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Anticoagulation in Venous Thromboembolism

These guidelines are not intended for use in pregnant patients.

These guidelines are not intended for use in patients with Atrial Fibrillation.

Introduction

This guidance document provides general information on various anticoagulant agents used in venous thromboembolism (VTE) management. It also includes some information on decision making regarding duration of therapy.

Index of headings

1. Enoxaparin

1.1 Enoxaparin is the Low Molecular Weight Heparin (LMWH) approved for use in SHSCT. When prescribing Enoxaparin, the brand name 'Inhixa®' must be endorsed on the kardex or prescription and in all communication regarding Enoxaparin, for example authorisation form for district nurse.

1.2 Check baseline full blood picture, U&E, LFT and coagulation screen before initiation of anticoagulation.

1.3 When renal function is normal or moderately impaired (eGFR >30ml/min), Enoxaparin is administered subcutaneously either as:

- **a once daily injection of 1.5mg/kg**: used in uncomplicated femoral or popliteal DVTs
- **or as twice daily injections of 1mg/kg**: used in all other patients such as those with obesity (>100kg), with symptomatic PE, cancer, recurrent VTE or proximal (iliac vein) thrombosis

Treatment of DVT / PE
eGFR >30ml/min

Uncomplicated femoral or popliteal DVT		**All other patients such as those with obesity, symptomatic PE, cancer, recurrent VTE or proximal (iliac vein) thrombosis**	
1.5mg/Kg ONCE DAILY		**1mg/Kg TWICE DAILY**	
Weight Kg	**Dose**	**Weight Kg**	**Dose**
37 – 43kg	60mg OD	40-45kg	40mg BD
44 – 50kg	70mg OD	46-55kg	50mg BD
51 – 56kg	80mg OD	56-65kg	60mg BD
57 – 63kg	90mg OD	66-75kg	70mg BD
64 – 73kg	100mg OD	76-85kg	80mg BD
74 – 85kg	120mg OD	86-95kg	90mg BD
86 – 95kg	135mg OD	96-110kg	100mg BD
96 – 100kg	150mg OD	111-125kg	120mg BD
		126-140kg	135mg BD
		141-155kg	150mg BD
		>155kg	Discuss with Haematology

* if patient self-administering consider amending dose to nearest commercially available syringe e.g. 20mg, 40mg, 60mg, 80mg, 100mg, 120mg, 150mg

1.4 All patients with severe renal impairment, classed as eGFR <30ml/min, require a reduced dose of enoxaparin of 1mg/kg once daily.

VTE Treatment Dose Adjustment For Renal Impairment*

(All Patients /Indications)

***eGFR <30ml/min.**
Dose: 1mg/kg ONCE daily

Weight Kg	Dose*
40 – 45	40 mg once daily
46 – 55	50 mg once daily
56 – 65	60 mg once daily
66 – 75	70 mg once daily
76 – 85	80 mg once daily
86 – 95	90 mg once daily
96 – 110	100 mg once daily
>110kg	Discuss with haematologist

* if patient self-administering consider amending dose to nearest commercially available syringe e.g. 20mg, 40mg, 60mg, 80mg, 100mg, 120mg, 150mg

1.5 LMWH does not prolong the APTT and routine monitoring is not required. Monitoring the anti-Xa activity is useful in patients with renal impairment (eGFR<30 ml/min) in whom LMWH may accumulate and in patients less than 50kg or over 150kg in weight.

- **Twice daily dosing**: Anti-Xa levels should be checked at their peak at **4 hours after LMWH dose** (sample usually taken after 3rd dose) = **0.6 - 1.1** units/ml.
- **Once daily dosing**: Anti-Xa levels should be checked at their peak at **4 hours after LMWH dose** (sample usually taken after 3rd dose) = **1.0 - 2.0** units/ml.

1.6 Routine monitoring of the full blood count (FBP) to identify heparin induced thrombocytopenia is not required.

1.7 All patients being discharged home on Enoxaparin must be given the patient information sheet on Inhixa®.

1.8 Abdominal wall haematoma must always be considered as a diagnosis in patients with abdominal pain injecting low molecular weight heparin (LMWH) into the subcutaneous tissue of the abdominal wall. Obesity and female gender are risks for massive haematoma formation and this can be life threatening. In those with severe obesity LMWH injection into subcutaneous tissue of the thighs (rather than the abdominal wall) should be considered to reduce the risk of haematoma formation.

Abdominal wall haematoma most often presents as acute onset of abdominal pain with a palpable abdominal mass. Pain is usually worse with movement and is often unilateral. Additional findings may include fevers, chills, nausea, vomiting, abdominal tenderness, and abdominal guarding. The nonspecific nature of these symptoms combined with the low incidence of the disorder lead to difficulty in considering this diagnosis. Conservative treatment is feasible in most cases. Early diagnosis is essential in order to avoid morbidity. Patients must be educated on injection technique and rotating sites for administration of LMWH.

