-2.1	3	**2.0-3.0**	2
2.2-3.0	2	**>3.0**	1
>3.0	1		

The patient's GP must be contacted prior to discharge to explain the slow induction schedule and to plan the next INR check. It may be preferable that the primary care physician initiates anticoagulation in this approach as it avoids dosing errors or misunderstandings on discharge. It should also be made clear to the patient that they are having treatment that may take several weeks to become maximally effective.

10.3 **Rapid anticoagulation** is the preferred schedule for the treatment of venous thrombo-embolism, prophylaxis for metal valves and other high risk conditions. This is appropriate for a majority of in-patients requiring anticoagulation. The bleeding risk should always be assessed and if risk factors are present, then the lower dose induction schedule should be followed (see page 1 of prescription chart – Appendix 3).

The objective of rapid initiation is to achieve full anticoagulation and reach the target INR as quickly yet safely as possible. Because warfarin therapy can take more than 5 days to reach a maximal effect and may induce a hypercoagulable state in the early stages, it is necessary to cover this initial phase with either low molecular weight heparin (LMWH) or standard unfractionated heparin (UH).

10.4 It is essential that all anticoagulants are prescribed and documented on the patient's main prescription chart **AND** on the specific anticoagulation prescription charts. Where this has not happened, doses have been missed or patients have been discharged without their anticoagulant therapy.

10.5 Patients older than 60 should only receive 5mg of Warfarin as their first loading dose. Other important reasons to consider more cautious loading include:

- Body weight < 60kg.
- Low serum albumin.
- Raised baseline INR.
- Interacting drugs (see BNF Interactions via NICE) especially those that inhibit its metabolism e.g.:
  Macrolide antibiotics such as erythromycin.
  Metronidazole.
- Liver or cardiac dysfunction.

11. HEPARIN FOR USE IN RAPID ANTICOAGULATION

11.1 Heparin doses should be written in full, documenting **"units"** not "U" to avoid ten-fold drug overdoses.

11.2 There is a single heparin policy within the Trust. This is to simplify prescribing and reduce errors. Trust policy is to recommend **dalteparin** as per the British National Formulary (BNF) and/or the Summary of Product Characteristics (SPC).

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Dalteparin will be used for all indications including venous thrombo-prophylaxis. Dose adjustments are generally unnecessary for obesity or low body weight. Simplified prescribing advice can be found on page 4 of the Anticoagulant Prescription Chart (see Appendix 3)

11.4 Dalteparin in Renal Failure:

Patients with severe renal dysfunction (eGFR<20ml/min) are at risk of accumulation of LMWHs. In these circumstances, dose adjustment based on anti-FXa level or the use of unfractionated heparin and discuss with renal physician is recommended. The dose of dalteparin should be reduced to 50% if the patient has a eGFR less than 20ml/min.

N.B: Tinzaparin will still be in use on the renal unit and in particular for haemodialysis patients. Please be aware of this when covering here, or receiving patients transferred from this area.

11.5 Anti- factor Xa monitoring should be considered in patients on prolonged therapy with dalteparin. It should also be considered in patients who are pregnant, are at extremes of body weight, and in those with a high bleeding risk. This will allow dose adjustment based on the assay findings. Please discuss these cases with the haematologist on call.

11.6 **Unfractionated Heparin**(UH): UH can be used to cover warfarin loading. It is especially useful in the following circumstances:

- Severe renal dysfunction (eGFR < 20ml/min).
- Massive deep vein thrombosis (DVT) / pulmonary embolism (PE) where the clinical evidence for LMWH remains somewhat weak.
- Where extremely rapid onset is deemed appropriate.
- Where there is a high risk of haemorrhage that may require rapid reversal.

A loading dose of 75 units/kg of UH (maximum 5000 units) over 5 minutes should be given if the baseline APTR is less than 1.5 followed by a continuous infusion of 18 units/kg/hour (maximum 1800 units/hour). Infusions should be made with standard, ready to use sodium heparin (1000 units / ml) so changes to dose can be made by varying the infusion alone. An alternative is to give the equivalent daily dose in two divided subcutaneous injections. If the baseline APTR is 1.5-2.5 start heparin infusion using the weight nomogram without a loading dose (Appendix 4, Tables 1 and 2). If the baseline APTR is greater than 2.5 review the need for heparin and discuss with senior staff and/or haematologist.

11.7 The dose of UH infusion should be varied according to regular APTR measurements, the target range being 1.5 – 2.5. After the infusion starts, the next check should be performed 4 hours after the infusion is commenced[18].

Adjustments should be based on table 3 of the UH prescription chart - see Appendix 4. If the APTR remains sub-therapeutic (less than 1.5) despite a maximum dose of 1800 units/hour consult seniors/haematologist. The APTT is not a perfect marker of the intensity of the anticoagulant effect of heparin and provided the anti-Xa heparin level is at least 0.35 IU/ml it is not necessary to increase the infusion rate. Antithrombin deficiency as a possible explanation for heparin resistance should also be considered.

Once the APTR is in the therapeutic range it should be checked at least daily thereafter, and 4 hours after any change in the rate of infusion.

Further information on heparin can be found in the BNF, EMC as well as the ACCP guidance and the BCSH guideline. Monitoring of heparin therapy and for Heparin-induced thrombocytopenia is detailed below.

11.8 Heparin-induced thrombocytopenia (HIT) can occur, typically between 5 and 10 days of treatment. Platelets should be routinely monitored at baseline and

during treatment. If HIT is suspected, please refer to the Trust "Clinical guideline for heparin induced thrombocytopenia". Please find the Link to the guideline here.

11.9 If initiating Warfarin therapy it should be initiated at the same time as heparin. The heparin therapy should be continued until the INR has been in the therapeutic range for two consecutive days (generally 4-5 days of treatment).

12. IN-PATIENT MONITORING OF ANTICOAGULATIONTHERAPY

Warfarin:

12.1 During the initiation of rapid anticoagulation, it is appropriate for patients to have their INR checked daily to guide subsequent doses. Deviations from this may allow dangerous sub- or supra-therapeutic levels to develop unbeknown to the clinician.

12.2 Especial care should be taken if other medications have recently been prescribed, changed or stopped, as they may alter the pharmacokinetics of warfarin to a significant degree. The frequency of INR monitoring should increase if there is likelihood of drug-drug or drug-disease interactions that may affect warfarin activity.

12.3 Patients stabilised on warfarin can have INRs measured less frequently, but it is essential that the frequency of testing is reviewed often, as changes in medication or clinical condition may lead to alterations in warfarin metabolism and degree of anticoagulation.

12.4 It is essential that all doses, INR results and changes to other treatments are clearly documented on the prescription chart and the patient's dosage record. This should be performed by the clinical team with overall responsibility for the patient and not delegated to out of hours ward cover.

12.5 The following practices in warfarin doses should be adopted to promote safety: Avoidance of fractional doses as they may require the halving of tablets.

- Constant daily dosing (as opposed to alternate day dosing). A 0.5 mg tablet is available.
- The least number of individual warfarin tablets to make up the prescribed dose.

Low Molecular Weight Heparins:

12.7 In general, patients with LMWH therapy do not require routine measurement of coagulation parameters.

12.8 Anti-Xa monitoring may permit dose alterations to improve safety and efficacy in certain groups in particular.

Please discuss anti-Xa monitoring with the haematologists in**:**

- patients with severe renal failure (eGFR < 20 ml/min)
- patients with extremes of body weight
- pregnant women
- patients at high risk of bleeding or re-thrombosis
- patients with severe liver dysfunction

A citrated sample (coagulation tube) is required for anti-Xa levels. Samples should

be taken between 3-4 hours after the dose of LMWH is administered, and the timing of the heparin dose should be recorded on the request form or samples will not be processed. Samples for anti-Xa testing can be sent to the laboratory on any day, but the assay will only be performed routinely on Tuesdays and Fridays, so the results may not be available immediately. In exceptional circumstances it may be possible to request an urgent *ad hoc* anti-Xa level on other days, but this must be discussed with a consultant haematologist.

In patients with severe renal impairment (eGFR < 20 ml/min) receiving treatment- dose LMWH, it is recommended that baseline anti-Xa activity is measured before the first dose, and then again 3-4 hours after the fourth dose to assess for accumulation. Anti-Xa activity should be measured again 3-4 hours after the fourth dose following any dose-adjustment. It is important to note that these results may not be immediately available (see above).

The therapeutic range for treatment-dose LMWH is an anti-Xa activity of 0.5-1.0 IU/mL, and for prophylactic-dose LMWH 0.2-0.5 IU/mL (only where it may be appropriate to monitor prophylaxis e.g. during pregnancy).

12.9 Monitoring of all heparin therapy should also include potassium levels as hyperkalaemia can occur due to suppression of aldosterone secretion. This is more common in diabetic patients, chronic renal failure, or those with pre-existing metabolic acidosis or hyperkalaemia.

