University Hospitals Dorset
NHS Foundation Trust

ANTICOAGULATION GUIDELINES

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Approval Committee	Version	Issue Date	Review Date	Document Author
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D&TC	4	July 2012	July 2015	Kareena Marotta, Jason Mainwaring
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Version Control

Version	Date	Author	Section	Principle Amendment Changes
4	July 2012	Kareena Marotta, Jason Mainwaring	6.3	Changed Enoxaparin to Dalteparin
5	Sept 2014	Moe Visram Stephen Fleck Alison Fitzpatrick	App 2 3 6.3 6.4 6.5	Removed as no longer applicable Updated Options for Muslim patients Addition of Fondaparinux Addition of DOACS
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				options in renal impairment
			6.5	Changed continuation time to 72 hours
			6.5.1.2	For DOAC patients, monitor weight regularly if at risk of fluctuating weight
			6.5.1.8	Addition of '5 days of treatment dose low molecular weight heparin will be required prior to starting Dabigatran in cases of VTE or PE'
			6.5.3.2	Dose changed from 5mgs to 5g Rivaroxaban 10mgs OD for thrombophlebitis
			6.5.5.2	Addition of '5 days of treatment dose low molecular weight heparin will be required prior to starting Dabigatran in cases of VTE or PE'
			7.0	INR > changed to INR <1.8
			8.0	Dosing Table of Dalteparin medium risk
			8.4.3	Bridging DOACS
11	March 2020	Hayley Flavell Faye Thornton Tracy Sandell Jason Mainwaring	1.	Hyperlink to Guideline for Thromboprophylaxis and Management of VTE in Pregnancy inserted
			5.6.	New subsection: Needle phobic patients
			6.1.14	Fax referrals changed to email addresses
			6.3	Info regarding enoxaparin removed
			6.4.6	No pharmacokinetic interaction removed
			6.5	CrCl divided by 10 is a good indication for frequency of monitoring. (www.sps.nhs.uk)
			6.5.2.2	Rivaroxaban taken with food and extended prophylaxis dose added Peripheral Artery Disease (PAD) and Coronary Artery Disease(CAD) dosing
			6.5.3.2	Maximum 6 months removed
			6.5.4.3	Addition of Apixaban dosing for DVT and PE
			8.2.1	Bridging management Edoxaban severe renal impairment and crcl>90 caution

				added.
			10.1.6	Updated link to Octaplex Admin Policy
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12	September 2020	September 2023		Changes from Dalteparin to Enoxaparin(Inhixa®) with addition of dose changes
			1.0	Addition of links to COVID-19 guidelines
			3.3	Stopping anticoagulation
			5.3	Update of contact details
			5.8	Paediatrics
			6.1.14	Change of fax number to email address'
			6.4.4	Addition of CrCl<20ml/min for fondaparinux
			6.5.1.8	Conversion of LMWH to Dabigatran
			6.5.1.9	Cardioversion and catheter ablation
			6.5.2.2	Addition of information regarding loading dose of rivaroxaban
			6.5.2.5	Addition of information on double dosing (as per SPC)
			6.5.2.8	Conversion of LMWH to Rivaroxaban
			6.5.2.9	Cardioversion
			6.5.3.8	Conversion of LMWH to Apixaban
			6.5.3.9	Cardioversion and catheter ablation
			6.5.4.8	Conversion of LMWH to Edoxaban
			6.5.4.9	Cardioversion
			12.1.3	Endoscopy on antiplatelet

ANTICOAGULATION GUIDELINES

Appendix 1 **Prescription Charts:**
Intravenous Heparin Prescription
Oral Anticoagulation Prescriptions
Parenteral Anticoagulation Prescriptions

Appendix 2 Anticoagulant Therapy Record and INR Test Request Form

Appendix 4 **Oral Anticoagulant Therapy – Important Patient Information:**

- Oral Anticoagulant Therapy – Information for Patients (yellow booklet)
- Anticoagulation Alert Card
- Oral Anticoagulant Therapy – Record Book (small yellow booklet)

Appendix 5 Guidelines for Thrombophilia Testing in the Laboratory

Appendix 6 Guidelines for Monitoring, Diagnosing and Managing Heparin-Induced Thrombocytopenia (HIT)

Appendix 7 Decision Aid - Patient Information Leaflet

Appendix 8 DOAC Alert Card

Appendix 9 DOACS - Counselling Checklist

1. Introduction

Anticoagulant drugs are one of the classes of medicines most commonly associated with fatal medication errors.

All staff that prescribe, adjust the dosage, dispense, prepare, administer, monitor and discharge patients on anticoagulant therapy should have adequate training and have acquired the necessary work competences, as part of safe medication practice. All practitioners should have completed both of the BMJ Learning modules on "Starting and maintaining anticoagulants: how to do it", and have completed the NPSA competencies before prescribing anticoagulant drugs. Links to the learning modules can be found on the hospital Intranet under e-learning, anticoagulation. http://rbhintranet/elearning/

It is vital that physicians assess the benefits and risks of anticoagulant therapy for individual patients. This assessment should include the cognitive status of the patient, and should clearly establish whether patients understand the potential hazards of anticoagulant therapy, the need for frequent monitoring by blood tests and the various drug and food interactions of oral anticoagulant drugs.

It is also essential that patients and their carers receive adequate verbal and written information about their treatment. When deciding which oral anticoagulant vitamin K antagonist (VKA) or Direct Oral Anticoagulant (DOAC) the RBCH Decision Aid may be helpful (Appendix 7).

As with warfarin the decision about whether to start treatment with a DOAC should be made after an informed discussion between the prescriber and the patient about the relative risks and benefits of each agent. The DOAC Decision Aid can be used (Appendix 7) The Direct Oral Anticoagulants (DOACs) checklist must be used when initiating a new DOAC (Appendix 9). All patients should be given a DOAC alert card (Appendix 8) and be advised to show it to all health care professionals. These are available from the Anticoagulant Clinic and Pharmacy.

This information should be provided before the first dose of anticoagulant is administered, and reinforced at hospital discharge, at the first Anticoagulation Clinic appointment, and when necessary throughout the course of their treatment. When a patient has verbally consented to take the drug as intended, this should be clearly documented in the patient's health record before anticoagulant therapy is commenced.

See Anticoagulation Prescriptions (parenteral and oral) for in-patients. (Appendix 1) Also displayed on the Intranet http://rbhintranet/elearning/ are movies explaining the use of the oral and parenteral anticoagulation prescriptions and an anticoagulation training workbook for nurses, which include competencies.

This document aims to provide guidelines on prescribing, administration and monitoring of anticoagulant drugs and management of their complications.

For pregnancy VTE treatment and prevention refer to separate guideline: Guideline for Thromboprophylaxis and Management of VTE in Pregnancy

For the VTE prevention in patients with confirmed or suspected COVID-19 infection refer to separate guideline: Thromboprophylaxis in suspected or confirmed COVID-19 infection in adult inpatients, excluding ICU admissions

For Management of confirmed or suspected VTE in confirmed or suspected COVID-19 infections at RBCH refer to separate guideline: Management of Suspected or Confirmed VTE in adult patients with suspected or confirmed COVID-19 infection (excluding patients on CRRT)

For Anticoagulation in ICU patients with confirmed or suspected COVID-19 at RBCH refer to separate guideline: Anticoagulation for adult ICU patients with suspected or confirmed COVID-19 infection

2. Contraindications to Anticoagulant Therapy

- Active bleeding
- Acquired bleeding disorders, e.g. acute liver failure
- Acute stroke – discuss with Stroke Consultant
- Gastro-intestinal bleed during previous 2 weeks
- Intracranial bleed during previous 2-4 weeks
- Head injury in the previous 2 weeks
- Uncontrolled hypertension
- Neurosurgery or spinal surgery in the previous 2-4 weeks
- Pericarditis
- Intra-ocular disease or eye surgery in the previous 2-4 weeks
- Lumbar puncture, epidural or spinal analgesia during previous 6 hours
- Untreated inherited bleeding disorders, e.g. haemophilia
- Thrombocytopenia with platelets $<75 \times 10^9$/L
  - if platelets $<75 \times 10^9$/L then discuss with Haematology Consultant
- Previous heparin-induced thrombocytopenia (for heparins only)
- See additional contra-indications under specific anticoagulant drugs

The thrombotic risk should be considered in each patient and weighed up against bleeding risk.

3. Indications and Duration for Anticoagulation Therapy

Groups of Drugs for Anticoagulants
Vitamin K Antagonist (VKA)
Low molecular weight heparin (LMWH)
Pentasaccharide (Fondaparinux)
Direct oral anticoagulant (DOAC)

Patients requiring long term anticoagulation therapy are normally managed on DOACs or VKAs. Exceptions are Cancer and Pregnancy (section 5).

If anticoagulation treatment is stopped, give advice about the risk of recurrence and provide:

- written information on symptoms and signs to look out for
- direct contact details of a healthcare professional or team with expertise in thrombosis who can discuss any new symptoms or signs, or other concerns
- information about out-of-hours services they can contact when their healthcare team is not available

3.1 Indications for Long-Term Warfarin Therapy (Table 1)

Indication	Target INR	Range
Systemic embolism including Pulmonary Embolus	2.5	2.0 – 3.0
Proximal deep vein thrombosis (DVT)	2.5	2.0 – 3.0
Distal thrombosis with temporary/permanent risk factors	2.5	2.0 – 3.0
Recurrence of venous thromboembolism when no longer on warfarin therapy	2.5	2.0 – 3.0
Recurrence of venous thromboembolism whilst on warfarin therapy with INR > 2.	3.5	3.0 – 4.0
Symptomatic inherited thrombophilia	2.5	2.0 – 3.0
Antiphospholipid syndrome	2.5	2.0 – 3.0
Atrial fibrillation	2.5	2.0 – 3.0
DC Cardioversion/ablation	3.0	2.5 – 3.5
Mural thrombus or akinetic segment	2.5	2.0 – 3.0
Mechanical aortic heart valve	3.0	2.5 – 3.5
Mechanical mitral heart valve	3.5	3.0 – 4.0
Bioprosthetic valve if anticoagulated	2.5	2.0 – 3.0
Aortic Bileaflet	3.0	2.5 – 3.5
Aortic Tilting Disc	3.0	2.5 – 3.5
Mitral Bileaflet	3.5	3.0 – 4.0
Aortic or Mitral Caged Ball 3	3.5	3.0 – 4.0
Ischaemic stroke without atrial fibrillation	Not indicated	
Retinal vessel occlusion	Not indicated	
Arterial grafts if anticoagulated	2.5	2.0 – 3.0
Peripheral arterial thrombosis	Not indicated	
Coronary artery thrombosis if anticoagulated	2.5	2.0 – 3.0
Coronary artery graft	Not indicated	
Coronary angioplasty and stents	Not indicated	
PNH with platelet count >100 x 10^9 / L	2.5	2.0 – 3.0
Dilated Cardiomyopathy	2.5	2.0 – 3.0
Non-CVL related Anticoagulation for 6 months – as for proximal DVT Splanchnic vein thrombosis Budd-Chiari syndrome Mesenteric venous thrombosis Extra hepatic venous thrombosis Gastroenterology and / or Gastrointestinal Surgery Consultant decision Discuss thrombosis risk / anticoagulation with Haematology Consultant	2.5	2.0 – 3.0

Adapted from British Society of Haematology Guidelines, 2011. Guidelines on oral anticoagulation with warfarin – fourth edition.

3.2 Duration of Anticoagulant Therapy (Table 2)

Indication	Duration
Pulmonary embolus	3 months and review Unprovoked – Consider Indefinite
Proximal deep vein thrombosis	3 months and review Unprovoked – Consider Indefinite
Distal deep vein thrombosis	3 months and review Unprovoked – Consider Indefinite
Recurrence of Venous Thromboembolism	Consider Indefinite
Venous Thromboembolism & inherited thrombophilia	3 months and Clinical Review with Haematology Consultant
Antiphospholipid syndrome	Indefinite
Atrial Fibrillation	Indefinite
Cardioversion	3 weeks pre and 4 weeks post then clinical review – Cardiology Consultant
Mural thrombus	3 months then clinical review – Cardiology Consultant
Aortic Mechanical prosthetic heart valve	Indefinite
Mitral Mechanical prosthetic heart valve	Indefinite
Bioprosthetic valve if anticoagulated	Minimum 3 months
Aortic Bileaflet	Indefinite
Aortic Tilting Disc	Indefinite
Mitral Bileaflet	Indefinite
Aortic or Mitral Caged Ball	Indefinite
Arterial grafts if anticoagulated	Indefinite
Coronary artery thrombosis if anticoagulated	Indefinite
Superficial Thrombophlebitis;	
Within 3 cm of saphenofemoral junction	6 weeks and review
Clot > 5cms or within 5 cms of deep veins	6 weeks and review
<10 cms of saphenofemoral junction	6 weeks and review
and previous VTE	6 weeks and review
and Cancer	6 weeks and review
and severe chronic insufficiency	6 weeks and review

Adapted from British Society of Haematology Guidelines, 2011. Guidelines on oral anticoagulation with warfarin - fourth edition.