1.9 Reversal of LMWH by protamine sulphate is partial and should only be used in severe bleeding within 12 hours of patient receiving a therapeutic dose of enoxaparin.
See guideline on Trust intranet on the use of protamine to reverse enoxaparin.

1.10 If the General Practitioner is to continue prescribing Enoxaparin after discharge from hospital, ensure that a 'Referral to GPs for arrangement of shared care for patients on enoxaparin' form is completed Enoxaparin Shared Care Letter for GP.
Enoxaparin Shared Care Guideline can be found at the following link. Shared Care – Interface Pharmacist Network Specialist Medicines (hscni.net).

2. Commencing Oral Anticoagulants

2.1 The decision on timing of transfer to oral anticoagulant therapy is made by the supervising clinician in each individual case. In many patients, it is often reasonable to start DOAC (apixaban or rivaroxaban) as soon as diagnosis of VTE is confirmed, without the need for any preceding enoxaparin.

The other DOACs (dabigatran and edoxaban) require at least 5 days treatment with a parenteral anticoagulant (ie. enoxaparin) before commencing oral therapy.

When a patient has had a dose of enoxaparin, the DOAC should be commenced when the next dose of enoxaparin is due.

In submassive PE or extensive DVT, using enoxaparin prior to commencing an oral anticoagulant may be desirable to ensure the patient is clinically improving i.e. delay start of oral therapy until response to anticoagulation is confirmed.

2.2 In young women exclude pregnancy before starting DOAC or warfarin as they are contraindicated in pregnancy.

2.3 Check baseline full blood picture, U&E, LFT and coagulation screen before initiation of anticoagulation.

3. DOACs

3.1 The four DOACs apixaban, rivaroxaban, edoxaban and dabigatran are all licensed and approved by NICE for the treatment and prevention of both deep vein thrombosis and pulmonary embolism.

3.2 Apixaban is recommended first line in SHSCT and Northern Ireland Formulary. Full prescribing information is available via BNF or eMC SPC and these information sources should be referred to by prescribers. Particular attention should be paid to body weight (see section 3.5 below), renal function, liver function and potential medication interactions. The dose of Apixaban for treatment of VTE is 10mg twice daily for 7 days, followed by 5mg twice daily. If anticoagulation treatment is to be continued beyond 6 months, the dose is reduced to 2.5mg twice daily after 6 months.

3.3 Renal impairment increases the risk of DOAC anticoagulants accumulating in the body, which can increase bleeding risk.

Apixaban, rivaroxaban and edoxaban are not recommended in patients with creatinine clearance < 15 mL/min.

Dabigatran is contraindicated in severe renal impairment (CrCL <30ml/min).

There is limited evidence on anticoagulant treatment for VTE in patients with severe renal impairment and a clinical decision may need to be made on an individual basis for such patients. It may be appropriate to seek advice from Anticoagulant Pharmacists.

3.4 Use DOACs with caution in patients concomitantly receiving medicines which increase or decrease plasma concentrations of the various DOACs.

3.5 DOACs can be used for patients, in the treatment and prevention of VTE, with body weight between 50kg and 150kg. Outside of this weight range discussion with Anticoagulant Pharmacist or Haematology is advised. Between 50kg and 150kg; APIXABAN is the recommended first choice DOAC (see also point 3.2 above).
(Note Edoxaban and Dabigatran should **not** be used in patients with body weight over 120kg).

3.6 Use the counselling checklists in the various DOAC starter packs to inform the patient about risks and benefits of the medication. The counselling checklists can be found on the Trust intranet (on Clinical Guidelines and Sharepoint). Anticoagulation starter packs.

4. Warfarin

4.1 Transfer to warfarin therapy as per fast induction warfarin schedule. If advice is required on starting warfarin, contact the Anticoagulant Pharmacist.

4.2 LMWH should be given along with warfarin for at least five days and until adequate oral anticoagulation is established, i.e. the INR has been in therapeutic range for 2 consecutive days. If the INR is >3.5 in the first few days of warfarin induction, enoxaparin should be continued and warfarin held until INR is within therapeutic range. If advice is needed, contact the Anticoagulant Pharmacist.

4.3 Referral to Anticoagulant services for warfarin monitoring.

It is the responsibility of the discharging doctor to arrange the first follow-up INR test for the patient at an anticoagulant clinic in hospital or at their GP surgery. They should contact the appropriate clinic and ensure that an appointment is made and that the anticoagulation therapy section of the electronic discharge prescription is completed. The patient should be informed of the arrangement and of their dose of warfarin until their appointment. The details should be written in the patient's yellow booklet or on an appointment card.