DOAC

12.10 In general DOACs do not need routing monitoring other than baseline renal and liver function. This should be repeated yearly.

12.11 Appendix 6[19] describes some of the options available and considerations in monitoring DOACS.

12.12 Potential indications for monitoring are as follows:

- In the presence of spontaneous or traumatic haemorrhage
- Following suspected overdose
- When patients are taking another interacting drug
- To monitor efficacy in patients presenting with new thrombosis whilst on the anticoagulant
- When emergency surgery is required
- In patients due to have neuraxial anaesthesia for elective or emergency procedures or surgery
- In patients requiring elective surgery and in whom the drug may still be present
- In patients with renal impairment
- When bridging from one anticoagulant to another
- To assess compliance
- At the extremes of body weight
- In subjects with prior intestinal surgery where it is unclear if absorption will be affected
- Trough levels may be useful to assess potential accumulation in very elderly patients

Routine clotting assays i.e. INR, PT and APTT, cannot be used to determine the drug concentration. Thrombin time (TT) is extremely sensitive to dabigatran therefore a normal TT exclude the presence of dabigatran. Diluted thrombin time for dabigatran and anti-Xa chromogenic assays for FXa inhibitors are not currently available in hospital laboratory, but it is likely the tests can be performed soon in the foreseeable future.

13. PERIOPERATIVE MANAGEMENT OF ORAL ANTICOAGULANTS IN ELECTIVE SURGERY

13.1 The following guidance is designed to assist the practitioner with the safe management of patients in the perioperative period who are receiving oral anticoagulation (OAC) including warfarin and Direct oral anticoagulants (DOACs). It is, as far as possible, evidence based and strikes a balance between the risks of thrombosis and bleeding[20-23].

Currently there is specialty specific guidance that takes priority in the fields of orthopaedics and Perioperative care. This guidance should be consulted for clinical decisions in those areas.

13.2 Not all patients need to stop their OAC before elective surgery. Examples include minor superficial surgery and surgery where the surgeon has stated that he / she is happy to perform the operation safely on OAC.

13.3 If coagulation needs to be normalised for surgery, a risk assessment to consider anticoagulant interruption and bridging therapy with Low Molecular Weight heparin (LMWH) is required. **Management of patients receiving long-term oral anticoagulants for elective surgery/procedure**

13.4 The actual rate of peri-procedural thromboembolism for unbridged OAC interruption is rare (<0.5%). Bleeding with bridging therapy is more common, suggesting that the net effect of bridging leans towards bleeding. There is compelling evidence from trials that routine bridging in moderate-risk patients is harmful[24-25].

13.5 In patients on warfarin, bridging therapy is recommended for patients at high risk of thromboembolism such as mechanical heart valves. Bridging therapy should be avoided in patients at low or moderate risk thromboembolism as long as other individualised risks (e.g. active cancer) do not exist.

13.6 DOACs have similar pharmacokinetics to LMWH, therefore no bridging therapy is required. Timing to interrupt and restart DOACs depends on the drug group and renal function. **Management of patients receiving long-term oral anticoagulants for elective surgery/procedure**

13.7 When a patient presents to the pre-assessment clinic that is not anti-coagulated but may benefit from anticoagulation they should have a management plan agreed with the anaesthetic and surgical team involved. The balance between bleeding and thrombosis risk should be made using the anticoagulation risk assessment tool attached **Management of patients receiving long-term oral anticoagulants for elective surgery/procedure**

13.8 LMWH and warfarin prescribing should be aligned to Trust policy. In the pre-operative assessment clinics, **LMWH should be prescribed by the pre-assessment practitioners** under a Patient Group Directive (PGD). The process of warfarin and LMWH administration should follow the algorithm **Management of patients receiving long-term oral anticoagulants for elective surgery/procedure**

13.9 **If patients are to be administered LMWH in a community facility, the prescription and the outline of the procedure includes time to check INR must be faxed or emailed to the appropriate General Practitioner. Those patients self-administering LMWH must undergo an assessment of their competence to do so.**

14. REVERSAL OF ORAL ANTICOAGULANTS

14.1 In many circumstances, there is the need to reverse the effects of anticoagulation of warfarin, DOACs and heparins. Depending on the instance, this may be necessary immediately, such as in the event of life threatening haemorrhage, or an emergency surgery. In all cases, a review of the patient's history and medications should also be undertaken to ascertain the reason for the excessive anticoagulation.

This protocol sets out the best practice in each of these circumstances. A summary of the guidance can be found in key points here.

14.2 **Management of bleeding in patients on OAC**:

It is vital to know what OAC patient is on and when is the last dose of ingestion. Moreover, assessment of bleed severity is crucial for treatment decisions to achieve haemostasis and preserve organ function.

14.3 Major bleed is defined:

- Haemodynamic instability with systolic blood pressure <90 mmHg, or a decrease of systolic blood pressure >40 mmHg, or orthostatic blood pressure changes (systolic blood pressure drop ≥20 mmHg or diastolic blood pressure drop ≥10 mmHg upon standing)
- Drop in Hb≥20g/L, or ≥2 unit of RBC transfusion
- Bleeding in a critical site

Type of Bleed	Initial signs and symptoms	Potential consequences of Bleed
Intracranial haemorrhage: **includes intraparenchymal, subdural, epidural, subarachnoid haemorrhages**	Unusually intense headaches, emesis. Neurological signs: e.g. reduced LOC, vision changes, numbness, weakness, aphasia, ataxia, seizures	Stupor or coma Permanent neurological deficit Death
Other central nervous system haemorrhage: **includes intraocular, intra- or extra-axial spinal haemorrhages**	Intraocular: monocular eye pain, vision changes, blindness Spinal: back pain, bilateral extremity weakness or numbness, bowel or bladder dysfunction	Intraocular: permanent vision loss Spinal: permanent disability, paraplegia, quadriplegia, death
Pericardial tamponade	SOB, tachypnoea, hypotension, muffled heart sounds	Cardiogenic shock Death
Airway, including poster epistaxis	Airway: haemoptysis, hypotension Posterior epistaxis: profuse epistaxis, haemoptysis, hypoxia, SOB	Respiratory failure Death
Haemothorax, Intra-abdominal bleeding, Retroperitoneal haemorrhage	Haemothorax: tachypnoea, hypotension, tachycardia Intra-abdominal/retroperitoneal bleed: abdominal pain and distention, hypotension	Haemothorax: respiratory failure RPH: femoral neuropathy All: hypovolemic shock, death

Extremity bleeds**: includes intramuscular and intra-articular bleeding**	Intramuscular: pain, swelling, paraesthesia, weakness, diminished pulse Intra-articular: joint pain, swelling, decreased range of motion	Intramuscular: compartment syndrome, paralysis, limb loss Intra-articular: irreversible joint damage

14.4 If patient presents with life-threatening or Major haemorrhage whilst on OAC therapy, the following actions should be considered, in addition to rapid reversal of anticoagulation effect by specific antidote.

14.5 Large bore cannula should be inserted for fluid resuscitation as appropriate. Start supportive measures with early involvement of the appropriate service (e.g. surgery, interventional radiology, gastroenterology) for definitive management.

14.6 Blood samples should be sent urgently for:

- Full blood count, renal function, liver function tests,
- A group and hold, or a cross match if indicated
- A full coagulation screen including an International normalised ratio (INR)
- If specific coagulation test required, please consult haematologist

14.7 Blood product such as red blood cells transfusion to keep Hb ≥70g/L, platelet transfusion to keep platelet ≥50 x 10^9/L, cryoprecipitate to keep fibrinogen > 100mg/dL. Also consider early administration of tranexamic acid 25mg-50mg/kg

14.8 **If patient is on warfarin**:

- 5-10 mg of Vitamin K_1 (phytomenadione) should be administered by slow intravenous infusion.
- If INR is ≥2 or not known, the trust recommends administration of 4F-PCC (Octaplex or Beriplex) at low fixed dose of 1000 IU which can be found in the Blood Bank fridge at all times. Discussion with a Haematologist is not required in cases of Major Haemorrhage, or emergency lifesaving surgery.

See APPENDIX 7

- FFP remains a viable and cheaper alternative but its effects are less complete than PCC. If PCC is unavailable or contraindicated, 15ml/kg of FFP should be administered.

14.9 **If patient is on dabigatran**:

- Consider activated charcoal for known recent ingestion (within 2-4 hours).
- Idarucizumab is the first agent to be licensed in the UK that reverses the anticoagulant effect of a DOAC. Its action is specific against dabigatran etexilate. In the interim analysis of an ongoing, phase III, uncontrolled, cohort study (RE-VERSE AD; n=90), treatment with a 5 g dose of idarucizumab completely reversed the anticoagulant effect of dabigatran etexilate in adults who had either serious bleeding or required urgent surgery[26].
- Haemodialysis can be considered though the evidence is not clear on benefits; each case would need to be discussed with the on call renal consultant.