See Guidelines for Diagnoses and Management of Deep Vein Thrombosis

3.3 Stopping Anticoagulation

If anticoagulation treatment is stopped, give advice about the risk of recurrence and provide:

- written information on symptoms and signs to look out for
- direct contact details of a healthcare professional or team with expertise in thrombosis who can discuss any new symptoms or signs, or other concerns
- information about out-of-hours services they can contact when their healthcare team is not available.

4. Thrombophilia Screening

Tests for thrombophilia are required only in special clinical circumstances and only at specific time points when anticoagulation treatment can be influenced by the results. See Guidelines for Thrombophilia Testing in the Laboratory

5. Special situations

5.1 Patients with Active Cancer /Palliation/ Chemotherapy /IVC

The first line anticoagulation in patients with active cancer/palliation or active chemotherapy should be LMWH. Some of the DOACs can be used on the advice of the patients oncologist. Discuss with the patients Oncology/Palliative Care Team.

The dose of Enoxaparin (Inhixa ®) for patients with an IVC should be discussed with a Consultant Haematologist.

5.2 Superficial Thrombophlebitis

First line treatment options include; prophylactic dose Enoxaparin (Inhixa®), Fondaparinux, or Rivaroxaban. Refer to Guidelines for Diagnoses and Management of Deep Vein Thrombosis

5.3 Pregnancy

- Female patients, in reproductive age group, should have HCG before initiating treatment.
- DOACs are not licensed in pregnancy.
- Patients should be cautioned regarding the teratogenic effects of warfarin.
- Should patients on warfarin become pregnant they need to inform their GP and anticoagulation clinic with a matter of urgency.
- Pregnant patients diagnosed with DVT should receive treatment dose LMWH only.
- When a pregnant woman is diagnosed with VTE, a referral should be made to the patient's Obstetrician with a copy to Ms P Eedarapalli, Consultant Obstetrician & Gynaecologist and to Dr J Mainwaring, Consultant Haematologist. Alternatively refer patient to the Obstetric Haematology Clinic at PHFT (Dr D Furby and Ms L Vinayakarao).
- Refer to Reducing the Risk and Management of Venous Thromboembolism (VTE) in Pregnancy

5.4 Stroke

5.4.1 When to start anticoagulation

In the case of patients with acute cardio embolic stroke, there is concern that anticoagulation may increase the risk of haemorrhagic transformation, and a delay for an arbitrary 2 week period is recommended. For patients with minor, non-disabling stroke and a lower risk of haemorrhagic transformation it may be appropriate to commence treatment sooner, at the

discretion of the treating clinician (Royal College Physicians, national Clinical Guidance for stroke, 2016)

5.4.2 Perioperative management of adult patients with a history of stroke or TIA undergoing elective non-cardiac surgery

Wait three months post stroke before surgery. Discuss with the stroke team if appropriate.

5.5 Intravenous Drug Users

Consider LMWH or DOACs

5.6 Needle Phobic Patients

Every effort should be taken to reassure and educate patients with needle phobia on the importance of parenteral prophylaxis. In severe cases, where despite documented reassurance and education, the patient continues to refuse treatment, prophylactic Rivaroxaban (10mg daily) may be considered (unlicensed). This may be off license and the necessary documentation surrounding the off-label use of this drug should be documented in the patient's notes.

5.7 Severe liver impairment

In patients with severe liver disease and ascites an individual risk/benefit assessment should be undertaken when deciding the use and dose of LMWH therapy.

5.8 Paediatrics

Anticoagulation in paediatric patients is a rare occurrence and treatment usually initiated by tertiary centres. On-going dosing and factor Xa monitoring can be provided by the local paediatric team and where commercial graduated syringes are not suitable for dosing, individual doses can be prepared by the pharmacy aseptic unit with sufficient warning Monday to Friday only. These should not be prepared using multi-dose vials as all current preparations contain benzoyl alcohol as a preservative, which is not appropriate for use in paediatric patients. Dose preparation should include an overage to allow for the volume retained in the lumen of the SC needle to be used for administration.

6. Anticoagulant drugs

The drugs available for prophylaxis and treatment are:
6.1 Vitamin K antagonist: Warfarin
6.2 Unfractionated Heparin sodium (UFH)
6.3 Low molecular weight heparin (LMWH): Enoxaparin (Inhixa®)
6.4 Fondaparinux
6.5 Direct oral anticoagulants (DOACS): Dabigatran, Rivaroxaban, Apixaban, Edoxaban

6.1 Warfarin

- Warfarin is the most commonly used oral anticoagulant

- Warfarin is a vitamin K antagonist. Vitamin K is essential for activation of clotting factors II, VII, IX X and anticoagulant proteins C and S

6.1.1 Monitoring

Warfarin prolongs prothrombin time (PT) and activated partial thromboplastin time (APTT)

- Treatment with warfarin has to be monitored with INR (international normalised ratio), INR is prothrombin time (PT) standardised for patients on warfarin
- Warfarin can be paradoxically pro-thrombotic in the first 24 hours when loading doses are used. When rapid anticoagulation is required, heparins (UFH or LMWH) should be used as first-line therapy. Rapid high loading of warfarin should only be commenced in heparinised patients and therapeutic heparin continued for at least 5 days OR until INR is therapeutic for 2 consecutive days.
- Normally patients with AF and low CHADSVASC score would not require loading doses and heparin cover.
- Other vitamin K antagonists, acenocoumarol or phenindione, may be used in cases of clear warfarin hypersensitivity. Contact Anticoagulation Clinic (ext. 4778) for advice on dosage adjustment.
- Warfarin has a narrow therapeutic window.
- Warfarin has major drug and food interactions (contact you ward pharmacist or see BNF for further detail)
  - Use reduced dose warfarin loading schedule (Table 4) to commence oral anticoagulation therapy in patients who are on medications which are known to interact with warfarin
  - In patients on warfarin therapy, check INR within 4 to 7 days of starting any medication which is known to interact with warfarin

Patients should be informed of risks, precautions and the need for regular INR tests before starting treatment with warfarin. Verbal consent must be recorded in patient's medical notes and on page 1 of the Oral Anticoagulation Prescriptions. (Appendix 1)

Concurrent anti-platelet therapy will increase the risk of bleeding in warfarinised patients. If patients are already on aspirin, clopidogrel, prasugrel, ticagrelor or dipyridamole, check with Cardiology Consultant if anti-platelet therapy can be stopped before commencing warfarin.

6.1.2 Contraindications

- Known bleeding disorders, e.g. haemophilia
- Thrombocytopenia with platelet count < 75 x 10^9 / L
  - if platelets <75x109/L then discuss with Haematology Consultant
- Recent heparin-induced thrombocytopenia if warfarin used as sole anticoagulant – speak to haematologist
- Recent cerebral haemorrhage
- Severe liver disease with oesophageal varices
- Major trauma
- Recent eye, brain, spinal cord surgery

6.1.3 Pregnancy

- Warfarin is teratogenic and is contra-indicated in the first trimester of pregnancy

- Women on warfarin therapy should be warned of teratogenicity when planning pregnancy and switched to LMWH for the duration of pregnancy
- Seek advice from Cardiology Consultant regarding anticoagulation in pregnant women with metallic heart valves

6.1.4 Cautions

- Concomitant use of drugs that increase risk of bleeding (refer to BNF)
- Drugs and food interacting with coumarins
- Hepatic impairment with prolonged prothrombin time (PT)
- Recent surgery
- Bacterial endocarditis
- Uncontrolled Hypertension
- Peptic ulcer
- Severe kidney disease – CrCl <10mL / min, close monitoring required

6.1.5 Initiation of warfarin

- Check baseline platelet count, INR and LFTs
  - if baseline INR and / or APTTR > 1.4, exclude clotting factor deficiency.
- Warfarin should be taken in the evenings, usually at 6pm
- When using loading doses bridge with LMWH until INR >2.

Use standard loading schedule (Table 3) for the following patients:

- Young fit patients without co-morbidities and requiring rapid oral anticoagulation.

Use reduced-intensity loading schedule (Table 4) for the following patients:

- Age > 65 years (consider if age > 60 years)
- Weight < 50kg
- Poor nutritional status/Low serum albumin
- Congestive heart failure or other co-morbidities
- Abnormal LFTs/Liver disease
- Baseline INR > 1.4
- Known bleeding risk
- Concurrent drugs which enhance warfarin effect: See BNF/Speak to ward pharmacist

Patients with **atrial fibrillation or those at low thrombotic risk, restarting after a short break**, do not require rapid anticoagulation and can start warfarin therapy as outpatients without loading doses. The usual starting dose is 1 to 3mg daily. INR is checked 5 to 7 days after starting low dose warfarin.

6.1.6 Standard Warfarin Loading (Not for patients with AF) (Table 3)

Day	INR	Dose
Day 1	<1.4	10mg
Day 2	<1.8	10mg
	1.8	1mg
	>1.8	Omit dose
Day 3	<2.0	10mg
	2.0 to 2.5	4mg
	2.6 to 3.0	3mg
	3.1 to 3.4	2mg
	3.5 to 4.0	1mg
	>4.0	Omit dose
Day 4 Predicted maintenance dose	<1.4	Consult Anticoagulation Clinic
	1.4	8mg
	1.5 to 1.7	7mg
	1.8 to 2.0	6mg
	2.1 to 2.6	5mg
	2.7 to 3.0	4mg
	3.1 to 3.5	3mg
	3.6 to 4.0	2mg
	>4.0	Omit dose

Modified from British Medical Journal 1988; 297: 1285 – 1288

6.1.7 Reduced Warfarin Loading (Table 4)

Day	INR	Dose
Day 1	<1.4	5mg
Day 2	<1.8	5mg
	1.8	1mg
	>1.8	Omit dose
Day 3	<2.0	5mg
	2.0 to 2.5	2mg
	2.6 to 3.0	2mg
	3.1 to 3.4	1mg
	3.5 to 4.0	1mg
	>4.0	Omit dose
Day 4 Predicted maintenance dose	<1.4	Consult Anticoagulation Clinic
	1.4	4mg
	1.5 to 1.7	4mg
	1.8 to 2.0	3mg
	2.1 to 2.6	3mg
	2.7 to 3.0	2mg
	3.1 to 3.5	2mg
	3.6 to 4.0	1mg
	>4.0	Omit dose

Modified from Annals of Internal Medicine 2003; 138: 714 - 719

6.1.8 Warfarin maintenance

To improve warfarin dosing the following dosing tables can be used to adjust a patient's warfarin dose according to their INR. If despite using these algorithms the patient's INR is difficult to control, contact the anticoagulation clinic for advice.

REMEMBER: always consider drug interactions.

Routine INR checks ideally should occur every **Monday, Wednesday** and **Friday**. This allows for the team to dose their patient's warfarin over the weekend, and to monitor the INR and dose accordingly throughout the week.