If the patient was on warfarin before admission, the next clinic appointment should be at the anticoagulant clinic that the patient was attending before admission. Where this cannot be done, out of hours or at a weekend, the discharging member of staff must ensure this is followed up on the next working day and the patient informed.

If the patient's GP is unable to accommodate the patient for the next INR test required after discharge, refer patient to the hospital anticoagulant clinic.

5. Choice of anticoagulant for DVT or PE in setting of active cancer

When choosing anticoagulation treatment for people with active cancer and confirmed DVT or PE, take into account the tumour site, interactions with other drugs including those used to treat cancer, and the person's bleeding risk.

Apixaban, Rivaroxaban or Edoxaban can be used for treatment if there are:
i) no medication interactions and
ii) no intact gastrointestinal or genitourinary tumour and
iii) no other contraindications/cautions as per BNF/SPC

Low Molecular Weight Heparin (LMWH) can be considered as an alternative if DOACs are not suitable.

Warfarin is not advised in cancer associated thrombosis.

6. Duration of anticoagulant therapy for venous thromboembolism

The information in this section does NOT apply to pregnant women.

'Provoked' and 'Unprovoked' VTE

The term 'provoked' DVT or PE is one that is caused by a known event. VTE can be provoked by:

- transient major risk factors (e.g. major surgery >30 minutes, hospitalization or immobility ≥3 days),

- transient minor risk factors (minor surgery <30 minutes, hospitalization <3 days, pregnancy, estrogen therapy, reduced mobility ≥3 days) or
- persistent risk factors - persistent risk factors include reversible conditions (e.g. curable malignancy, inflammatory bowel disease that resolves) and irreversible conditions (e.g. chronic heart failure, and metastatic malignancy).

The term 'unprovoked' deep vein thrombosis or PE implies that no identifiable provoking environmental event for the DVT or PE is evident.

Duration of therapy

It is critical that the duration of anticoagulant therapy be individualised according to the presence or absence of provoking events and risk factors, the risk for recurrence and bleeding, and the individual patient preferences and values.

UK NICE guidance (NG158) advises:

In first episode of provoked proximal DVT or PE, anticoagulation for a limited duration of three months (three to six months if active cancer) is typically advised, provided the provoking factor is no longer present and the clinical course has been uncomplicated. If the provoking factor remains present at the completion of the treatment course then ongoing anticoagulation should be considered depending on the risks of thrombosis, risks of bleeding and patient preference.

In first episode of unprovoked proximal DVT or PE, consider continuing anticoagulation beyond 3 months (ie. long term anticoagulation). Base this decision on the balance between the person's risk of VTE recurrence and their risk of bleeding. Discuss the risks and benefits of long-term anticoagulation with the person, and take their preferences into account. Explain to patients with unprovoked DVT or PE and a low bleeding risk that the benefits of continuing anticoagulation treatment are likely to outweigh the risks.

7. Screening for cancer in patients with unprovoked VTE

Patients with unprovoked DVT or PE, who are not known to have cancer, should have a thorough medical history and physical examination. In addition they should have blood tests for FBP, U&E, LFT and bone profile. PSA should also be checked in males over 40 years of age. Further investigations for cancer are not routinely advised unless the history, examination or tests listed above raise a clinical suspicion of malignancy.

8. Recurrent thrombosis on anticoagulation

Recurrence should be confirmed with radiological investigation. If thrombus is identified, consideration should be given to this being persistent old thrombus, rather than a new event. Take into account the recent history, clinical findings and D dimer result. Remember that chronic venous incompetence is an important cause of ongoing symptoms.

Subtherapeutic anticoagulation is the most common reason for recurrent thrombosis on anticoagulation.

In the case of a patient in DOAC, check medication compliance and for any medication interactions involving DOACs.

In the case of a patient on warfarin, check the INR and review recent INR records to determine if warfarin has been therapeutic or subtherapeutic. This information is useful to guide future therapy.

Other causes including ongoing thrombotic stimulus (e.g. cancer) may be present. Review the patient's history and undertake a thorough physical examination.

Occasionally no obvious cause is evident (idiopathic).

In the acute setting the usual practise is to replace an oral anticoagulant with therapeutic enoxaparin for a limited time period, before reverting to oral anticoagulation again, possibly with a different agent.

Depending on INR results, a decision can then be made about the long term oral anticoagulant to be used and in the case of warfarin, if the INR was therapeutic at the time of recurrence, then a higher target INR should be considered.

Less commonly used anticoagulants

9. Unfractionated Heparin (UFH)

9.1 The anticoagulant effect of UFH can be corrected by stopping the intravenous infusion (the half-life of IV heparin is 90 minutes); in case of a planned procedure, stop the infusion 4 hours before the procedure and check the APTT. In extreme emergencies UFH can be reversed with protamine sulphate.