14.10 The recommended dose of idarucizumab is 5 g given intravenously as 2 consecutive infusions of 2.5 g/50 ml over 5 to 10 minutes each or as 2 consecutive 2.5 g bolus injections. Administration of a second 5 g dose of idarucizumab may be considered in the following clinical situations:

- recurrence of clinically relevant bleeding together with prolonged clotting times
- if potential re-bleeding is life-threatening and prolonged clotting times are observed

- patients require a second emergency surgery or urgent procedure and have prolonged thrombin time

  2 free packs (4 vials in total) of idarucizumab are kept in the **TRANSFUSION LAB [redacted] FRIDGE**. This will facilitate rapid access to the treatment 24/7.

  Access to the stock will be granted by a haematologist who effectively will clinically be the gate keepers.

14.11 **If patient is on FXa inhibitors (Rivaroxaban, Apixaban, Edoxaban),** currently there is no approved reversal agent for Factor XA inhibitors though it is anticipated that Adexenat alfa will be approved for licence in the future.

- Consider activated charcoal for known recent ingestion (within 2-4 hours)
- The trust recommends administration of 4F-PCC (Octaplex or Beriplex) at low fixed dose of 1000 IU which can be found in the Blood Bank fridge at all times. Discussion with a Haematologist is not required in cases of Major Haemorrhage. See Appendix 7 for PCC algorithm

14.12 It is important to note that if last dose of DOACs ingestion is >24 hours ago, it is likely that there is minimal in vivo anticoagulation effect to account for bleeding, unless patient has severe renal impairment. Regrettably laboratory assay for DOACs is not available in the trust laboratory to streamline the use of reversal agent; however these tests are likely to become available in 2019.

Patients on OAC requiring an unplanned surgical intervention

14.13 If an emergency intervention is required, OAC should be discontinued immediately. Specific management will then depend of the level of urgency – immediate vs urgent.

It is prudent to determine the last dose of OAC ingested, particularly with DOACs.

Blood test includes FBC, U&E, LFT and clotting assay should be obtained, as it is important to assess patient coagulation status. It is important to remember that a normal routine clotting test (PT & APTT) does not exclude DOACs drug level. However, a normal Thrombin time (TT) excludes the presence of dabigatran. For management please refer to the algorithm in the key point section.

Timing of Anticoagulation Re-initiation after Bleeding

14.14 Determining the optimal timing for reinitiation of OAC has the dual therapeutic aim of preventing thrombotic events while minimizing rebleeding.

14.15 After a bleeding event, the indication for OAC should be reassessed to determine whether continued therapy is warranted. If there is an ongoing indication for OAC, the clinician must evaluate the net clinical benefit of OAC in the context of a recent bleed to decide whether the risk of bleeding temporarily or permanently outweighs the benefit of OAC treatment.

14.16 This risk-benefit assessment should be conducted in consultation with other specialists involves in the care of patient.

14.17 Optimal and early patient engagement in the decision to restart OAC involves shared decision making with patients or caregivers. Discussion should outline the risks of

bleeding that come with resuming anticoagulation, implications for thrombotic events and death without anticoagulation.

14.18 Conditions with high thrombotic risk favor early reinitiatin of OAC after 24-48h once haemostasis is achieved. However for pateints at high rebleeding risk for whom the thombotic risk is unacceptaby high and anticoagulation is deemed necessary, inidivdulised strategies should be conisdered. Following are the examples:

- Consider intravenous UH, due to its short half-life and an available reversal agent (protaminesulfate) that can rapidly reverse anticogulation in the event of bleeding
- Consider start with prophylactic dose of LMWH with close clinical monitring and titration to therapeutic dose
- Consider non-pharmacological devices such as temporary inferior IVC filter

14.19 The timing of anticoagulation reinitiation following intracranial haemorrhage, has not been systemactically studied and is lack of general consensus. However, ACC guideline recommends delaying the resumption of anticoagulation for at least 4 weeks in patients without high thrombotic risk.

14.20 A comprehensive medication reivew should identify drugs that can increase OAC drug levels

15. MANAGEMENT OF MINOR BLEEDING OR ASYMPTOMATIC RAISED INR

15.1 In the Case of DOACs omitting the next dose is often sufficient. This can be restarted once the bleeding has ceased.

15.2 In cases of Warfarin the objective in these circumstances is to return the INR to therapeutic levels in a timely manner but without exposing the patient to unnecessary treatments or rendering their anticoagulation sub-therapeutic. PCCs or FFP are not indicated in these situations. In all cases, a review of the patient's history and medications should also be undertaken to ascertain the reason for the excessive anticoagulation.

15.3 Please refer to the BNF (British National Formulary) for the most up to date advice for sections.

15.4 If the INR is greater than 8.0 but there is no bleeding or only minor bleeding, then warfarin should be stopped and not recommenced until the INR falls below 5.0.

15.5 If the INR is greater than 8.0 and the patient has other risk factors for bleeding, they should be given 500 micrograms of vitamin K_1 (phytomenadione) by slow IV injection or 5mg orally. Smaller doses can be used if partial reversal is the objective. The doses of vitamin K_1 can be repeated if the INR remains elevated after 24 hours.

15.6 If the INR is between 6.0 and 8.0 and there is no bleeding or minor bleeding, withholding warfarin alone until the INR falls below 5.0 is appropriate.

16. REVERSAL OF HEPARIN THERAPY

16.1 If bleeding occurs on heparin, it may be sufficient to merely withdraw the heparin.

If rapid reversal of required, please refer to section 3.3 Heparin toxicity of the BNF 76 (2018/19) for the correct use of protamine sulphate for unfractionated and low molecular weight heparins. The maximum recommended dose is 50mg.

16.2 The efficacy of protamine in reversing the effects of LMWHs can be unpredictable, especially due to their prolonged half-life. This should be considered when using protamine in this situation.

17. PLAN FOR DISCHARGE AND SUBSEQUENT MONITORING

17.1 Patients are frequently discharged from hospital with inadequate communication to the GP or other receiving wards regarding their anticoagulation.

17.2 Upon discharge, a competent member of staff should re-iterate verbal advice regarding anticoagulation therapy and monitoring to the patient and answer any queries the patient may have.

17.3 A check should be undertaken to ensure all the documents detailed in Section 5.2 are fully completed, and that the patient has all of these in their possession.

17.4 The clinician who will be monitoring the next phase of anticoagulation (usually the GP) should be contacted to inform them of the initiation of anticoagulation.

17.5 The discharge letter should be completed detailing the indication and duration of therapy. If the patient is on Warfarin the target INR and recommended monitoring instructions. Additional documentation of any special circumstances or identified concerns regarding therapy should also be made clear. The standard CDM template for discharging patients commenced on anticoagulation is recommended for this correspondence. This should be sent to the GP at the time of discharge, and the patient should also retain a copy. If possible a copy of the anticoagulant prescription chart should also be sent to the patient's GP.

17.6 Near to or at the time of discharge, a member of staff should ensure that the patient is fully informed about the anticoagulant treatment, that doses (and INR results) have been transcribed in the patient record, that all accompanying information is in the patient's possession, and that the discharge letter contains the necessary information for the GP to safely monitor the anticoagulation (see Sections 17.4 and section 17.5).

17.7 A small number of patients may require "dosette boxes" prepared by pharmacy. Pharmacy requires 24 hours' notice for preparation of these. Note – Warfarin and Dabigatran can't be placed in dosette boxes.

17.8 Pharmacy will dispense dalteparin at discharge for courses up to 28 days.

18. TRAINING AND EDUCATION OF STAFF INITIATING ANTICOAGULATION

18.1 It is essential that all staff caring for patients on anticoagulant therapy are skilled in the necessary competencies. Staff with training deficiencies must attend the necessary educational sessions before contributing to the initiation or monitoring of therapy. All staff involved in anticoagulation prescription, administration and monitoring should complete the e-learning modules available on the NPSA, British Journal of Cardiology and BMJ websites and retain the printable certificate for their personal portfolios:

- VTE Module available on ESR
- http://www.npsa.nhs.uk/health/alerts

- http://new-learning.bmjknowledge.org/learning/user/login.html
- https://bjcardio.co.uk/2016/02/revised-anticoagulation-module-4-clinical-aspects-of-anticoagulation/

18.2 Staff unsure of the appropriate action when prescribing or administering anticoagulant therapy should seek senior advice and consider their training requirements immediately.

19. ARCHIVING ARRANGEMENTS

The original of this policy will remain with the author. An electronic copy will be maintained on the Trust Intranet Hub. Archived electronic copies will be stored on the Trust's [redacted] and will be held indefinitely.