Target INR 2.5 (range 2-3)

INR result	Current dose	Dose change	Days to next test
<2.0	≤6mg	Increase 0.5mg	3
	>6mg	Increase 1mg	
2.0 - 3.0	All doses	No change*	3 (5-7**)
3.1 - 4.0	≤6mg	Decrease 0.5mg	3
	>6mg	Decrease 1mg	
4.1 - 5.0	≤6mg	Omit 1 day then decrease 0.5mg	3
	>6mg	Omit 1 day then decrease 1mg	
5.1 - 6.0	≤6mg	Omit 2 days then decrease 0.5mg	2
	>6mg	Omit 2 days then decrease 1mg	
6.1 - 8.0	All doses	Omit until INR therapeutic, decrease 1-2mg	1 to 2
>8.0	All doses	Omit warfarin, IV vit K 1-2mg, restart once INR therapeutic, reduce dose 1-2mg	Daily
>8.0 and significant bleeding	All doses	Stop warfarin, IV PCC (or FFP), IV vit K 5-10mg, consider indication for anticoagulation	1-2 times/day

6.1.9 Target INR 3.5 (range 3-4)

INR result	Current dose	Dose change	Days to next test
≤1.9	≤6mg	Increase 1mg	3
	>6mg	Increase 2mg	
2.0 - 2.9	≤6mg	Increase 0.5mg	3
	>6mg	Increase 1mg	
3.0 - 4.0	All doses	No change*	3 (5-7**)
4.1 - 5.0	≤6mg	Decrease 0.5mg	3
	>6mg	Decrease 1mg	
5.1 - 6.0	≤6mg	Omit 1 day then decrease 0.5mg	2
	>6mg	Omit 1 day then decrease 1mg	
6.1 - 8.0	All doses	Omit until INR therapeutic, decrease 1-2mg	1 to 2
>8.0	All doses	Omit warfarin, vit K 1-2mg IV, restart once INR therapeutic, reduce dose 1-2mg	Daily
>8.0 and significant bleeding	All doses	Stop warfarin, IV PCC (or FFP), vit K 5-10mg IV, consider indication for anticoagulation	1-2 times/day

**If INR has increased or decreased by >1 unit, a slightly lower or higher dose may be required to reach the therapeutic range*
***If patient is medically stable, the dose, and the INR are stable for 6 or more days, the patients INR can be rechecked 5 to 7 days later.*

6.1.10 INR Control

Optimal INR control is defined as TTR ≥65% (time in therapeutic range). Factors to consider in improving TTR are as follows:

- Patient education
- Concordance – identify patients with poor compliance by comparing recommended dose over 3-6 months with quantity of prescription issued
- Inconvenient or inappropriate monitoring arrangements – confirm suitability of arrangements for each patient
- Consider domiciliary monitoring arrangements for patients with reduced mobility
- Alcohol consumption
- Drug interactions

6.1.11 Supply of warfarin tablets

The Pharmacy will routinely supply warfarin 0.5mg, 1mg and 3mg tablets to patients. Supply of 5mg tablets will be restricted to exceptional circumstances where there is a clear need and there is no risk of confusion between 5mg and 0.5mg tablets.

The National Patient Safety Agency (NPSA) recommends:

- Constant daily dosing instead of alternate day dosing
- Use the lowest number of tablets possible for daily dosing
- Use whole tablets only

6.1.12 Patient Information

When starting warfarin the counselling must be documented on page 2 of the Oral Anticoagulation Prescriptions

- Doctor to counsel the patient or carer about the first three points on page 1
- Doctor and pharmacist to reinforce information with counselling using page 2 during the admission
- Nurse to check the patients understanding of information on page 2 at discharge

When counselling patients they should be given an oral anticoagulation pack (Appendix 4) each consisting of:

- Oral Anticoagulant Therapy – Information for Patients (yellow booklet)
- Anticoagulation Alert Card
- Oral Anticoagulant Therapy – Record Book (small yellow booklet)

The name of the anticoagulant, indication for treatment, therapeutic range (INR) plus target INR, date treatment started and duration of treatment must be recorded in all three of the above.

6.1.13 Anticoagulation Clinic Referrals

Patients should be referred to the Anticoagulation Clinic if they require oral anticoagulation therapy after discharge from the hospital.

Complete the discharge section (Page 2) of the oral anticoagulation prescription, email the completed prescription chart (Page 1 and 2) to either:

1. If GP managing warfarin; chart faxed to GP (anticoagulant clinic can advise on surgeries currently conducting their own anticoagulation service).
2. Or email the appropriate anticoagulation clinic:

   Bournemouth - anticoagulation.clinic@rbch.nhs.uk

   Poole - warfarin.clinic@poole.nhs.uk

   Salisbury - sft.anticoagulation.service@nhs.net

   Dorchester - dhc.anticoag.weymouth@nhs.net

For patients at Bournemouth contact the Clinic by telephone on ext. **4778** to arrange the first appointment, with INR test, within 2 to 5 days of discharge and forward referral to them as above.

Walk in blood tests can take place at Bournemouth (before 2pm) and at Christchurch (before 12pm) but the clinic will advise as needed after referral. If a patient's first blood test is going to take place at Poole hospital – an appointment will need to be made

(tel: 0300 019 8087) but contact anticoagulant service for advice.

Once managed by the Bournemouth Anticoagulant service patients can have a booked appointment at either Bournemouth or Christchurch Hospitals, appointments will be booked by the service. Patients may also have their INR taken at their GP surgery by arrangement

If warfarin has to be stopped, document the reason on page 1 of the Oral Anticoagulation Prescription, e.g. “warfarin stopped” or “warfarin on hold, review after surgery” (Document this on the dosing table i.e. where daily dosing is prescribed on page 1)”.

When the Anticoagulation Clinic sends dosing information to the patient they will post the BLUE forms, Anticoagulant Therapy Record and INR Test Request Form (Appendix 3). These forms are computer generated and contain the following information:

- Patient’s daily dose in mg
- Patient’s daily dose in tablet numbers and colour of each tablet
- Date of the next blood test
- Request form for the next blood test

When the anticoagulation course has been completed, warfarin can be stopped abruptly; there is no need to taper the dose. If patients were taking aspirin or other anti-platelet drugs before the warfarin course which were stopped, these may need to be restarted if appropriate (discuss with the patients cardiologist).

High citrate concentrations will give spuriously high INRs so care must be taken not to under fill sample bottles or to pour two small samples into one bottle to make up the volume.

The Royal Bournemouth Anticoagulation Clinic manages patients for all Bournemouth GP practices with the exception of Denmark Road Medical Centre, Strouden Park, Crescent Surgery and Providence Road Surgery. Patients belonging to these practices should be referred directly to the GP surgery.

Poole Anticoagulant Service manages patients cared for by Poole, Wimborne, Ferndown and some Verwood practices.

Patients not requiring rapid anticoagulation should be referred directly to anticoagulation clinic, where they are counselled and given written information. Thereafter patients are managed by a dose and post service.

6.2 Unfractionated Heparin (UFH)

- Indirect inhibitor of coagulation factors IIa (Thrombin) and Xa (Prothrombinase)
- Half-life is 45 to 60 minutes after usual intravenous doses

6.2.1 Contraindications

- Known bleeding disorders, e.g. haemophilia
- Thrombocytopenia with platelet count < 75 x 10^9/L
- if platelets <75x109/L then discuss with Haematology Consultant
- History of heparin-induced thrombocytopenia (HIIT)

- Hypersensitivity to heparins
- Peptic ulcer
- Recent cerebral haemorrhage
- Major / life threatening bleeding
- Severe liver disease with oesophageal varices
- Major trauma
- Recent eye, brain, spinal cord surgery
- Acute bacterial endocarditis

6.2.2 Cautions

- Concomitant use of drugs that increase bleeding
- Liver disease
- Recent surgery
- Pre-existing diseases or concomitant use of drugs that cause hyperkalaemia
- Osteoporosis
- Severe hypertension

6.2.3 Monitoring (treatment doses)

Venepuncture should not be performed on the same arm as an active IV infusion. If the patient has bilateral infusions then the least critical infusion should be stopped and then the bloods taken after the time recommended by the medical team.

- Check baseline FBC and APTT ratio.
- Recheck APTT ratio within 6 hours.
- Maintain APTT ratio within the range of **1.5 to 2.5**.
- Check platelet count on the 5th day of heparin treatment to exclude heparin-induced thrombocytopenia (HIIT), then every 3 to 5 days whilst on UFH for up to 3 weeks
- Check platelet count after 24 hours of UFH treatment if patient has been exposed to heparin in the previous 100 days.
- Check serum potassium in those at risk of hyperkalaemia
- Blood should be taken from the non-infusion arm to check APTT ratio

6.2.4 Dosing

6.2.4.1 Prophylactic dosing

Patients with **a CrCl <15mL/min** should be prescribed unfractionated heparin at a dose of 5000units SC twice daily (using 5000units in 1mL or 5000units in 0.2 ml ampoules)

6.2.4.2 Therapeutic dosing;

Recommended dose for treatment of venous and arterial thrombosis is heparin 75units/kg (to the nearest 100 units)using actual body weight, with a maximum dose of 5000 units intravenously. Followed by a continuous intravenous infusion at 18 units/kg/hr and adjusted to maintain APTT ratio between 1.5 to 2.5

- Use heparin 1000 units / mL (DO NOT dilute)

- Nurses can request APTTR and then adjust the heparin infusion as in **Table 5** below. If it is not possible to obtain the sample then a decision to consider ongoing anticoagulation options needs to be urgently escalated to a senior clinician
- Prescribe on the Intravenous Heparin Prescription**.**

6.2.4.3 Dosing schedule for continuous intravenous infusion of unfractionated heparin (Table 5)

APTTR*	Adjustment to heparin rate (1000units / mL)	Monitor APTT Ratio**
> 5	Stop for 1 hour then reduce by 0.6mL / hr Inform Dr	After 2 hours
4.1 to 5.0	Reduce by 0.4mL / hr	After 6 hours
3.1 to 4.0	Reduce by 0.2mL / hr	After 6 hours
2.6 to 3.0	Reduce by 0.1mL / hr	After 10 hours
1.5 to 2.5	NO CHANGE	After 10 hours
1.2 to 1.4	Increase by 0.2mL/hr	After 6 hours
< 1.2	Increase by 0.4mL / hr Discuss with Dr to consider a bolus.	After 4 hours

Modified from British Medical Journal 1988; 297: 1285-1288.

* If the APTTR result is quoted to 2 decimal places, round up or down to the nearest decimal e.g. result of 4.14 round down to 4.1, result of 4.15 round up to 4.2

** Time for blood test starts from the time of rate adjustment.

6.2.5 Complications of UFH therapy

- Bleeding is reversed by protamine sulphate: 1mg of protamine neutralises 100 units of UFH **(**see section 10.1.2**)**. Consult Haematologist for advice
- Osteoporosis is a complication of long-term heparin use only
- Hyperkalaemia - the risk appears to increase with duration of therapy, but is usually reversible. Serum potassium should be measured in those at risk e.g.
  - Diabetes mellitus
  - Chronic renal failure
  - Pre-existing metabolic acidosis
  - A raised serum potassium
- Heparin-induced thrombocytopenia (HIT) with thromboembolism (HITT)
  See Guidelines for Monitoring, Diagnosing and Managing Heparin-Induced Thrombocytopenia (HIT)

6.3 Enoxaparin (Inhixa®)

- LMWH mainly inhibit prothrombinase (Factor Xa) and weakly inhibit thrombin (Factor IIa)
- Enoxaparin (Inhixa®) is the low molecular weight heparin (LMWH) on the hospital formulary.
- Inhixa ® is a biosimilar of enoxaparin
- Enoxaparin (Inhixa®) only moderately affects the APTT ratio; this should only be measured in suspected overdose and not be monitored routinely.
- Anti-Factor Xa level can be used to monitor the anticoagulant effect but has limited predictive value for bleeding complications or antithrombotic efficacy.

- Renal function must be checked before prescribing.
- The patient's creatinine clearance should be calculated using the Creatinine Clearance Calculator available on the Intranet under Doctors Information.
- In obese patients (those with a BMI>30) the use of ideal body weight in the creatinine clearance calculation should be considered.

6.3.1 Contra-indications

- Known bleeding disorders, e.g. haemophilia
- Thrombocytopenia with platelet count < 75 x 10^9/L
  - if platelets <75x109/L then discuss with Haematology Consultant
- History of heparin-induced thrombocytopenia (HIIT)
- Hypersensitivity to heparins or its derivatives
- Gastrointestinal ulcer
- Recent cerebral haemorrhage
- Major / life threatening bleeding
- Severe liver disease with oesophageal varices
- Major trauma
- Recent eye, brain, spinal cord surgery
- Acute bacterial endocarditis
- Epidural or Spinal anaesthesia (with treatment doses)

6.3.2 Cautions

- Severe hypertension
- Concomitant use of drugs that increase bleeding
- Liver disease
- Renal impairment
- Recent surgery
- Pre-existing diseases or concomitant use of drugs that cause hyperkalaemia
- Osteoporosis

6.3.3 Monitoring

Routine monitoring of anticoagulant effect is not required except in special circumstances listed below:

- Obesity (BMI > 30kg/m^2)
- Pregnancy
- Those at increased risk of bleeding

Samples for anti-Factor Xa activity are taken 3 to 4 hours after injection to check peak level, and 24 hours after injection to check trough level, discuss levels with haematology.