9.2 Use the UFH prescription chart on the Trust intranet; Follow directions for dosing and monitoring. Request APTT and not coagulation screens.

9.3 Reversal of intravenous UFH is rarely needed because the half-life is short (90 minutes) and stopping the infusion is sufficient in most cases. Use of protamine is a consultant's decision in view of the risk for anaphylaxis, severe changes in blood pressure (systemic hypotension and pulmonary hypertension) and rebound bleeding due to over correction of incomplete neutralization. 1mg protamine neutralises 80 -100 units heparin when given within 15 minutes of heparin; if longer than 15minutes less protamine is required. Maximum dose is 50mg. Consult product literature.

9.4 Platelet monitoring for HITT is indicated in patients receiving unfractionated heparin within 100 days of previous exposure or when treatment is continued beyond 5 days.

- Check platelet count before first dose of unfractionated heparin and within 24hours if previous exposure is within 100 days.
- Check platelet count on day 4 and while the patient is in hospital continue to check counts every 2 to 4 days until day 15 of therapy
- If the platelet count falls from baseline by at least 50% between day 5 and 21 without other obvious cause and/or the patient develops thrombosis (arterial or venous) or

skin necrosis at injection site, HITT should be considered and the HITT score calculated using the tool on the intranet. If indicated, the assay for 'HITT' should be arranged by contacting the haematology registrar covering haemostasis at BCH. In addition discuss with local haematologist.

10. Fondaparinux

10.1 Fondaparinux is the drug of choice when a patient has a history of allergic reaction to heparin such as heparin induced thrombocytopenia thrombosis (HITT), and when the patient does not wish to receive a porcine product. Use of fondaparinux should be discussed with the trust Anticoagulant Pharmacist or Consultant Haematologist.

10.2 For treatment of VTE use with caution if eGFR 30 – 50 ml/min/1.73m^2. Avoid if eGFR is less than 30ml/min/1.73m^2; in this case consider use of danaparoid.

To treat DVT or PE fondaparinux is given by subcutaneous injection. The dose is determined by weight and renal function as indicated above.

- Body-weight under 50kg (eGFR >30): dose is 5mg every 24hours.
- Body-weight 50 -100 Kg (eGFR >30): dose is 7.5mg every 24 hours.
- Body-weight over 100kg (eGFR >30): dose is 10mg every 24 hours.

Consult the BNF and product literature for more information.

11. Thrombolytic Therapy

11.1 Deep Vein Thrombosis;

Consider catheter directed thrombolytic therapy for patients with symptomatic ileofemoral DVT who have -

- symptoms of less than 14 days duration AND
- good functional status AND
- life expectancy of 1 year or more AND
- a low risk of bleeding.

Discuss with Consultant responsible for patient and Vascular Surgery in RVH.

11.2 Pulmonary Embolism;

See Trust guideline on Thrombolysis therapy in acute pulmonary embolism.

Guideline-for-Thrombolysis-Therapy-in-Acute-Pulmonary-Embolism.pdf.

12. Compression stockings for DVT

As per NICE guidance, elastic graduated compression stockings should not be offered to patients to prevent post-thrombotic syndrome or VTE recurrence after a proximal DVT. Though they may be used for the management of leg symptoms after DVT.

If compression stockings are required for the management of leg symptoms after DVT:

- **Below knee Class 2 stockings** (18 mmHg to 24 mmHg) are recommended.
- Compression stockings should be put on first thing in the morning (before any leg swelling develops or worsens) and taken off at bedtime.
- The prescription for compression stockings should be renewed **every 3–6 months** if the stockings are used every day.

13. Patient information

13.1 Give patients who are receiving Enoxaparin injections the patient information sheet on Inhixa®.

13.2 If the patient or their carer is administering the Enoxaparin, they should be given the leaflet 'How to inject with Inhixa®'. Follow Trust guidance when teaching a patient or carer to administer a subcutaneous injection.

13.3 Patients treated with warfarin should be given an Oral Anticoagulant Therapy information pack and monitoring book with record of warfarin dose and date and venue for next INR test.

13.4 Patients treated with a DOAC should be given written information and an alert card.

14. IVC Filters

In patients with recent (ie. in past six weeks) acute venous thrombosis who develop a contraindication to anticoagulation a temporary IVC filter may be appropriate.

Prior to placing a temporary filter, a multidisciplinary discussion should occur involving senior medical staff from the referring specialty, Interventional Radiology and Haematology. If a filter is placed, consideration must be given to when it will be removed and to future anticoagulation needs.

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Disclaimer:

Whilst every care has been taken to ensure that the format of this guideline is correct, the SHSCT can accept no responsibility whatsoever for the actual content of the guideline.

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