20. PROCESS FOR MONITORING COMPLIANCE WITH AND EFFECTIVENESS OF THE POLICY

20.1 To evidence compliance with this policy, the following elements will be monitored:

What areas need to be monitored?	How will this be evidenced?	Where will this be reported and by whom?
Compliance with NICE guidance standards	Baseline assessment tool (BAT) for NICE Guidance CG180: Atrial fibrillation: Management (2014)	Divisional Governance Group and to CEC by exception

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32. B Mullins et al., Should surgery be delayed in patients taking direct oral anticoagulants who suffer a hip fracture? A retrospective, case-controlled observational study at a UK major trauma centre. BMJ Open, 2018;8: e020625

APPENDIX 1: PHARMACOLOGY OF DOACS

	Warfarin	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
Class	Vitamin K antagonist (reduces factors II, VII, IX and X)	Direct oral anti-thrombin	Oral anti-Xa	Oral anti-Xa	Oral anti-Xa
Bioavailability	>95%	~6%	>50%	>80%	60%
Tmax	Variable but requires alternative additional anticoagulant until INR therapeutic for 2 days if immediate anticoagulation is required	2 hours	1-3 hours	2.5-4 hours	1.5 hours
Half-life	35-45 hours	12-17 hours	8-15 hours	5-9 hours	10-14 hours
Renal clearance	0%	80% (contra- indicated with GFR<30mls/min, consider dose reduction to 110mg bd in those patient with GFR 30- 50mls/min and increased bleeding risk)	25% (contra- indicated with GFR<15mls/min, use with caution 15-30mls/min, for atrial fibrillation dose reduce to 2.5mg/day in patients with creatinine >133mmol/L)	66% (contra- indicated with GFR<15mls/min, use with caution 15-30mls/min)	33% (contra-indicated with GFR<15mls/min, use with caution 15-50mls/min with dose reduction to 30mg od)
Protein binding	99%	35%	87%	>90%	10-59%
Drug interactions	Multiple - any drug that affects the CYP2C9, 3A4, 1A2 enzymes*, alcohol or things that affect vitamin K (antibiotics and foods)	P-gp inhibitors* PPI	Potent CYP3A4 inhibitors* P-gp inh bitors*	Potent CYP3A4 inhibitors* P-gp inh bitors*	Potent CYP3A4 inhibitors* P-gp inh bitors*
Monitoring of anticoagulant effect	INR	Has some effect on the APTT, if prolonged patient likely to be anticoagulated, if normal cannot exclude residual anticoagulant activity. Laboratory likely to be able to measure effect by late 2016.	Has some effect on the PT, if prolonged patient l kely to be anticoagulated, if normal cannot exclude residual anticoagulant activity. Laboratory l kely to be able to measure effect by late 2016.	Has some effect on the PT, if prolonged patient likely to be anticoagulated, if normal cannot exclude residual anticoagulant activity. Laboratory likely to be able to measure effect by late 2016.	Has a linear effect on both the PT and APTT but interpretation unclear.
Licensed	Multiple	NVAF VTE prevention following hip or knee replacement Treatment of VTE	NVAF VTE prevention following hip or knee replacement Treatment of VTE	NVAF VTE prevention following hip or knee replacement Treatment of VTE	NVAF Treatment of VTE
Daily cost (BNF)	£0.03-0.18 per day but does not include cost of monitoring. NHS average of £25 per INR clinic visit.	£2.20 per day	£2.19 per day	£2.10 per day	£2.10 per day

APPENDIX 2: SUMMARY OF EVIDENCE SURROUNDING DOACS

	Apixaban				Dabigatran			Rivaroxaban		Edoxaban		
Trial	ARISTOTLE		AVERROES		RE-LY			ROCKET		ENGAGE AF-TIMI 48		
Groups	Apixaban	Warfarin	Apixaban	Aspirin	Dabigatran	Dabigatran	Warfarin	Rivaroxaban	Warfarin	Edoxaban		Warfarin
Dose	5mg bd	As per NR	5mg bd	81- 324mg	110mg bd	150mg bd	As per INR	20mg od	As per INR	60mg	30mg	As per INR
Numbers	9088	9052	2808	2791	6015	6076	6022	7131	7133	7035	7034	7036
Stroke or embolism	1.27%*	1.60%	1 6%*	3.7%	1.53%	1.11%*	1 69%	1.7%	2 2%	1.18%*	1.61	1.5%
NNT	307		47			169				132		
Major bleeding	2.13%*	3.09%	1.4%	1.2%	2.71%*	3.11%	3 36%	3 6%	3.4%	2.75%*	1.61%*	3.43%
NNT	104				148					57	23	
Clinically relevant non- major bleeding	1.94%*	2.92%	3.1%	2.7%				11.8%	11.4%	6 60%*	8.67%*	10.15%
NNT	102									25	11	
Minor Bleeding			6 3%	5.0%	13.16%	14.84%	16.37%			4.12%*	3.52%*	4.89%
NNT										52	32	
Death	3.52%*	3.94%	3 5%	4.4%	3.75%	3 64%	4.13%	4 5%	4 9%	3 99%	3.80%	4.35%
NNT	238											

Percentages are yearly rates. *denotes statistically significant difference when compared to the warfarin control group. NNT – number needed to treat to prevent an event, calculated when there is a significant difference from warfarin.

RE-LY – Dabigatran versus Warfarin in Patients with Atrial Fibrillation. NEJM 361:1139-1151.
http://www.nejm.org/doi/pdf/10.1056/NEJMoa0905561
AMPLIFY - Oral Apixaban for the Treatment of Acute Venous Thromboembolism. NEJM 369:799-808.
http://www.nejm.org/doi/pdf/10.1056/NEJMoa1302507
ARISTOTLE – Apixaban versus Warfarin in Patients with Atrial Fibrillation. NEJM 365:981-992
http://www.nejm.org/doi/pdf/10.1056/NEJMoa1107039
AVERROES – Apixaban in Patients with Atrial Fibrillation. NEJM 364:806-817
http://www.nejm.org/doi/pdf/10.1056/NEJMoa1007432
ROCKET-AF – Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. NEJM 365:883-891
http://www.nejm.org/doi/pdf/10.1056/NEJMoa1009638
ENGAGE AF-TIMI 48 – Edoxaban versus Warfarin in Patients with Atrial Fibrillation NEJM 369:2093-2104
http://www.nejm.org/doi/full/10.1056/NEJMoa1310907#t=article

Four trials Compared LMWH/Warfarin with the DOACS in initial treatment of DVT/ PTE.

	Apixaban		Rivaroxaban		Edoxaban		Dabigatran	
Trial	AMPL FY		EINSTE N		HOKUSAI-VTE		RE-COVER	
Groups	Apixaban	Enoxaparin then warfarin	Rivaroxaban	Enoxaparin then warfarin	Edoxaban	Warfarin	Dabigatran	Warfarin
Dose	10mg bd for 7 days then 5mg bd for 6 months	1mg/kg bd enoxaparin for 5 days then warfarin as per INR for 6 months	15mg bd for 3 weeks then 20mg od for either 3, 6 or 12 months, average 7.7 months	1mg/kg bd enoxaparin for 5 days then warfarin as per NR for either 3, 6 or 12 months average 7.7 months	Initially 'treatment' dose heparin for 5 days then Edoxaban 60mg or 30mg for 3-12 months	Initially 'treatment' dose heparin for 5 days then warfarin as per NR for 3-12 months	Initially 'treatment' dose heparin for 5 days then dabigatran 150mg bd for 6 months	Initially 'treatment' dose heparin for 5 days then warfarin as per INR for 6 months
Numbers	2691	2704	4151	4131	4118	4122	1273	1266
Recurrent VTE	2 3%*	2.7%	2.1%	2 3%	3 2%	3.5%	2.4%	2.1%
NNT	237							
Major bleeding	0 6%*	1.8%	1 0%*	1.7%	1.4%	1.6%	1 6%	1.9%
NNT	48		49					
Clinically relevant non-major bleeding	3 8%*	8.0%	8 5%	8 6%	7 2%*	8.9%	4 0%*	6.9%
NNT	24				50		34	
Minor Bleeding								
NNT								
All bleeding	15.5%*	25 8%			21.7%*	25 6%	16.1%*	21 9%
NNT	10				33		17	
Death	1 5%	1.9%	2 3%	2.4%	0 6%	0.6%	1 6%	1.9%

*denotes statistically significant difference when compared to the warfarin control group. NNT – number needed to treat to prevent an event, calculated when there is a significant difference.