6.3.4 Doses

6.3.4.1 Prophylactic dose in patient with CrCl ≥30ml/min

Weight (kg)	Daily Dose
<50	Enoxaparin (Inhixa®) 20mg daily
50-100	Enoxaparin (Inhixa®) 40mg daily
101-150	Enoxaparin 40mg (Inhixa®) twice daily
>150	Enoxaparin (Inhixa®) 60mg twice daily

In patients with a CrCl 15 - 29mL/min

- Use Enoxaparin (Inhixa®) 20mg daily

In patients with a CrCl <15mL/min

- Use Unfractionated heparin SC 5000units twice daily

In patients with severe liver disease and ascites an individual risk/benefit assessment should be undertaken when deciding the use and dose of LMWH therapy.

Note: the recommendations for dosing Enoxaparin (Inhixa®) by bodyweight are not licensed by the manufacturer but have been implemented in this policy based on expert opinion.

Should a prescriber believe it is in an individual patient's best interest to receive the licensed dose regardless of body weight; this can be adhered to, but should be documented in the patient's medical notes.

6.3.4.2 Therapeutic dose

Prescribe on the Parenteral Anticoagulation Prescriptions
The maximum effect of Enoxaparin (Inhixa®) is not seen until 1 to 4 hours after administration, for immediate anticoagulant effect prescribe **IV heparin** 5,000units bolus followed by Enoxaparin (Inhixa®) as below
For treatment of VTE in pregnancy please refer to Reducing the Risk and Management of Venous Thromboembolism (VTE) in Pregnancy

	Enoxaparin (Inhixa®) dose 1mg of Enoxaparin(Inhixa®) is equivalent to 100 international units of anti-Xa activity			
	Uncomplicated patients with low risk of VTE recurrence		All other patients including: obesity*, symptomatic PE, cancer, recurrent VTE or proximal iliac vein thrombosis * Obesity – BMI > 30kg/ m2	
Weight (kg)	CrCl ≥30mL/min (1.5mg/kg SC OD)	CrCl 15-29mL/min (1mg/kg SC OD)	CrCl ≥30mL/min (1mg/kg SC BD)	CrCL 15-29mL/min (1mg/kg SC OD)
40-49	60mg	40mg	40mg BD	40mg
50-59	80mg	60mg	60mg BD	60mg
60-74	100mg	60mg	60mg BD	60mg
75 - 89	120mg	80mg	80mg BD	80mg
90 – 109	150mg	100mg	100mg BD	100mg
110 – 125 *	180mg	120mg	120mg BD	120mg
>125**	1.5mg/kg Appropriate dose to the nearest practical dose	Contact Consultant Haematologist		

*Consider checking Anti-Xa levels
** Check Anti-Xa levels

6.3.4.3 In patients with CrCl<15ml/min

Prescribe IV Unfractionated heparin on separate prescription chart. Enoxaparin (Inhixa®) is contraindicated

6.3.4.4 Extended treatment of venous thromboembolism in oncology patients

- Month 1 = Standard dosing (1mg/kg twice daily) as below
- Months 2 to 6 = To discuss with patients oncologist if appropriate to continue on 1mg/kg twice daily or to switch to 1.5mg/kg once daily
- In patients with severe liver disease and ascites an individual risk/benefit assessment should be undertaken when deciding the use and dose of LMWH therapy.

Weight (kg)	Enoxaparin (Inhixa®) 1mg/kg BD dose CrCl ≥30ml/min	Enoxaparin (Inhixa®) 1mg/kg OD dose CrCl 15- 29ml/min*
40-49	40mg BD	40mg OD
50-59	60mg BD	60mg OD
60-74	60mg BD	60mg OD
75 - 89	80mg BD	80mg OD
90 - 109	100mg BD	100mg OD
110 – 125	120mg BD	120mg OD
>125kg	Contact Consultant Haematologist	

*CrCl <15ml/min discuss with haematology

Relevance of continuing treatment beyond 6 months should be evaluated according to individual risk/benefit ratio, particularly taking into account the progression of the cancer

Dose modifications in chemotherapy-induced thrombocytopenia:

- Platelets 50 to 100 x 10^9/L - decrease daily Enoxaparin (Inhixa®) dose by 20mg until platelets ≥ 100 x 10^9/L (as recommended by consultant haematologists)
- Platelets < 50 x 10^9/L - discontinue Enoxaparin (Inhixa®) until platelets > 50 x 10^9/L

6.3.5 Low dose Rivaroxaban

- For patients requiring pharmacological thromboprophylaxis during admission, Rivaroxaban 2.5mg twice daily is not sufficient. Rivaroxaban should be suspended and Enoxaparin (Inhixa®) prescribed as per the standard VTE prophylaxis protocol.
- On discharge or when a patient becomes mobile (whichever occurs first), Enoxaparin (Inhixa®) should be discontinued and Rivaroxaban 2.5mg twice daily resumed.
- If pharmacological thromboprophylaxis is not required during admission, Rivaroxaban should be continued (except if contraindicated due to bleeding). Mechanical prophylaxis can be prescribed in addition to Rivaroxaban 2.5mg twice daily if indicated.

6.3.6 Administration

- Enoxaparin (Inhixa®) should be given subcutaneously (SC), preferably with the patient sitting/lying down.
- DO NOT expel the air bubble from the syringe before injection
- If the quantity of the drug to be injected requires to be adjusted, use the graduated pre-filled syringes to reach the desired volume by discarding the excess before injecting.
- Inject into the SC tissue of the anterolateral or posterolateral abdomen alternating from the left to right side **(Inhixa® is not licensed for injection into the thigh).**
- Vertically introduce the whole length of the needle into the thickness of the skin held between the thumb and forefinger. Hold the skin throughout the duration of the injection.
- Do not rub the injection site (helps to avoid bruising).
- The syringes are fitted with an automatic safety system which is triggered at the end of the injection

6.3.7 Overdose

- Protamine sulphate only partially reverses the effect of Enoxaparin (Inhixa®) so additional measures may be required if bleeding is uncontrollable and life-threatening.
- See section 10.1.2

6.3.8 Complications

- Bleeding
- Osteoporosis is a complication of long-term heparin use only
- Hyperkalaemia - the risk appears to increase with duration of therapy, but is usually reversible. Serum potassium should be measured in those at risk e.g.

- Diabetes mellitus
- Chronic renal failure
- Pre-existing metabolic acidosis
- A raised serum potassium

6.3.9 Heparin-induced thrombocytopenia (HIT) with thromboembolism (HITT)

See Guidelines for Monitoring, Diagnosing and Managing Heparin-Induced Thrombocytopenia (HIT)

6.3.10 Halal requirements for Muslim patients

All unfractionated heparin and low molecular heparins (including Enoxaparin [Inhixa®] in the UK are derived from porcine material. Muslim religious leaders have previously issued guidance that use of porcine derived low molecular weight heparins are suitable for use in life-threatening conditions. Use should be discussed with individual patients, if this is possible. Alternatively Fondaparinux [Arixtra®] is a synthetic anticoagulant, and therefore may be a suitable alternative for patients who wish not to receive porcine material. Consult BNF for treatment doses and licensed indications.

6.4 Fondaparinux

Fondaparinux is a synthetic pentasaccharide and selective inhibitor of activated factor X (Xa). The antithrombotic activity of Fondaparinux is the result of antithrombin III (ATIII) mediated selective inhibition of factor Xa. By binding selectively to ATIII, Fondaparinux potentiates (by about 300 times) the innate neutralisation of factor Xa by ATIII. Neutralisation of factor Xa interrupts the blood coagulation cascade and inhibits both thrombin formation and thrombus development. Fondaparinux does not inactivate thrombin (activated Factor II) and has no effects on platelets. Its half-life is approximately 17 – 21 hours.

Fondaparinux licensing includes treatment of Unstable angina (UA), non-ST elevated myocardial infarction (NSTEMI) and ST-elevated myocardial infarction (STEMI) in patients for whom urgent (<120 mins) invasive management (PCI) is not indicated.

6.4.1 Contraindications

- Hypersensitivity to Fondaparinux or other excipients
- Active, clinically significant bleeding
- Acute bacterial endocarditis
- Severe renal impairment with creatinine clearance < 20ml / min (for ACS patients receiving 2.5mg once daily dosage) or < 30ml / min for other doses / indications.

6.4.2 Cautions

- Patients with increased risk of haemorrhage
- Congenital or acquired bleeding disorders
- Active ulcerative gastrointestinal disease
- Recent Intracranial haemorrhage
- Recent brain, spinal or ophthalmic surgery
- Concomitant use of drugs that increase bleeding

- Liver disease
- Pregnancy and breast feeding

6.4.3 Monitoring

- Routine monitoring of anticoagulant effect is not required.
- Fondaparinux does not affect routine coagulation tests such as aPTT, ACT, PT or INR.

6.4.4 Dosage

Treatment of UA, STEMI and NSTEMI

- Fondaparinux 2.5mg S/C once daily. Treatment should be initiated as soon as possible following diagnosis and continued for 72 hours following the last episode of chest pain or up until angiogram. It can be used for a maximum of 8 days.
- Fondaparinux should not be used if CrCl < 20ml / min
- If CrCl< 20ml/min a heparin infusion should be started
- If Fondaparinux stopped consider prescribing prophylactic Enoxaparin (Inhixa®) see section 6.3.4.1

6.4.5 Administration

- Subcutaneous administration: Deep subcutaneous injection while the patient is lying down. Sites should alternate between left and right anterolateral and left and right posterolateral abdominal wall.
- Fondaparinux should not be administered intra muscularly**.**

6.4.6 Complications:

Interactions with other medicinal products

- Bleeding risk is increased with concomitant administration of Fondaparinux and agents that may enhance the risk of haemorrhage.

6.4.7 Undesirable effects

- Bleeding complications
- Anaemia
- Rash, pruritus
- Dyspnoea

6.4.8 Overdose

- Fondaparinux dose above the recommended regimen may lead to an increased risk of bleeding.
- There is no known antidote to Fondaparinux
- If overdose suspected, discuss with consultant haematologist

6.5 Direct Oral Anticoagulants (DOAC's)

DO NOT USE IN MECHANICAL HEART VALVES

MHRA/CHM advice: Direct-acting oral anticoagulants (DOACs): increased risk of recurrent thrombotic events in patients with antiphospholipid syndrome (June 2019)

Patients should have a baseline blood test before initiating DOACs. Renal function can decline whilst on treatment and should be regularly monitored. The SPC recommends that a patient's CrCl is calculated from the Cockcroft and Gault formula. CrCl divided by 10 is a good indication for frequency of monitoring. (www.sps.nhs.uk)
Dose adjustment may be required during DOAC therapy due to changes in weight, see individual DOAC for details. Monitor weight regularly in patients at risk of rapidly fluctuating weight (e.g. heart failure) or where a patient is border-line for requiring a dose change because of their weight.

Obesity may render a DOAC less effective. SPCs do not recommend dose adjustments but local haematology guidance states:

- DOACs can be used in patients up to and including 120kg.
- **Do not** use if a patient weighs 150kg or over
- If 121kg to 149kg, discuss with haematology as factor Xa levels may be required
- Consider confirming appropriate action with the patient's consultant
- If at risk of sudden fluctuation of weight (e.g. heart failure, dieting) closely monitor and adjust dose as appropriate – see individual drug for more information on weight based dosing.

There are currently four DOACs available:

- Dabigatran is a potent, competitive, direct thrombin inhibitor. As thrombin enables conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombus. Dabigatran also inhibits free thrombin, fibrin bound thrombin and thrombin induced platelet aggregation.
- Apixaban, Edoxaban and Rivaroxaban are highly selective direct factor Xa inhibitors. Inhibition of factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. They do not inhibit thrombin (activated factor II) and no effects on platelets have been demonstrated.

6.5.1 Dabigatran

6.5.1.1 Indications

- Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, such as symptomatic heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA).
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults
- NICE TA 249. Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation.
- May be considered in patients who have failed/allergic to Factor Xa inhibitors

N.B Dabigatran **cannot** go in regular compliance aids however it can be supplied with its own compliance aid if it is felt to be the most appropriate choice of DOAC.