Extended VTE

	Apixaban			Rivaroxaban	
Trial	AMPLIFY-EXT			E NSTEIN	
Groups	Apixaban	Apixaban	Placebo	Rivaroxaban	Placebo
Dose	5mg bd for 1 year	2.5mg bd for 1 year	Placebo for 1 year	20mg od for 6-12 months	Placebo for 6-12 months
Numbers	815	842	829	602	595
Recurrent VTE	4 2%*	3.8%*	11.6%	1.3%*	7.1%
NNT	13	13		17	
Major bleeding	0.1%	0.2%	0 5%	0.7%	0%
NNT					
Clinically relevant non-major bleeding	4 2%	3.0%	2 3%	5.4%	1 2%†
NNH				24	
Death				0.2%	0 3%

* denotes statistically significant difference when compared to the placebo control group where DOAC is superior. NNT – number needed to treat to prevent an event, calculated when there is a significant difference. †denotes statistically significant difference when compared to the placebo control group where placebo is superior. NNH – number needed to harm, calculated when placebo is superior to DOAC.

AMPLIFY - Oral Apixaban for the Treatment of Acute Venous Thromboembolism. NEJM 369:799-808. http://www.nejm.org/doi/pdf/10.1056/NEJMoa1302507

EINSTEIN-PE - Oral Rivaroxaban for the treatment of symptomatic pulmonary embolism. NEJM 366:1287-1297. http://www.nejm.org/doi/pdf/10.1056/NEJMoa1113572 EINSTEIN-DVT - Oral Rivaroxaban for the treatment of symptomatic venous thromboembolism. NEJM 363:2499-2510. http://www.nejm.org/doi/pdf/10.1056/NEJMoa1007903
AMPLIFY-EXT - Apixaban for Extended Treatment of Venous Thromboembolism. NEJM 368:699-708. http://www.nejm.org/doi/pdf/10.1056/NEJMoa1207541

HOKUSAI-VTE – Edoxaban versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism. NEJM 369:1406-1415. http://www.nejm.org/doi/full/10.1056/NEJMoa1306638#t=article

APPENDIX 3: ORAL ANTICOAGULANT PRESCRIPTION CHART

Royal Devon and Exeter NHS
NHS Foundation Trust

HIGH RISK MEDICATION

ANTICOAGULANT PRESCRIPTION & ADMINISTRATION CHART

ANTICOAGULANTS MUST ALSO BE PRESCRIBED ON THE MAIN PRESCRIPTION CHART

Hospital: Consultant:
Ward: Date of prescription: DD MM YY

Patient name:
NHS no:
Hospital no:
DOB:
Attix Patient ID Label

INITIATION OF ORAL ANTICOAGULATION - Please refer to Trust Guideline on Intranet for full details

1. **Risk assessment of anticoagulation therapy** - the prescriber must perform a full risk-benefit analysis including concordance issues, risk of bleeding (e.g. falls), co-morbidity, contraindications and potential interactions (see page 3), access to monitoring, alcohol intake, current/subsequent pregnancy and baseline monitoring (see point 3 below).

2. **Indication, duration and target INR for oral anticoagulation therapy** - see below and page 3

Oral anticoagulant: (highlight if not warfarin) **Indication(s):** **Duration:** tick appropriate box

Target INR:	Weight (kg):	Previous stable / maintenance dose:	Duration: tick appropriate box			
			6 weeks ☐	3 months ☐		
			6 months ☐	Lifelong ☐		
			Other ☐ - specify _____			

Baseline risk factors for bleeding: if present use lower dose schedules for initiation and regular monitoring

- Age > 80 years ☐
- Baseline INR > 1.4 ☐
- Liver disease/abnormal LFTs ☐
- Likely drug interactions (see page 4) ☐
- Consider full dose dalteparin rather than warfarin for VTE in patients with active malignant disease
- Weight < 60 kg ☐
- Renal impairment ☐
- Active malignancy* ☐
- Previous bleeding disorders ☐

Women of childbearing age: Pregnancy excluded ☐ Conception/contraception advice ☐

Document interacting drugs and other cautions:

3. **Baseline monitoring** - patient weight, INR (& APTR if LFH used), urea & electrolytes, LFTs, Hb and platelets.

4. **Verbal and written communication of information to patient ± carers** - see page 3 and complete below.

Communication/action	Date	Staff completing task	Sign
Risk-benefit discussion with patient/carer	DD MM YY		
Provide patient with information & dosing booklets	DD MM YY		
Complete pages 1-4 of NPSA documentation	DD MM YY		
Provide patient with alert card	DD MM YY		

5. **Prescription of warfarin and concomitant low-molecular weight heparin therapy** - please document which protocol this patient requires and follow the appropriate instructions.
N.B. Prescribe unfractionated heparin/reduced dose dalteparin if severe renal dysfunction (eGFR < 20 ml/min) - see page 4

Warfarin protocol	Please tick	Actions
Patient already on warfarin	☐	Use current dose if INR / condition allows
Patient requiring "rapid induction" of warfarin:	**LMWH should be co-administered in rapid induction**	
- with risk factors for bleeding	☐	Use 5mg warfarin nomogram
- with no high risk factors for bleeding	☐	Use 10mg warfarin nomogram
Patient suitable for "slow induction" of warfarin	☐	See slow induction (page 3)
Patient peri-operative warfarin management	☐	See peri-operative section (page 4)

See page 3 (See 2 Above)

Anticoagulant Prescription & Administration Chart
Approved by: Records Management & D&T Committees 10/05/10
Review date: February 2011

Health Records: Charts and Special Sheets

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Royal Devon and Exeter NHS
NHS FoundationTrust

PRESCRIBING NOTES

Risk-benefit analysis
It is the prescriber's responsibility to ensure that a full risk-benefit assessment is made prior to starting therapy. Please see page 1 and consult product literature and BNF for contraindications and cautions.

Indications, duration and target INRs
Please see page 3 for details.

Information for patients/carers

Verbal information to patient must include:
- A definition and the purpose of anticoagulation.
- The indication and the anticipated duration of treatment.
- That the individual's dose is adjusted to achieve the desired level of anticoagulation.
- That doses are made up of different strength tablets.
- The need for regular blood test monitoring to guide dosing.
- Warfarin is contraindicated in pregnancy (first & third trimesters), and women of childbearing age should avoid falling pregnant & use contraception during warfarin treatment.
- The risk of haemorrhage especially if poorly monitored.
- The need to report excessive bleeding or bruising.
- The need to keep the anticoagulation record safe and up to date with dosage and INR results.
- The need for caution when stopping or starting new drugs or OTC medications.
- The potential interactions with drugs, OTC preparations, alcohol and foodstuffs (e.g. cranberry juice).

Written information to patient must include:
- The NPSA Patient Information Booklet (pharmacy)
- The NPSA Monitoring Booklet

Disease specific information as appropriate.

Interactions to consider (check BNF Appendix 1)

Enhancing warfarin effect (↑INR) include:
Alcohol, anabolic steroids, antidepressants, antidiabetics, allopurinol, amiodarone, most antibiotics (particularly erythromycin, clarithromycin & ciprofloxacin), azole antifungals, aspirin & NSAIDs, clopidogrel, dipyridamole, eritoritib, omeprazole, orlistat, phenytoin, some statins, tamoxifen, thrombolytics, levothyroxine, cranberry & grapefruit juice, smoking cessation, zafirlukast.

Reducing warfarin effect (↓INR) include:
Chronic alcohol use, azathioprine, barbiturates, broccoli and green leafed vegetables, carbamazepine, rifampicin, some herbal remedies eg St John's wort, oral contraceptive pills.

Variable effect on warfarin include:
Alcohol, corticosteroids, nevirapine, ritonavir, thyroid disease.

Highest risk medications - include therefore:
Antibiotics — Anticonvulsants
Analgesics - NSAIDs — Antidepressants
Anticoagulants — Anti-platelet drugs

Perioperative anticoagulation - general points
- Surgery, in which there is a low risk of severe bleeding, can be performed with an INR of <2.5. For surgery where there is a significant risk of bleeding, warfarin should be stopped 5 days prior.
- Where there is a significant risk of perioperative thrombosis, bridging therapy with therapeutic dose dalteparin should start on the second day after warfarin cessation. Consider the use of unfractionated heparin bridging therapy in patients with an e-GFR < 20ml/min.
- If surgery needs expediting and target INR cannot be achieved through warfarin cessation, consider reversing with low-dose vitamin K (see Trust Policy on Warfarin reversal). The timing & speed of re-anticoagulation depends on risk of postoperative bleeding & must be discussed with surgeon.
- Ensure bridging therapy continued until INR therapeutic.

Dalteparin dosing

Dalteparin for DVT/PE
Consider unfractionated heparin in massive DVT/PE

Weight (kg)	Dalteparin Dose (in IUnits)	Weight (kg)	Dalteparin Dose (in IUnits)
< 46	7,500 units SC OD	69-82	15,000 units SC OD
46-56	10,000 units SC OD	≥ 83	18,000 units SC OD
57-68	12,500 units SC OD	Maximum Dose 18,000 units	

- Dalteparin should continue for 5 days & until the INR is in the therapeutic range for 2 consecutive days.
- Do not use multidose vials in pregnant patients

Dalteparin for Acute Coronary Syndromes (guidance)
Use graduated syringe of 10,000 Units/ml ampoule

Weight (kg)	Dalteparin Dose (in IUnits)	Volume
30-33	4,000 units SC BD	0.40 ml
34-37	4,500 units SC BD	0.45 ml
38-41	5,000 units SC BD	0.50 ml
42-45	5,500 units SC BD	0.55 ml
46-50	6,000 units SC BD	0.60 ml
51-54	6,500 units SC BD	0.65 ml
55-58	7,000 units SC BD	0.70 ml
59-62	7,500 units SC BD	0.75 ml
63-66	8,000 units SC BD	0.80 ml
67-70	8,500 units SC BD	0.85 ml
71-75	9,000 units SC BD	0.90 ml
76-79	9,500 units SC BD	0.95 ml
≥ 80	10,000 units SC BD	1.00 ml

- Patients with suspected ACS warranting LMWH should receive dalteparin subcutaneously BD as above for up to 8 days. Maximum dose is 10,000 units SC BD. Patients with ST-elevation MI who are not undergoing primary percutaneous intervention should also receive this dose if appropriate.

Renal failure and monitoring of therapy
When eGFR is < 20ml/min, use half the recommended dose of dalteparin. Doses should also be adjusted based on anti-Factor Xa monitoring in prolonged therapy. Also discuss anti-Xa monitoring with haematologist in patients who are pregnant, have a high bleeding risk or are extremely over/underweight.
N.B. Haemodialysis patients will generally receive Tinzaparin - see renal unit policy for full details.

Further information and references
For full information, see "Anticoagulation Policy" on Trust intranet and the Summary of Product Characteristics for warfarin and low molecular weight heparins.

For details of reversal of anticoagulant therapy, see the "Reversal of Anticoagulation Therapy" guideline on Trust intranet.

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ANTICOAGULANT PRESCRIPTION

Prescribing information for warfarin is on pages 3 and 4
Dalteparin dosing is described on page 4

Patient name: ....
NHS no: ....
Hospital no: ....
DOB: ....
Affix Patient ID Label

DALTEPARIN	*				WARFARIN	*			
* If other anticoagulants are used, delete "DALTEPARIN" or "WARFARIN" and write new drug name clearly									
Timing can be 06:00, 10:00, 12:00, 18:00, 22:00 or 24:00					Dose is generally given at 18:00				
Date	Prescription		Administration		INR Result	Prescription		Administration	
	Dose / Time	Name / Sign	Time Given	Name / Sign		Dose	Name / Sign	Time Given	Name / Sign
All oral or parenteral anticoagulants must also be prescribed on the main prescription chart. Please do not use this chart for unfractionated heparin									
DD MM YY	units HH:MM		HH:MM		Daily INRs Recommended	mg		HH:MM	
DD MM YY	units HH:MM		HH:MM			mg		HH:MM	
DD MM YY	units HH:MM		HH:MM			mg		HH:MM	
DD MM YY	units HH:MM		HH:MM			mg		HH:MM	
DD MM YY	units HH:MM		HH:MM			mg		HH:MM	
DD MM YY	units HH:MM		HH:MM			mg		HH:MM	
DD MM YY	units HH:MM		HH:MM			mg		HH:MM	
DD MM YY	units HH:MM		HH:MM			mg		HH:MM	
DD MM YY	units HH:MM		HH:MM			mg		HH:MM	
DD MM YY	units HH:MM		HH:MM			mg		HH:MM	
DD MM YY	units HH:MM		HH:MM			mg		HH:MM	
DD MM YY	units HH:MM		HH:MM			mg		HH:MM	

DISCHARGE PLAN - It is essential that the patient's GP receives full details of the anticoagulant treatment.
Please ensure every section is complete and actioned.

Discharge Dose:	Next INR Check Please:	Information to Patient:	Name:
Target INR:	Anticoagulant Supplied:	Verbal Explanation Yes / No NPSA Yellow Book Yes / No NPSA Monitoring Book Yes / No	Sign:

Please send a copy of this dosage chart to the patient's General Practice on discharge from hospital.

Copied / Faxed to:	Date & Time: DD MM YY HH:MM	Name of Staff Member:	Sign:

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PRESCRIBING NOTES

Royal Devon and Exeter **NHS**
NHS Foundation Trust

Indications, duration and target INRs:

Clinical indications for oral anticoagulation and target INR values		
Indication	**Target INR**	**Duration**
DVT Prophylaxis inc. surgery in high risk patients	2.0 – 2.5	Until Mobile
Proximal deep vein thrombosis or pulmonary embolus	2.5	3-6 months
Calf vein thrombus (post-operative or post-partum)	2.5	6 weeks
Calf vein thrombus	2.5	3 months
Recurrent VTE when no longer on warfarin therapy	2.5	Long term
Recurrent VTE while on warfarin therapy	3.5	Long term
Symptomatic inherited thrombophilia	2.5	Long term
Antiphospholipid syndrome	2.5	Long term
Non-rheumatic atrial fibrillation	2.5	Long term
AF 2º to rheumatic or congenital heart disease, and thyrotoxicosis	2.5	Long term / Seek Advice
Cardioversion	2.5 or 3.0	Seek Advice
Mural thrombus	2.5	Seek Advice
Cardiomyopathy	2.5	Long term
Mechanical prosthetic heart valve: aortic	3.0 or 2.5	Long term
Mechanical prosthetic heart valve: mitral	3.5 or 3.0	Long term
Bioprosthetic valve	2.5 if anticoagulated	Long term
N.B. Guidance only. Targets and durations should be determined based on individual cases		

Warfarin loading schedules - use only for initiation of warfarin, not for maintenance dose adjustments

Dosing schedules for initiation of warfarin - PLEASE USE CORRECT NOMOGRAM				
Day	**INR (am)**	**Lower dose rapid induction (5 mg)** Risk factors for bleeding	**Higher dose rapid induction (10 mg)** NO risk factors for bleeding	**Slow Induction** (See below for details) Only for low risk AF
1	< 1.4	5 mg	10 mg	2 mg
	>1.4	Seek senior ± haematology advice if baseline INR > 1.4		
2	< 1.8	5 mg	10 mg	Patients with low risk atrial fibrillation who do not need rapid anticoagulation can be prescribed 2 mg of warfarin per day usually without heparin. INR should be checked after 1 week. This method is ideal for patients being discharged, but clear instructions must be given to patient and GP. If slow induction appropriate, it may be preferable to ask the GP to initiate the whole process as an outpatient. Slow induction is not suitable for patients who: -need rapid anticoagulation -are unstable or ill -are at high risk of bleeding -have significant co-morbidity or interacting drugs. See anticoagulation policy for further details.
	1.8	1 mg	1 mg	
	Above 1.8	Omit dose	Omit dose	
3	< 2.0	5 mg	10 mg	
	2.0 - 2.5	2 mg	4 mg	
	2.6 - 3.0	2 mg	3 mg	
	3.1 - 3.4	1 mg	2 mg	
	3.5 - 4.0	1 mg	1 mg	
	Above 4.0	Omit dose	Omit dose	
4	< 1.4	Seek senior ± haematology advice		
	1.4	4	8	
	1.5 - 1.7	4	7	
	1.8 - 2.0	3	6	
	2.1 - 2.6	3	5	
	2.7 - 3.0	2	4	
	3.1 - 3.5	2	3	
	3.6 - 4.0	1	2	
	Above 4.0	Omit dose	Omit dose	

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APPENDIX 4: UNFRACTIONED HEPARIN INFUSION CHART

PRESCRIBING NOTES

1. **Pre-infusion:** baseline **APTR**, Hb, potassium, renal function and platelet count - and see monitoring section below.

2. **Loading dose:** using baseline APTR, decide on loading dose using Table 1.

Table 1: Loading dose of unfractionated heparin

Baseline APTR	Prescribing Advice
< 1.5	Loading dose of 75 units/kg (to nearest 100 units)
1.5 - 2.5	Start heparin infusion using weight nomogram **without** loading dose
> 2.5	Review need for heparin /discuss with seniors/haematologist
Max Loading dose 5000 units (10,000 units in massive PE)	

Table 2: Initial infusion rates (MAX 1.8 ml/hr)

Weight (kg)	Heparin rate (ml/hr)	Weight (kg)	Heparin rate (ml/hr)
35 - 39	0.6	70 - 74	1.3
40 - 44	0.7	75 - 79	1.4
45 - 49	0.8	80 - 84	1.4
50 - 54	0.9	85 - 89	1.5
55 - 59	1.0	90 - 94	1.6
60 - 64	1.1	95 - 99	1.7
65 - 69	1.2	Above 100	1.8

3. **Initial infusion rate:** decide using the weight nomogram (Table 2).
   - Draw up 20mls of Heparin (1,000 Units in 1ml - e.g. PumpHep) in a syringe which makes 20,000 units (1,000 units/ml)
   - Start infusion based on patient's weight to the nearest 5kg using the weight nomogram above (Table 2) - max 1.8 ml/hour

4. **Infusion rate adjustments:** please see Table 3 below for full details.