6.5.1.2 Dosage

- For prevention of stroke in patients with NVAF
  - Age <80 years - 150mg twice a day
  - Age > 80 years or taking verapamil – 110mg twice a day
  - Also consider 110mg twice a day if:
    - Thromboembolic risk is low and bleeding risk is high,
    - Age 75 – 80 years,
    - Patients with gastroesophageal reflux, oesophagitis or gastritis.
    - Body weight < 50kg
    - CrCl 30-50ml/min
- For the treatment of DVT or PE
  - As above however 5 days of treatment dose LMWH will be required prior to starting Dabigatran
- For patients weighing 121kg or more, see advice above

6.5.1.3 Contraindications (refer to SPC)

- Hypersensitivity
- A lesion or condition to be considered a significant risk factor for major bleeding
- Active bleeding
- Hepatic disease or impairment expected to impact on survival
- Other anticoagulant medication (except during switching – see below)
- Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole, tacrolimus and dronedarone
- CrCl < 30ml/min
- Prosthetic heart valves - not studied therefore not recommended.
- Women of childbearing potential should avoid pregnancy during treatment with Dabigatran etexilate

6.5.1.4 Cautions

- Hepatic impairment: Patients with liver enzyme values > 2ULN were excluded from main trials. No treatment experience in this population.
- Conditions with an increased risk of bleeding or concomitant use of drugs that increase risk of bleeding (refer to BNF)
- Decreased renal function (30-50ml/min), age >75 years, extremes of body weight < 50kg or >120 kg, or mild - moderate P-gp inhibitor concomitant medication (e.g. amiodarone, quinidine or verapamil, see BNF) can increase Dabigatran levels.
- Surgical or invasive procedures
- Active cancer patients
- Dabigatran should not be used during pregnancy unless clearly necessary
- Breast feeding should be discontinued during treatment with Dabigatran
- Dabigatran capsules contain Sunset yellow colorant (E110) which may cause allergic reactions.

6.5.1.5 Missed doses

- Dabigatran has a shorter half-life than warfarin therefore missed doses may result in more time without anticoagulation and greater risk of thromboembolic complications. If a dose is missed it may still be taken up to 6 hours prior to the next scheduled dose.
- If it is within 6 hours of the next dose, the missed dose should be omitted.
- Do not double dose within the same day to make up for missed dose.

6.5.1.6 Conversion from Warfarin to Dabigatran

- Discontinue warfarin and start Dabigatran when INR < 2.0

6.5.1.7 Conversion from Dabigatran to warfarin

- CrCl > 50ml/min – start warfarin 3 days before discontinuing Dabigatran
- CrCl 30- 50ml/min – start warfarin 2 days before discontinuing Dabigatran

Cautions: INR values will be falsely elevated. INR testing should not be performed until Dabigatran has been stopped for at least 2 days.

6.5.1.8 Conversion from LMWH to Dabigatran

- The parenteral anticoagulant should be discontinued and Dabigatran should be started 0-2 hours prior to the time that the next dose of the alternate therapy would be due
- or at the time of discontinuation in case of continuous treatment (e.g. intravenous Unfractionated Heparin (UFH))

6.5.1.9 Cardioversion or Catheter ablation for atrial fibrillation (SPAF)

- Catheter ablation and cardioversion can be conducted whilst on Dabigatran

6.5.1.10 Complications (refer to SPC)

- Bleeding
- Dyspepsia and gastrointestinal symptoms

6.5.1.11 Reversal

- See section 10.1.6

6.5.2 Rivaroxaban

6.5.2.1 Indications

- Prevention of stroke and systemic embolism (SE) in adult patients with NVAF with one or more risk factors, congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.
  - NICE TA 256 Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation. May 2012
- Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults.

- NICE TA 287 Rivaroxaban for treating pulmonary embolism and preventing recurrent venous thromboembolism. June 2013
- Thrombophlebitis (This indication is off license)
- Prevention of atherothrombotic events in people with coronary or peripheral artery disease
  - NICE TA 607 Rivaroxaban for preventing atherothrombotic events in people with coronary or peripheral artery disease

6.5.2.2 Dosage

- Prevention of stroke and SE in adult patients with NVAF:
  - Rivaroxaban 20mg each day, reduced to 15mg each day if CrCl is 15–50 ml/min
- Treatment of DVT and PE and prevention of recurrent DVT and PE in adults:
  - 15mg twice a day for 21/7 then 20mg each day (min 3/12 and review)
  - Decrease maintenance dose to 15mg daily, after initial loading dose, if CrCl is 15-50ml/min
  - If a patient has received treatment dose LMWH prior to commencing rivaroxaban these days can be deducted from the loading dose i.e. 3 days of treatment dose enoxaparin (Inhixa®) would mean only 18 days of 15mg twice daily rivaroxaban (unlicensed but based on expert opinion)
- Extended prevention of recurrent DVT and PE following 6 months therapy
  - the recommended dose is 10 mg once daily. Consider 20 mg once daily in those at high risk of recurrence
- Thrombophlebitis – 10mg once daily for 6 weeks (this indication is off license)
- Coronary Artery Disease(CAD)/Peripheral Artery Disease (PAD)
  - 2.5mg twice daily in combination with Aspirin 75mgs daily

- For patients requiring pharmacological thromboprophylaxis during admission, <u>Rivaroxaban 2.5mg BD is not sufficient</u>. Rivaroxaban should be suspended and Enoxaparin (Inhixa®) prescribed as per the standard VTE prophylaxis protocol.
- On discharge or if patient becomes mobile (whichever occurs first), Enoxaparin (Inhixa®) should be discontinued and Rivaroxaban 2.5mg BD resumed.
- If pharmacological thromboprophylaxis is <u>not</u> required during admission, Rivaroxaban should be continued (except if contraindicated due to bleeding). Mechanical prophylaxis can be prescribed in addition to Rivaroxaban 2.5mg BD if indicated.

For patients weighing 121kg or more, see advice above

Rivaroxaban at doses above 10mgs must be taken with food.
Rivaroxaban **can** be used in a compliance aid.

6.5.2.3 Contra-indications (refer to SPC)

- Hypersensitivity
- A lesion or condition, if considered a significant risk factor for major bleeding
- Active bleeding
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk
- Anticoagulant use (except during switching)
- Avoid concomitant treatment with strong inhibitors of both CYP3A4 and P-gp e.g. ketoconazole, itraconazole and HIV protease inhibitors.

- Pregnancy and breast feeding
- CrCl < 15ml/min
- Prosthetic heart valves - not studied therefore not recommended.

6.5.2.4 Cautions

- Hepatic impairment
- Conditions with an increased risk of bleeding or concomitant use of drugs that increase risk of bleeding (refer to BNF)
- CrCl 15-49ml/min
- Caution with strong CYP3A4 inducers e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St John's Wort as they may lead to reduced Rivaroxaban concentrations.
- Caution with Dronedarone
- Surgical or invasive procedures
- Elderly patients – monitor renal function closely
- Contains lactose, use with caution in patients with lactose intolerance

6.5.2.5 Missed Doses

- Missed dose should be taken immediately and then continued on the following day with once daily dosing
- Do not double dose within the same day to make up for missed dose, unless during treatment phase.
- If a dose is missed during the 15 mg twice daily treatment phase (day 1 - 21), the patient should take Rivaroxaban immediately to ensure intake of 30 mg Rivaroxaban per day. In this case two 15 mg tablets may be taken at once. The patient should continue with the regular 15 mg twice daily intake as recommended on the following day.

6.5.2.6 Conversion from warfarin to Rivaroxaban

- Discontinue warfarin and start Rivaroxaban when:
  - INR ≤3.0 for prevention of stroke and systemic embolism
  - INR ≤2.5 for DVT, PE and prevention of recurrence
  - *(Note: this information is taken from the manufacturers SPC for Rivaroxaban [Bayer] and is a different threshold than Dabigatran and Apixaban)*

6.5.2.7 Conversion from Rivaroxaban to warfarin

- Co-administer Rivaroxaban and warfarin until INR >2.0. Test INR 24 hours after previous dose but prior to next dose of Rivaroxaban.
- Start warfarin as standard initial dosing followed by dosing guided by INR testing. Once Rivaroxaban is discontinued INR testing may be done reliably at least 24 hours after last dose.
- Caution: INR values will be falsely elevated by Rivaroxaban

6.5.2.8 Conversion from LMWH to Rivaroxaban

- For patients currently receiving a parenteral anticoagulant, discontinue the parenteral anticoagulant and start Rivaroxaban 0 to 2 hours before the time that the next scheduled administration of the parenteral anticoagulation would be due
- Or at the time of discontinuation of a continuously administered parenteral anticoagulation (e.g. intravenous unfractionated heparin).
- If a patient has received treatment dose LMWH prior to commencing rivaroxaban these days can be deducted from the loading dose i.e. 3 days of treatment dose enoxaparin (Inhixa® would mean only 18 days of 15mg twice daily rivaroxaban (unlicensed but based on expert opinion)

6.5.2.9 Cardioversion

- Rivaroxaban can be initiated or continued in patients who may require cardioversion.

6.5.2.10 Complications (refer to SPC)

- Haemorrhage, epistaxis and GI bleeding.

6.5.3 Apixaban

6.5.3.1 Indications

- Prevention of stroke and SE in adult patients with NVAF, with at least one additional risk factor.
- NICE TA 275. Apixaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation. Feb 2013
- NICE TA 341. For the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism

6.5.3.2 Dosage

- Prevention of stroke in adult patients with NVAF:
  - 5mg twice a day
  - 2.5mg twice daily if patient has 2 of the following criteria:
    - Age≥80 years,
    - Body weight ≤60kg,
    - serum creatinine >133micromol/L
    - **OR** CrCl 15-29mL/min
- Treatment of DVT and PE:
  - 10mg twice daily for 7 days then 5mg twice daily (min 3/12, max 6/12)
  - If CrCl 15-29ml/min or patient meets 2 of the above criteria – consultant decision if it is appropriate to reduce the dose to 2.5mg twice daily or continue on the recommended 5mg twice daily
- Extended prevention of recurrent DVT and PE following 6 months therapy:
  - the recommended dose is 2.5mg twice daily. Consider 5mg twice daily in those at high risk of recurrence
- For patients weighing 121kg or more, see advice above

Apixaban **can** be used in a compliance aid.

6.5.3.3 Contra-indications (refer to SPC)

- Hypersensitivity
- A lesion or condition, if considered a significant risk factor for major bleeding
- Active bleeding
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk
- Anticoagulant use (except during switching)
- Avoid concomitant treatment with strong inhibitors of both CYP3A4 and P-gp e.g. ketoconazole, itraconazole and HIV protease inhibitors.
- CrCl < 15ml/min
- Prosthetic heart valves- not studied, not recommended.

6.5.3.4 Cautions

- Hepatic impairment
- Conditions with an increased risk of bleeding or concomitant use of drugs that increase risk of bleeding (refer to BNF)
- Moderate renal impairment (CrCl 15-29mL/min)
- Caution with strong CYP3A4 inducers e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St John's Wort as they may lead to reduced concentrations.
- Surgical or invasive procedures
- Contains lactose, use with caution in patients with lactose intolerance

6.5.3.5 Missed Doses

- Missed dose should be taken immediately and then continued with twice a day as before.
- Do not double dose within the same day to make up for missed dose.

6.5.3.6 Conversion from Warfarin to Apixaban

- Discontinue warfarin and start Apixaban when INR < 2.0

6.5.3.7 Conversion from Apixaban to Warfarin

- Continue Apixaban for at least 2 days after starting warfarin therapy
- Check INR after 2 days of co-administration. Obtain INR before next schedule dose of Apixaban.
- Continue co-administration until the INR is > 2.0 then discontinue Apixaban.

6.5.3.8 Conversion from LMWH to Apixaban

- Switching treatment from parenteral anticoagulants to Apixaban can be done at the next scheduled dose

6.5.3.9 Cardioversion or Catheter ablation for atrial fibrillation (SPAF)

- Apixaban can be initiated or continued in NVAF patients who may require cardioversion or catheter ablation.

6.5.3.10 Complications (refer to SPC)

- Haemorrhage, contusion, epistaxis and haematoma

6.5.4 Edoxaban

6.5.4.1 Indications

- Prevention of stroke and SE in adult patients with NVAF, with at least one additional risk factor.
- NICE TA 355 Edoxaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation. Sep 2015.
- NICE TA 354 Edoxaban for treating and preventing recurrent deep vein thrombosis or pulmonary embolism.

6.5.4.2 Dosage

- For prevention of stroke in adult patients with NVAF and the treatment:
  - 60mg once a day
  - Decrease dose to 30mg daily if
    - CrCl 15–50ml/min
    - Weight <60kgs
    - Concurrent use of ciclosporin, dronedarone, erythromycin, ketoconazole
- For the treatment of DVT or PE
  - As above however 5 days of treatment dose LMWH is required prior to starting Edoxaban
- For patients weighing 121kg or more, see advice above

For patients with CrCl>90ml/min an alternative DOAC should be considered. Evidence has shown that in patients with a high CrCl Edoxaban is less effective than warfarin.

Edoxaban **can** be used in compliance aids

6.5.4.3 Contra-indications (refer to SPC)

- Hypersensitivity
- A lesion or condition, if considered a significant risk factor for major bleeding
- Clinically Significant Active bleeding
- Uncontrolled severe hypertension
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk
- Anticoagulant use (except during switching)
- Severe renal impairment (CrCl < 15ml/min)
- Pregnancy and breast feeding
- Prosthetic heart valves- not studied, not recommended.

6.5.4.4 Cautions

- Hepatic impairment
- Conditions with an increased risk of bleeding or concomitant use of drugs that increase risk of bleeding (refer to BNF)
- The co-administration of aspirin in elderly
- Concomitant use of antiplatelet and thrombolytics
- Moderate renal impairment (CrCl 15-49mL/min). Deterioration in renal function should be monitored closely and adjust dose as appropriate.
- Edoxaban SPC notes may be less effective than warfarin for AF in high creatinine clearance (>90ml/min)
- Caution with strong CYP3A4 inducers e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St John's Wort as they may lead to reduced Edoxaban concentrations.
- Avoid concomitant treatment with strong inhibitors of both CYP3A4 and P-gp e.g. ketoconazole, itraconazole and HIV protease inhibitors.
- Surgical or invasive procedures

6.5.4.5 Missed Doses

- Missed dose should be taken immediately and then continued with once a day as before.
- Do not double dose within the same day to make up for missed dose.

6.5.4.6 Conversion from Warfarin to Edoxaban

- Discontinue warfarin and start Edoxaban when INR < 2.5

6.5.4.7 Conversion from Edoxaban to Warfarin

- For patients on 60mg convert to 30mg together with appropriate maintenance dose of warfarin therapy
- For patients on 30mg convert to 15mg together with appropriate maintenance dose of warfarin therapy
- **DO NOT USE LOADING DOSES**
- Check INR after 2 days of co-administration. Obtain INR before next schedule dose of Edoxaban.
- Continue co-administration until the INR is > 2.0 then discontinue Edoxaban. This should be achieved within 14 days. After 14 days discontinue Edoxaban and continue to titrate VKA to achieve INR.
- It is recommended during concomitant therapy to take blood just prior to Edoxaban dose to minimise effect of Edoxaban on INR measurements.

6.5.4.8 Conversion from LMWH to Edoxaban

- Discontinue subcutaneous anticoagulant and start edoxaban at the time of the next scheduled subcutaneous anticoagulant dose.
- Discontinue the Unfractionated Heparin Infusion and start edoxaban 4 hours later.

6.5.4.9 Cardioversion

- Edoxaban can be initiated or continued in patients who may require cardioversion

6.5.4.10 Complications (refer to SPC)

Haemorrhage, contusion, epistaxis and haematoma.

7. Management of sub-therapeutic INRs in Patients with Mechanical Heart Valves

Patients with mechanical prosthetic heart valves are at increased risk for arterial thromboembolism, which includes stroke, systemic embolism and valvular or intracardiac thrombosis.

Because of this increased risk, patients with mechanical prosthetic valves need long-term anticoagulation therapy. Anticoagulation is usually achieved with the use of a vitamin K antagonist (VKA), such as warfarin. DOACs are not licensed for patients with mechanical heart valves.

Patients with an INR <1.8 require bridging therapy with a low molecular weight heparin. The use of Low Molecular Weight Heparin (LMWH), such as Enoxaparin (Inhixa®), as bridging therapy for patients with mechanical prosthetic valves is unlicensed. There are however clinical trials and registry data assessing LMWH for this use, showing that is both safe and effective compared to UFH for most patient groups.

8. Anticoagulation for Procedures and Bridging

At PGH all elective surgical admissions will be reviewed and bridged at the Pre-assessment clinic, Ext 2034. Endoscopy patients at PGH should be referred to the Anticoagulation Clinic at Poole, Ext 8006.

At RBH all patients should be referred to Bridging clinic no later than 12 days prior to admission. Complete an anticoagulant referral and place in Bridging Folder in Pre-Assessment. A peri-operative management plan based on bridging guidelines will be made for each patient. Contact Hayley Flavell, Ext. 5862, or Anticoagulation Clinic, Ext. 4778 for advice.

8.1 Warfarinised Patients

The risk of stopping oral anticoagulation for a procedure has to be assessed by comparing the risk of thrombosis versus the risk of bleeding. Patients who have Mechanical Heart Valves and INR <1.8 or patients within 4 weeks of DVT or PE should be considered for Enoxaparin (Inhixa®) cover.

Peri-operative warfarin management protocol

5 days pre-surgery

- Check INR, APTT, FBC and renal profile

- Stop warfarin 5 days pre-surgery
  - If INR is < 2, start bridging anticoagulation on the same day
  - If INR is 2 – 2.9, start bridging anticoagulation 4 days pre-surgery
  - If INR is 3 – 3.9, start bridging anticoagulation 3 days pre-surgery
  - If INR is ≥ 4.0 start bridging anticoagulation 2 days pre-surgery

2 days pre-surgery
- Re-check INR if possible. This may allow better planning and prevent last-minute cancellation of operation
- If INR is > 3, consider stat dose of 2mg oral vitamin K (discuss with Haematologist).

1 day pre-surgery stop bridging anticoagulation at least 12 –24hours (mechanical valves) or preferably 24 hours (all other cases) before surgery

Day 0 (pre-surgery)
- Re-check INR, FBC and renal profile
- If INR is < 1.5, proceed with surgery (plan for late morning or early afternoon)
- If INR is ≥ 1.5, delay surgery and repeat INR in 24 hours. Proceed if INR is < 1.5

Day 0 (post-surgery) re-load warfarin at 6pm with twice the patient's usual therapeutic dose

Day 1 post surgery
- Re-start bridging anticoagulation 24 hours after surgery when haemostasis is achieved. If anticipated bleeding risk is high, consider low-dose bridging anticoagulation (e.g. Enoxaparin (Inhixa®) 40mg)
- Continue warfarin at patient's usual therapeutic dose

Day 2 post surgery onwards
- Check INR daily and adjust warfarin dose using the loading algorithm
- Continue bridging anticoagulation until patient's INR is within therapeutic range

Refer to anticoagulation clinic at discharge from hospital.

8.1.1 Algorithm for stopping warfarin and bridging prior to a procedure in venous thromboembolic disease*, stroke, AF and mechanical heart valves in patients with CrCl≥30ml/min

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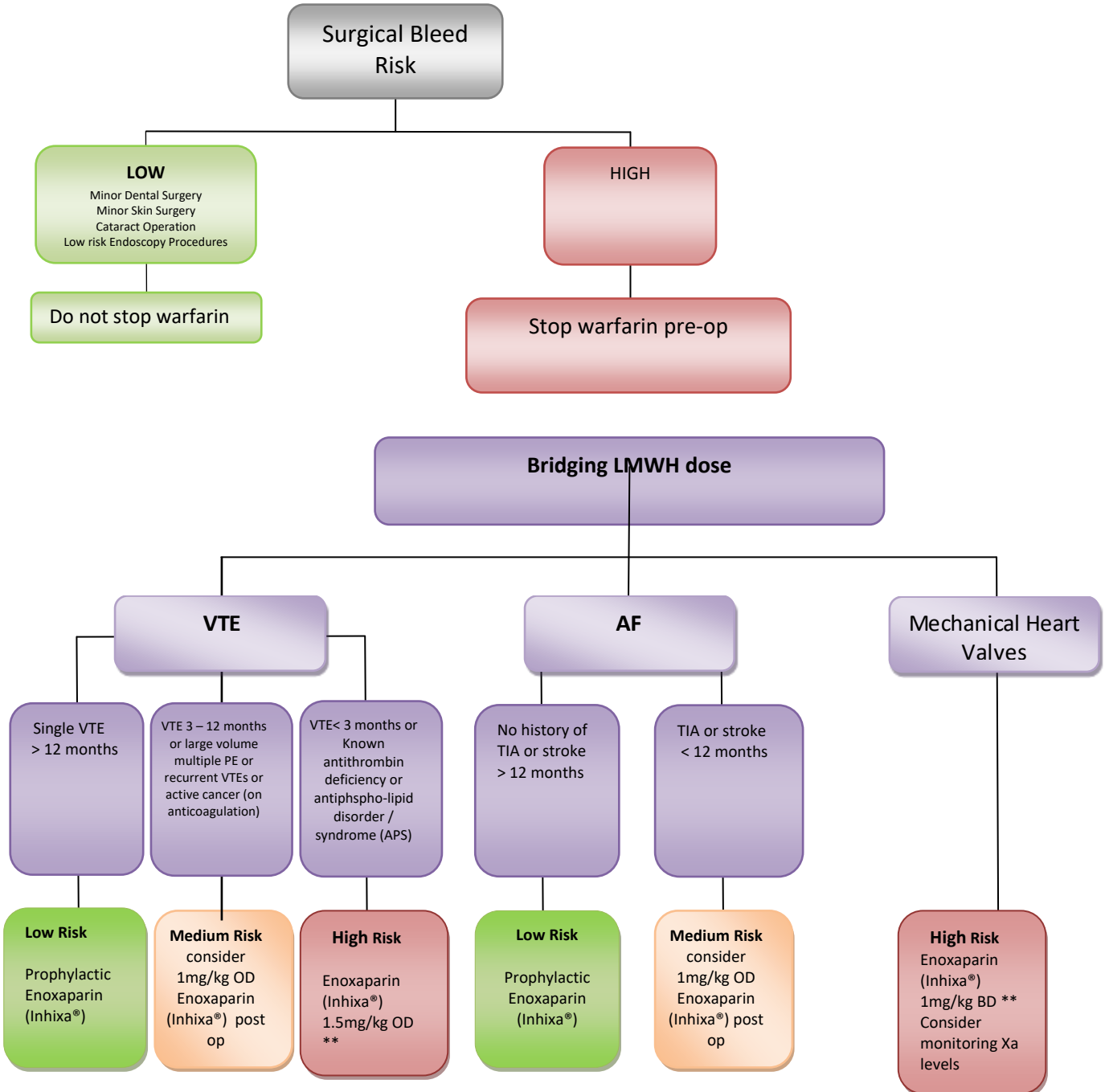


* for stopping anticoagulation in arterial thromboembolic disease please seek haematology advice
** Some patients may be deemed very high risk and an IVC filter may be considered.

Continue bridging anticoagulation until patient's INR is >2

8.1.2 Enoxaparin (Inhixa®) Bridging Dosing
****please note *two different high risk tables* according to indication****

Mechanical heart valve treatment dose
1mg/kg BD

Weight (kg)	CrCl ≥30mL/min (1mg/kg SC BD)	CrCl 15-29mL/min (1mg/kg SC OD)
40-49	40mg BD	40mg OD
50-59	60mg BD	60mg OD
60-74	60mg BD	60mg OD
75 – 89	80mg BD	80mg OD
90 – 109	100mg BD	100mg OD
110 – 125	120mg BD	120mg OD
>125kg	Contact consultant haematologist	

High Risk treatment dose 1.5mg/kg OD

Weight (kg)	CrCl ≥30mL/min (1.5mg/kg SC OD)	CrCl 15-29mL/min (1mg/kg SC OD)
40-49	60mg	40mg
50-59	80mg	60mg
60-74	100mg	60mg
75 – 89	120mg	80mg
90 – 109	150mg	100mg
110 – 125	180mg	120mg
>125kg	Contact consultant haematologist	

Medium risk treatment dose 1mg/kg OD

Weight (kg)	CrCl ≥30mL/min (1mg/kg SC OD)	CrCl 15-29mL/min (1mg/kg SC OD)
40-49	40mg OD	40mg OD
50-59	60mg OD	60mg OD
60-74	60mg OD	60mg OD
75 – 89	80mg OD	80mg OD
90 – 109	100mg OD	100mg OD
110 – 125	120mg OD	120mg OD
>125kg	Contact consultant haematologist	

Low risk patients are dosed with prophylaxis Enoxaparin (Inhixa®)

8.1.2.1 Enoxaparin (Inhixa®) bridging doses in renal impairment

- Low risk patients see section 6.3.4.1

- Medium and high risk patients

CrCl 15 to 29 mL/min	Enoxaparin (Inhixa®) 1mg/kg OD (as per the table above)
CrCl < 15mL/min	Unfractionated Heparin by continuous intravenous infusion

8.2 DOACs

Deciding if and when to stop DOACs prior to any diagnostic/ interventional procedure is based on the associated risk of bleeding and the patients' clinical status. Consideration of renal function is required as clearance of these drugs can be affected by renal function.