   A baseline APTR should always be sent before prescribing unfractionated heparin. The next APTR should be sent 4 hours after the infusion starts, and 4 hours after any changes to the infusion rate. Excess bleeding should also prompt a repeat APTR and the stopping of the infusion. Once stable, the APTR should be checked every 24 hours.

Table 3: Infusion rate adjustments based on APTR

APTR	Rate adjustments for unfractionated heparin infusions		Timing of next APTR measurement
	Patient weight less than 70kg	Patient weight 70kg or more	
Below 1.20	75 units/kg Bolus Increase rate by 0.2 ml/hr	75 units/kg Bolus Increase rate by 0.3 ml/hr	4 hours
1.20 - 1.49	40 units/kg Bolus Increase rate by 0.1 ml/hr	40 units/kg Bolus Increase rate by 0.2 ml/hr	
1.50 - 2.50	NO CHANGE		24 hours
2.51 - 3.00	Reduce rate by 0.1 ml/hr	Reduce rate by 0.1 ml/hr	4 hours
3.01 - 4.00	**STOP INFUSION FOR 1 HOUR** Reduce rate by 0.1 ml/hr	**STOP INFUSION FOR 1 HOUR** Reduce rate by 0.2 ml/hr	
Above 4.00	**STOP INFUSION FOR 2 HOURS** Recheck APTR Recommence infusion once APTR in target range. Reduce rate by 0.2 ml/hr	**STOP INFUSION FOR 2 HOURS** Recheck APTR Recommence infusion once APTR in target range. Reduce rate by 0.3 ml/hr	2 hourly until APTR is less than 4.00

Additional boluses should be prescribed on the infusion chart on a seperate row prior to the new infusion rate.

5. **Monitoring:** please see Table 3 above.

   Platelets: baseline level and then daily monitoring. If platelets fall greater than 50% or unexplained additional thrombosis, discuss with Consultant Haematologist immediately to assess risk of heparin induced thrombocytopenia (HIT).

   Potassium: baseline level plus twice weekly whilst on treatment. Risk of hyperkalaemia if diabetes mellitus, chronic renal failure, pre-existing metabolic acidosis or potassium sparing drugs.

6. **Reversal of unfractionated heparin:** please see BNF section 2.8.3 for up-to-date information.
   - If bleeding occurs, stopping the infusion may be sufficient. UH has a half life of 60 minutes in therapeutic range.
   - If rapid reversal required, consider protamine sulphate.
   - Refer to the British National Formulary (section 2.8.3) for most up to date guidance on protamine use.
   - 1mg of protamine reverses 100 Units heparin. Give slowly with maximum dose 50mg.
   - Risk of allergic reactions if fish allergy, post vasectomy, or previous treatment with protamine insulin.

7. **Perioperative use of unfractionated heparin:** see Trust "Anticoagulation Policy" on intranet for full details.

   The use of unfractionated heparin should be considered in the perioperative period when warfarin bridging therapy is required in patients with an e-GFR < 20ml/min or when rapidly reversible anticoagulation is required.
   - Stop warfarin 5 days pre-operatively.
   - Start UH when the INR less than 2.0 and monitor UH as above.
   - Stop the UH 4-6 hours pre-operatively and re-institute 6 – 12 hours post-operatively when the risk of bleeding has diminished.
   - Consider switching to treatment dose LMWH if appropriate.

   Restart warfarin as soon as possible and continue bridging therapy until INR is therapeutic for two consecutive days.

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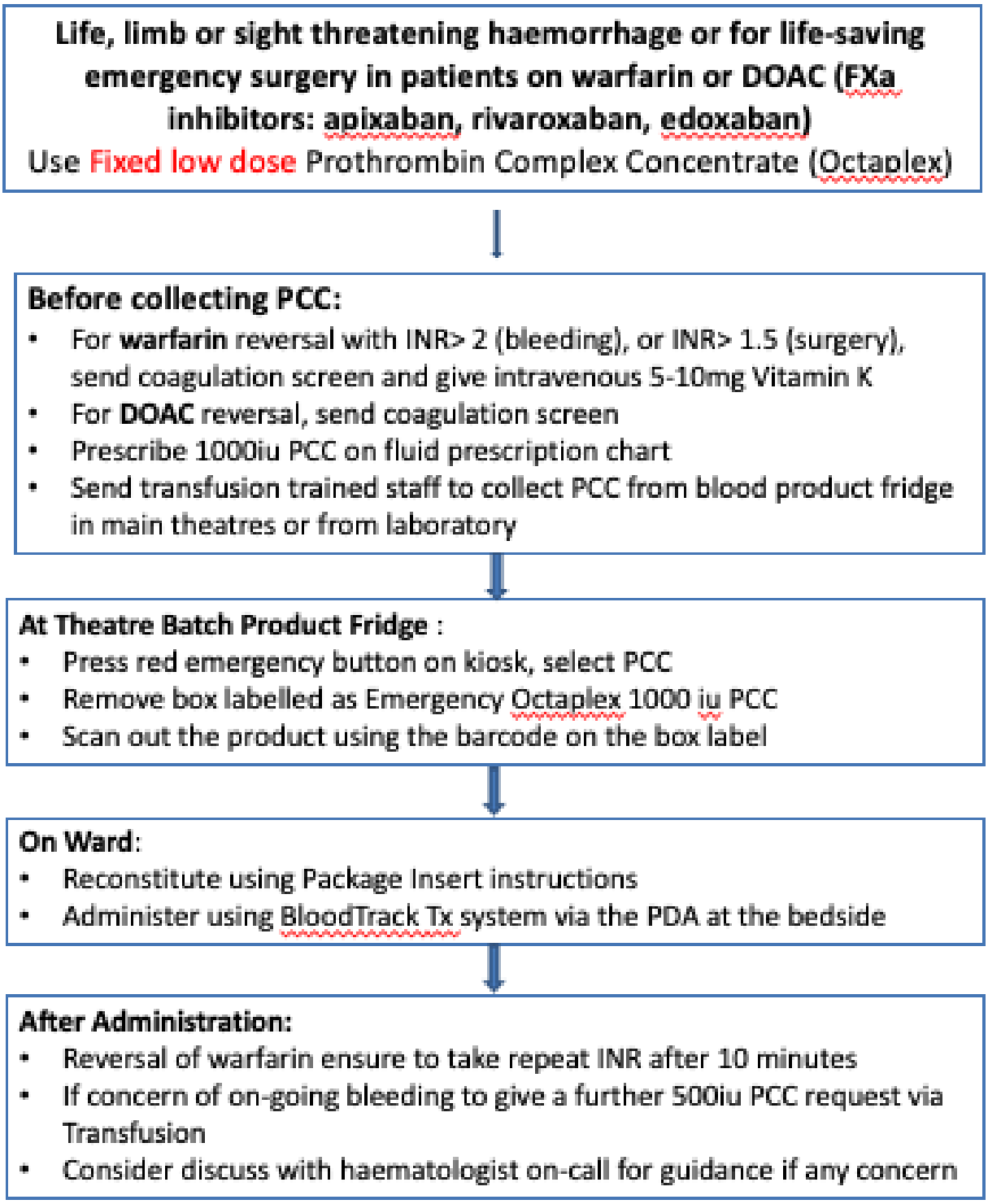
APPENDIX 5: TESTS INVOLVED IN THE MONITORING OF DOACS

Table 1 Characteristics of coagulation tests for estimating plasma concentrations of direct oral anticoagulants or their relative intensity of anti-coagulation*