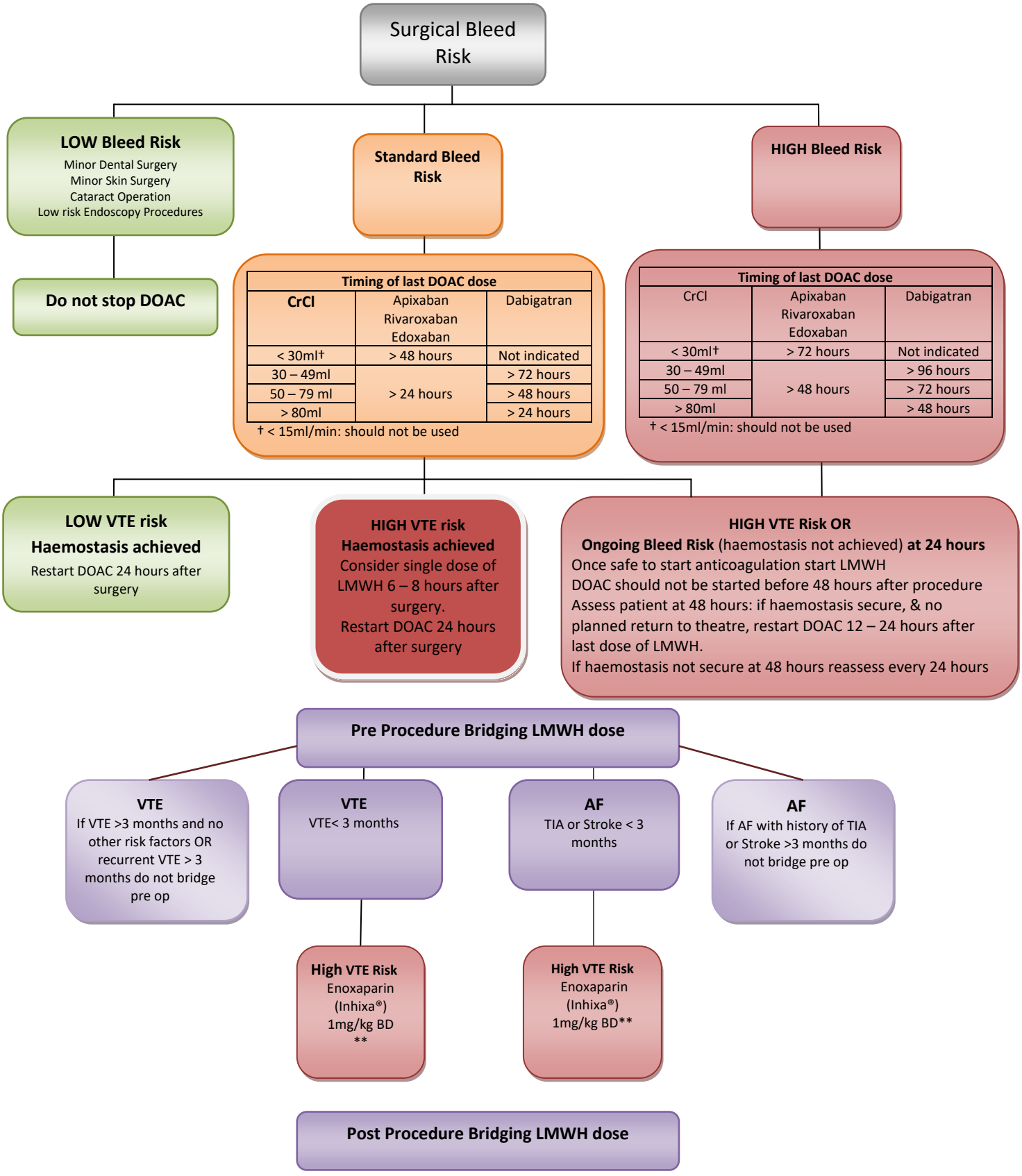
If required, Enoxaparin (Inhixa®) bridging should start at least 24 hours after the last dose of the DOAC and last dose of Enoxaparin (Inhixa®) should be 24 hours before the procedure.

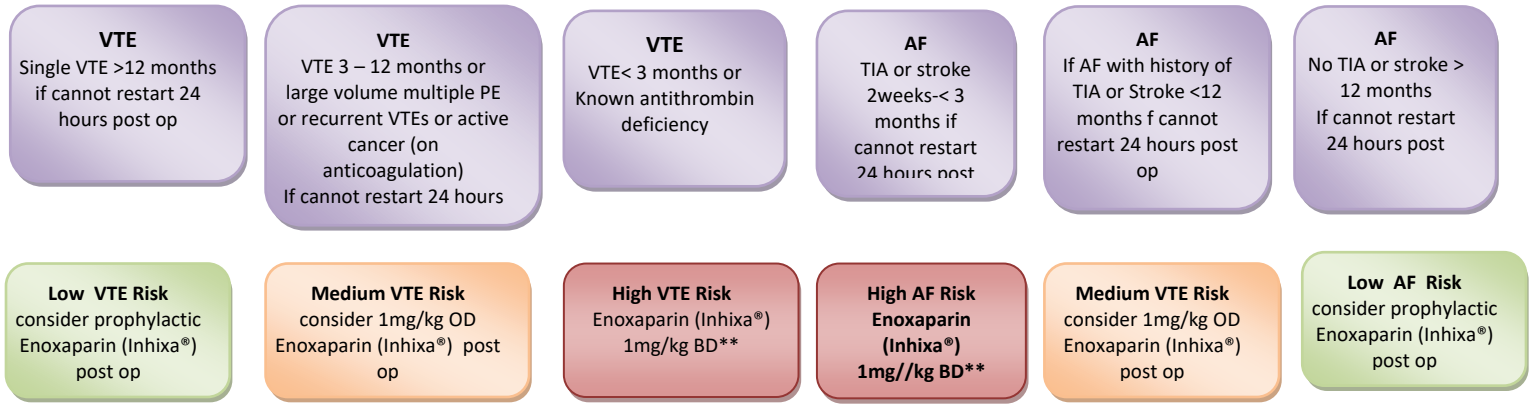
Following the surgery / procedure, the DOAC should only be re-commenced when haemostasis is secured. DOAC anticoagulation should be re-started 24 – 48 hours post-operatively.

8.2.1

For patients who cannot start DOAC and have had a thromboembolic event <3 months consider bridging as warfarin flow chart

Algorithm for stopping DOAC and bridging prior to a procedure in venothromboembolic disease*, stroke, and AF in patients with CrCl≥30ml/min





* for stopping anticoagulation in arterial thromboembolic disease please seek haematology advice
** Some patients may be deemed very high risk and an IVC filter may be considered.

8.2.1.1 Enoxaparin (Inhixa®) bridging doses in renal impairment

- Low risk patients see section 6.3.4.1

- Medium and high risk patients

CrCl 15 to 30 mL/min	Enoxaparin (Inhixa®) 1mg/kg OD (as per table in Section 8.1.2)
CrCl < 15mL/min	Unfractionated Heparin by continuous intravenous infusion

8.3 Dental procedures

- INR check is not required prior to minor non-invasive procedures
- Patients taking DOACS and requiring dental fillings the advice is to continue the DOAC as the bleeding risk of the procedure is low.
- Check INR in patients taking warfarin 2-3 days prior to invasive dental surgery.
- If INR is stable at 2.0 to 4.0, invasive dental procedures may be carried out without discontinuing oral anticoagulants.
- In patients taking a DOAC and requiring an extraction, unless the patient is high risk for recurrent thrombosis it is advised to liaise with a haematologist and consider stopping the DOAC for approx. 24 hours (assuming normal hepatorenal function); in view of the uncertain bleeding risk after an extraction and the difficulty reversing the effects of the DOAC if a bleed did occur.
- Patients requiring single dose antibiotic prophylaxis prior to invasive dental procedures do not require dose reduction or discontinuation of oral anticoagulants.
- Post-operatively, tranexamic acid 5% solution can be used as mouthwash four times daily for 2 days, and is available from Pharmacy for topical use.
- Do not use NSAID or COX-2 inhibitors for post-operative pain control.

9. Emergency Surgery

9.1.1 Warfarin

- Stop warfarin and check FBC and full clotting screen (INR/APTT/fibrinogen).
- If INR is >1.5 and surgery can be delayed for >6 hours then administer IV vitamin K (phytomenadione) (see section 10.1.1).
- If surgery is required in <6 hours, administer IV Octaplex plus IV vitamin K (phytomenadione). The dose of the Octaplex and vitamin K will depend on INR and type of surgery required – refer to RBCH Octaplex Administration Guideline

- The risk of thrombotic complications with the current PCCs is probably no more than 1%.
- If a PCC is unavailable, FFP may be given at 15mL/kg in conjunction with IV vitamin K (phytomenadione).
- Re-check INR every 15-30 minutes after PCC / FFP administration, and again at 6 hourly intervals thereafter, as further agents may be needed.
- Restart appropriate anticoagulation as soon as is safely possible post-operatively.

9.1.2 DOACs

- Stop DOAC
- The decision if surgery can be delayed ≥24 hours after last dose of DOAC (see section 8.2) should be taken by senior surgeon / anaesthetist.

- If not:
  - If the patient is on Dabigatran discuss with Consultant Haematologist re administration of Idarucizumab (see section 10.1.6)
  - If the patient is on Apixaban, Rivaroxaban and Edoxaban discuss with consultant haematologist

- Vitamin K and protamine will have **no effect** on bleeding; and Fresh Frozen Plasma is **not** recommended.
- A consultant haematologist should advise on the need for clotting factor concentrates such as Octaplex.
- Refer also to Major Haemorrhage Policy Section 17: Anticoagulation Reversal - https://intranet.poole.nhs.uk/uploads/pathology/Haematology_and_Transfusion_Science/Major_haemorrhage_policy_1.2_path_pol_55_2019.pdf

10. Reversal Agents

10.1.1 Vitamin K1 (Phytomenadione)

Indication:

- bleeding due to vitamin K deficiency
- sustained reversal of warfarin effect

Administration:

- To completely reverse the effect of warfarin then 5mg of IV vitamin K (phytomenadione) should be given (NOTE do not attempt to completely reverse mechanical valves unless life threatening bleed)
- if patient has high INR and is bleeding: 2.5 to 5 mg IV
- if patient has high INR only, is not bleeding and complete reversal is not required: 0.5 to 2 mg IV as depicted in table below, or oral administration of the IV preparation (Konakion-MM) can be given

Dose of vitamin K required to reverse warfarin when an INR < 1.5 is required

INR	Phytomenadione dose (vitamin K)
> 1.5 but < 2.0	0.5 mg
≥ 2.0 < 3.0	1mg
≥ 3.0	2mg

Phytomenadione is fat soluble. In patients with liver dysfunction menadiol, the water soluble form of vitamin K, should be used for oral administration.

Adverse effects

- Anaphylactoid reactions have been reported.

Dose of Vitamin K required to reverse warfarin when patient is bleeding:

TARGET INR			
2.5	3.5		
Presenting INR		Bleeding	Intervention
2.0 - 3.0	3.0 - 4.0	Minor/major	Investigate for local causes of bleeding
3.1 - 4.5	4.1 - 5.5	None	Reduce warfarin dose. Repeat INR in a week. No vitamin K required
4.6 - 5.9	5.6 - 5.9	None / minor	Omit warfarin for 1 day and reduce dose. Repeat INR within a week. No vitamin K required
6.0 - 8.0	6.0 - 8.0	None / minor	Omit warfarin for 2 to 3 days. Repeat INR on 3rd day. Re-start warfarin when INR < 5.0 at reduced dose. Consider IV vitamin K 2 mg orally (iv preparation can be given orally)
> 8.0	> 8.0	None / minor	Omit warfarin for 2 to 3 days. Inject Vitamin K 1 to 2 mg intravenously. Repeat INR daily. Re-start warfarin when INR is in therapeutic range and consider reduced dose.
> 8.0	> 8.0	Major	Stop warfarin treatment. Inject PCC and Vitamin K 5 mg intravenously. Repeat INR 1 hour after PCC and daily. Review indication for anticoagulation and target INR.