Drugs	Laboratory tests	Utility/interpretation	Availability	Dependence of the reagent
Dabigatran	APTT*	Interpretation: Normal APTT excludes above on-therapy dabigatran levels but does not exclude the presence of dabigatran in the on-therapy range	24/7, all laboratories	Yes
	TT	Interpretation: Normal TT excludes the presence of dabigatran. A prolonged TT could suggest either the presence of clinically relevant or trivial levels of dabigatran.	24/7, all laboratories	Yes
	dTT	Interpretation: Based on plasma concentration estimation in relation to the clinical context. Note: Some methodologies (i.e. the Hemoclot Thrombin Inhibitors (HTI)) require specific calibrators for plasma concentrations < 50 ng mL^{-1}	Can be implemented with all coagulometers	No
	ECA	Interpretation: Based on plasma concentration estimation in relation to the clinical context	Can be implemented with all coagulometers	No
Rivaroxaban (Edoxaban)	PT*	Interpretation: Rivaroxaban: normal PT (with sensitive reagents) excludes above on-therapy rivaroxaban levels but does not exclude the presence of rivaroxaban in the on-therapy range. Edoxaban: normal PT (with sensitive reagents) would exclude above on-therapy edoxaban levels at peak but would not exclude the presence of above on-therapy edoxaban at trough.	24/7, all laboratories	Yes
Rivaroxaban Apixaban Edoxaban	Chromogenic anti-Xa assays*	Interpretation: Based on plasma concentration estimation in relation to the clinical context. Note: Some methodologies (i.e. the Biophen Direct Factor Xa Inhibitors (DiXaI)) require specific calibrators for plasma concentrations < 30–50 ng mL^{-1}. Note: If near to the LOQ, heparin or LMWH-calibrated chromogenic anti-Xa assays can be used to rule out the presence of clinically relevant direct FXa inhibitors.	Can be implemented with all coagulometers	No
Dabigatran Rivaroxaban Apixaban Edoxaban	LC-MS/MS	Interpretation: Based on plasma concentration estimation in relation to the clinical context	Requires trained staff; only in specialized laboratories	Not applicable
	dRVV-T (DRVV-DOAC)*	Interpretation: Normal dRVV result can exclude DOAC concentrations > 50 ng mL^{-1}.	Can be implemented with all coagulometers	Yes, but < than PT or APTT

APTT, activated partial thromboplastin time; dRVVT, diluted Russell's viper venom time; dTT, dilute thrombin time; ECA, ecarin chromogenic assay; ECT, ecarin clotting time; HPLC-MS/MS, high-performance liquid chromatography–tandem mass spectrometry; LOD, limit of detection; LOQ, limit of quantitation; PT, prothrombin time; TT, thrombin time. *None of these tests are able to discriminate between therapies. Thrombin-specific tests can easily identify dabigatran because it is the only direct oral thrombin inhibitor, but also other direct thrombin inhibitors such as argatroban or hirudin can influence them. For direct factor (F) Xa inhibitors, only the Biophen® Direct Factor Xa Inhibitor assay can discriminate between heparins and direct FXa inhibitors but cannot differentiate between direct FXa inhibitors. Mass spectrometry is the only technique able to directly discriminate between therapies.

APPENDIX 6: USE OF PROTHROMBIN COMPLEX CONCENTRATE



APPENDIX 7: HIP FRACTURE PATIENTS ON DIRECT ORAL ANTICOAGULANTS

Hip Fracture Patients on Direct Oral Anticoagulants (DOACs)

DOAC: Indication: Completed by:

1. STOP the anticoagulant □
2. Date & time of last dose: ___ /___ /_____ @ ___:____ □
3. Hydration: oral fluids + slow IV fluids □
4. Blood tests: FBC/U&E/renal profile (eGFR= ____ ml/min) □
5. Transfusion: 2x valid group and saves □
6. Establish minimum time to surgery: _____ hrs □

GA is preferable if time to surgery is < 120 hours (5 days)

APIXABAN / RIVAROXABAN / EDOXABAN:

Time to surgery depends less on RENAL FUNCTION
(circle if applicable)

GFR ≥ 30 (circle if applicable):
- Surgery **>24 hrs** after last dose
- GA preferable

GFR < 30 (circle if applicable):
- Surgery **>48 hrs** after last dose
- If concern of further delay, consider fixed dose PCC and discuss with haematology

DABIGATRAN:

Time to surgery depends on RENAL FUNCTION
(circle if applicable)

GFR ≥ 80 (circle if applicable):
- **Surgery >24 hours last dose**
- Check Thrombin time (TT)

If normal, proceed for surgery
If prolonged, delay surgery

GFR < 80 (circle if applicable):
- Surgery ≥ **36 hours last dose**
- Check Thrombin Time (TT)

If normal, proceed for surgery
If prolonged, delay surgery

- Recheck Thrombin Time (TT) every 12 hours until it normalises then proceed to surgery
- If concern of further delay, consider Idarucizumab (reversal agent) and discuss with haematology

7. PRE-OPERATIVE VENOUS THROMBOEMBOLIC RISK ASSESSMENT: □

- No pharmacological thromboprophylaxis required whilst waiting for effects of DOAC to wear off
- If considerable delay > 72 hours then prophylactic dose LMWH recommended
- Intermittent pneumatic compression recommended

8. POST-OPERATIVELY (unless specified in post-op instructions or by haematology):

Prophylactic dose LMWH, starting 6 hours after surgery and then daily until restart usual dose DOAC on day 3

APPENDIX 8: COMMUNICATION PLAN

COMMUNICATION PLAN

The following action plan will be enacted once the document has gone live.

Staff groups that need to have knowledge of the policy	All clinical departments as anticoagulation has a wide reach into all specialties
The key changes if a revised policy	Anticoagulation is a fast evolving field that effects everyone's practice and this policy brings together the latest evidence and guidance. There are significant updates on the choice, administration and guidance around the use of anticoagulation. This Policy now includes guidance around anticoagulation reversal. **Feb 2020**: Incorporation of Clinical Guideline on Management of patients receiving long-term oral anticoagulants for elective surgery/procedures.
The key objectives	This policy provides clinical guidance on prescribing, administering and reversing anticoagulation in different clinical situations and reflects best practice evidence
How new staff will be made aware of the policy and manager action	Policy summary and link will be emailed to clinical leads. Must read on Hub
Specific Issues to be raised with staff	• AF – Guidance for anticoagulation with recommendation of Warfarin or Apixaban for both primary and secondary stroke prevention • VTE – Guidance for anticoagulation with recommendation of Warfarin or Apixaban • Use of DOACs in Cancer Associated Thrombosis including Rivaroxaban and Edoxaban • Use of Fondaparinux in ACS replacing dalteparin • Reversal of Anticoagulation including DOACs and how to rapidly access resources • Updated Periprocedural policy
Training available to staff	There are specific links within the policy on training
Any other requirements	None
Issues following Equality Impact Assessment (if any)	Nil
Location of hard / electronic copy of the document etc.	The original of this policy will remain with the author. An electronic copy will be maintained on the Trust Intranet Hub. Archived electronic copies will be stored on the Trust's "archived policies" shared drive, and will be held indefinitely.

APPENDIX 9: EQUALITY IMPACT ASSESSMENT TOOL

Name of document	Anticoagulation and Reversal of Anticoagulation Therapy Policy
Division/Directorate and service area	Medicine/Haematology
Name, job title and contact details of person completing the assessment	[redacted] Consultant and [redacted], Consultant Haematologist
Date completed:	14/03/19

The purpose of this tool is to:

- **identify** the equality issues related to a policy, procedure or strategy
- **summarise the work done** during the development of the document to reduce negative impacts or to maximise benefit
- **highlight unresolved issues** with the policy/procedure/strategy which cannot be removed but which will be monitored, and set out how this will be done.

1. What is the main purpose of this document?

To advise clinicians on the appropriate use and indication of anticoagulation and to provide guidance on its reversal.

2. Who does it mainly affect? *(Please insert an "x" as appropriate:)*

Carers ☐ Staff ☐ Patients ☒ Other (please specify)

3. Who might the policy have a 'differential' effect on, considering the "protected characteristics" below? (By *differential* we mean, for example that a policy may have a noticeably more positive or negative impact on a particular group e.g. it may be more beneficial for women than for men)

Please insert an "x" in the appropriate box *(x)*

Protected characteristic	Relevant	Not relevant
Age	☐	☒
Disability	☐	☒
Sex - *including: Transgender, and Pregnancy / Maternity*	☐	☒
Race	☐	☒
Religion / belief	☐	☒
Sexual orientation – *including: Marriage / Civil Partnership*	☐	☒

4. Apart from those with protected characteristics, which other groups in society might this document be particularly relevant to… (e.g. those affected by homelessness, bariatric patients, end of life patients, those with carers etc.)?

n/a

5. Do you think the document meets our human rights obligations? ☒

Feel free to expand on any human rights considerations in question 6 below.

A quick guide to human rights:
• ***Fairness*** *– how have you made sure it treat everyone justly?* • ***Respect*** *– how have you made sure it respects everyone as a person?* • ***Equality*** *– how does it give everyone an equal chance to get whatever it is offering?* • ***Dignity*** *– have you made sure it treats everyone with dignity?* • ***Autonomy*** *– Does it enable people to make decisions for themselves?*

6. Looking back at questions 3, 4 and 5, can you summarise what has been done during the production of this document and your consultation process to support our equality / human rights / inclusion commitments?

There are no concerns that this would adversely affect any patient group or affect their human rights.

7. If you have noted any 'missed opportunities', or perhaps noted that there remains some concern about a potentially negative impact please note this below and how this will be monitored/addressed.

"Protected characteristic":	N/A
Issue:	
How is this going to be monitored/ addressed in the future:	
Group that will be responsible for ensuring this carried out:	