10.1.2 Protamine Sulphate

Indications:

- reversal of heparin effect

Stopping the heparin infusion is usually sufficient however if this is not the case:

- 1 mg of protamine will neutralise 100 units of UFH **given within the previous hour**
- Halve protamine dose if heparin stopped for one hour.
- Quarter protamine dose if heparin stopped for two hours.
- Maximum dose is 50 mg.
- Maximum rate of IV injection is 5 mg/min.
- Avoid exceeding these doses as excess protamine itself has anticoagulant properties
- Monitor APTT ratio
- Neutralisation of LMWH is incomplete with protamine sulphate
- Refer to BNF and SPC of heparin, LMWH and protamine for further details.

10.1.3 Prothrombin complex concentrate (PCC, Octaplex)

Octaplex is the PCC available in the Trust and is stored in the transfusion laboratory.
The use of Octaplex must be authorised by a Consultant Haematologist.

Plasma derived clotting factor concentrate

- contains factors II, VII, IX, X, protein C, protein S
- contains heparin as an excipient

Indications:

- Emergency reversal of warfarin effect,
- Life-threatening bleeding in the presence of warfarin
- Replacement therapy for factor II, X deficiencies when the specific factor is not available

Dosage for reversal of warfarin effect: Discuss with Registrar / Consultant in Haematology and Refer to Trust guidelines for Octaplex: Octaplex Administration Policy

Check pre- and post-INR after Octaplex administration
Note: Thrombosis can occur following administration of Octaplex

10.1.4 Fresh frozen plasma (FFP)

The use of FFP must be authorised by a Consultant Haematologist

Indications

- emergency reversal of warfarin if PCC is contra-indicated
- See RBCH hospital **transfusion policy (**section 6.3) or PHFT Major Haemorrhage Policy (section 12) for details of administration

10.1.5 Recombinant FVIIa (NovoSeven)

The use of NovoSeven must be authorised by a Consultant Haematologist.

Indications:

- Haemophilia with inhibitors,
- Acquired haemophilia,
- Factor VII deficiency

Prior to requesting NovoSeven, ensure that local and general haemostatic measures have been implemented.

- Platelet count > 50 x 10^9/L
- FFP 15 mL/kg to correct DIC
- Cryoprecipitate 1.5 units /10 kg to correct fibrinogen < 1.0 g/L
- Correction of acidosis

NovoSeven is available through the Transfusion laboratory.

Contra-indications:

- allergy to bovine, hamster or mouse proteins

Cautions:

- Recent MI or PCI,
- Prosthetic heart valves,
- Recent PE or very high risk for VTE,
- Recent ischaemic stroke

Side-effects**:**

- thrombosis, e.g. MI and Stroke

10.1.6 Idarucizumab (Praxbind®)

The use of this product must be authorised by a Consultant Haematologist.

Indications:

- specific reversal agent for Dabigatran

Dose and Administration:

- 5 g (2 x 2.5g vials) administered as two consecutive intravenous infusions over 5 to 10 minutes each or as a bolus injection
- Dabigatran can be re-started 24 hours after administration of idarucizumab; administration of other anticoagulant therapy (e.g. LMWH) can be started at any time

Idarucizumab is available through the Transfusion laboratory

Cautions:

- Risk of thrombus
- Fructose intolerance
- Hypersensitivity

10.2 Apixaban, Rivaroxaban and Edoxaban Reversal

Any case requiring immediate DOAC reversal should be discussed with a consultant haematologist.

The use of activated charcoal: Administered via a nasogastric tube it can reduce GI absorption if given within 2 hours of taking the drugs.
The use of haemofiltration / haemodialysis: DOACs are heavily protein bound hence haemodialysis / haemofiltration would be of **no value** in eliminating the drugs.

10.3 Fondaparinux Reversal

- There is no known antidote to Fondaparinux.
- Overdose associated with bleeding complications should lead to treatment discontinuation and appropriate therapy such as surgical haemostasis, blood replacements, fresh plasma transfusion and plasmapheresis should be considered
- Consult haematologist for advice

11. Spinal or epidural anaesthesia and antithrombotic drugs

11.1.1 Neuraxial (epidural or spinal) anaesthesia and analgesia

The following guidelines are based on the ASRA and ESRA guidelines. The Consultant Anaesthetist will decide on the timing of neuraxial blockade.

- Avoid neuraxial blockade in patients who are therapeutically anticoagulated.
- Neuraxial block should not be performed for 6 hours after administration of IV heparin
- IV heparin should not be administered for 1 hour after neuraxial blockade
- Neuraxial blocks should not be performed for 18 hours if CrCl < 30mL/min after administration of prophylactic LMWH
- Neuraxial blocks should not be performed for 36 hours after administration of therapeutic Enoxaparin (Inhixa®) if CrCl < 30mL/min.
- Epidural catheters should not be removed within 12 hours after last dose of prophylactic Enoxaparin (Inhixa®) and 24 hours from last therapeutic dose.
- Avoid concurrent use of epidural analgesia and oral anticoagulant drugs. If this is unavoidable, ensure INR < 1.5 prior to neuraxial block or removal of epidural catheter.

11.1.2 Regional Anaesthesia and Anticoagulation

Drug	Time to peak effect	Elimination half life	Acceptable time after drug for block insertion	Drug administration whilst spinal or catheter in place	Time after block / catheter removal for next drug dose
Heparins					
Heparin sc prophylaxis	<30 mins	1-2h	4h or normal APTTR	caution	6h
Heparin IV Treatment Dose	<5 mins	1-2h	4h or normal APTTR	caution	6h
LMWH sc prophylaxis	4hours	3-7h	12h	caution	6h
LMWH sc Treatment Dose	4hours	3-7h	24hr	no	6h
Oral Anticoagulants					
Warfarin	3-5 days	4-5days	INR<1.4	No	6h
DOACs					
Rivaroxaban Prophylaxis	1 to 3h	5 to 13 h	18h	no	6h
Rivaroxaban Treatment	1 to 3h	5 to 13 h	24 - 48h	no	6h
Apixaban	1 to 3 h	12h	24-48 h	no	6h
Edoxaban	1 to 3 h	10-14h	24 to 48 h	no	6h
Dabigatran	1 to 3h	12 – 17h	Not recommended	no	
CrCl > 80 ml/min	0.5- 2h	15h	48h	no	6h
CrCl 50–80 ml/min	0.5- 2h	15h	72h	no	6h
CrCl 30–50 ml/min	0.5- 2h	18h	96h	no	6h
Antiplatelet drugs					
Aspirin	12-24h	irreversible	7 days	no extra precaution	no extra precaution
Clopidogrel	12-24h	irreversible	7 days	no	6h
NSAIDs	1-12h	1-12h	no extra precaution	no extra precaution	no extra precaution

It is common for IV UFH to be given a short time after spinal blockade or insertion of an epidural catheter during vascular and cardiac surgery. Local clinical governance guidelines should be followed and a high index of suspicion should be maintained if any signs attributable to vertebral canal haematoma develop

12. Anti-Platelets and Other Anticoagulants

Only general recommendations are made and any intervention i.e. stopping an antiplatelet or DOAC must take into account the type of surgery planned including bleed risk, the patient's cardiac history (risk of thromboembolic event/ cardiovascular event (CVE) – especially recent history of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Consult the patients cardiologist where indicated.

Patients at **low risk** of a VTE/CVE taking one antiplatelet agent or cilostazol – stop this agent 7 days prior to surgery. Patients taking an NSAID or dipyridamole should stop these 24 hours prior to surgery.

Patients at **moderate to high risk** of a VTE / CVE taking one antiplatelet agent, this should be continued or discussed with a cardiologist.

12.1.1 Patients with Stents (PCI) undergoing any surgery

Aspirin (or alternative antiplatelet in aspirin allergic patients) should **never** be stopped in a patient with a coronary stent - these patients should **always** be on an anti-platelet drug lifelong.

In patients with a coronary stent who are receiving dual anti-platelet therapy ('DAPT' - aspirin plus either clopidogrel/ prasugrel/ ticagrelor) and require any form of surgery - recommend deferring surgery for at least 1 month after placement of a bare-metal stent and ideally for at least 12 months after placement of a drug-eluting stent.

If patients require surgery within these time frames this MUST be discussed with the interventional cardiologist who implanted the stent AND the anaesthetists - as these are high risk patients (in regards to patency of stent and use of general anaesthetic)

For patients who are receiving dual anti-platelet drugs following a coronary artery stent and have a life threatening bleed, apart from stopping both drugs, there may be a case for transfusing platelet concentrates but only if this is agreed by a Consultant Cardiologist and/or Consultant Haematologist.

12.1.2 Patients undergoing cardiac surgery

For patients undergoing cardiac surgery the advice with antiplatelet drugs is:

- Patients who are having elective cardiac surgery are advised to stop Aspirin and Clopidogrel Prasugrel/ Ticagrelor / a week prior to cardiac surgery.
- For inpatients - Clopidogrel / Prasugrel / Ticagrelor should be stopped when the decision is made for inpatient surgery, ideally a week prior to cardiac surgery. Aspirin should be stopped 3 days prior to cardiac surgery if the time frame permits
- Clopidogrel / Prasugrel/ Ticagrelor should only be continued if the patient has had a recent PCI or at the discretion of the Cardiologist (severe LMS stenosis etc.)

12.1.3 Patients undergoing endoscopy

For patients on antiplatelets undergoing endoscopy see separate guidelines
https://intranet.rbch.nhs.uk/policies/acute-medicine/gastro/Endoscopy_Anticoagulation_Antiplatelet.pdf

13. Glossary

ACS acute coronary syndrome
AF atrial fibrillation
APTTR activated partial thromboplastin time ratio
AVR atrial valve replacement
BMI body mass index
BMS biomedical scientist
CCF congestive cardiac failure
CrCl creatinine clearance
DIC disseminated intravascular coagulation
DOAC Direct oral anticoagulant
DVT deep vein thrombosis
FBC full blood count
FFP fresh frozen plasma
GECS graduated elastic compression stockings
GFR glomerular filtration rate
HIT heparin induced thrombocytopenia
INR International Normalised Ratio
IPC intermittent pneumatic compression
IV intravenous
LFT liver function tests
LMWH low molecular weight heparin
MDRD modification of diet in renal disease
MI myocardial infarction
MVR mitral valve replacement
NSAID non-steroidal anti-inflammatory drug
NSTEMI non ST elevation myocardial infarction
PCI percutaneous coronary intervention
PE pulmonary embolus
PNH paroxysmal nocturnal haemoglobinuria
PCC prothrombin complex concentrate
PT prothrombin time
SC subcutaneous injection
SE systemic embolism
TEDS commonly used brand name for Graduated Elastic Compression Stockings (GECS)
UA unstable angina
U&E urea and electrolytes
UFH unfractionated heparin
VFP venous foot pump
VKA vitamin K antagonist
VTE venous thromboembolism

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15. Consultation Process

Version	Date	Author	Level of Consultation
3	March 2010	Dr J Chacko, Hayley Flavell, Jacqui Bowden	D&TC
5	Sept 2014	Moe Visram, Alison FitzPatrick, Stephen Fleck	D&TC
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9	January 2019	HF, JM, Tracy Sandell (PGH)	D&TC
11			
12	August 2020	Faye Thornton, Hayley Flavell, Jason Mainwaring, Craig Prescott	Thrombosis committee, D&TC

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1. Title of document/service for assessment	Anticoagulation Guidelines
2. Date of assessment	September 2020
3. Date for review	September 2023
4. Directorate/Service	Trust-wide
5. Approval Committee	D&TC

	Yes/No	**Rationale**
6. Does the document/service affect one group less or more favourably than another on the basis of:		
• Race	No	
• Gender (including transgender)	No	
• Religion or belief	No	
• Sexual orientation, to include heterosexual, lesbian, gay and bisexual people	No	
• Age	No	
• Disability – learning disabilities, physical disabilities, sensory impairment and mental health issues	No	
• Marriage and Civil Partnership	No	
• Pregnancy and Maternity	No	
7. Does this document affect an individual's human rights?	No	
8. If you have identified potential discrimination, are the exceptions valid, legal and/or justified?	N/A	
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10. Screener(s)

Print name: Jacqui Bowden

11. Date Policy approved by Committee	

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