UNIVERSITY HOSPITAL DIVISION
ANTITHROMBOTIC GUIDE (ADULTS)
Version 4.0

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It is important that the most current version is used.
It is available on the front page of the intranet and Healthcare A-Z, Haematology, Policies section.

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Date: September 2018
For annual review

Abbreviations:

DOAC:	direct oral anticoagulant
DVT:	deep vein thrombosis
GECS:	graduated elastic compression stockings
HIT:	heparin-induced thrombocytopenia
IPC:	intermittent pneumatic compression
IV:	intravenous
LMWH:	low-molecular-weight heparin
PE:	pulmonary embolism
PTS:	post-thrombotic syndrome
SC:	subcutaneous
UFH:	unfractionated heparin
VTE:	venous thromboembolism

Contents:

General Issues

This guide intends to provide general advice on antithrombotic therapy for non-pregnant adult patients only. It is divided into 2 sections: (i) venous thromboprophylaxis, and (ii) issues surrounding therapeutic anticoagulation, with a focus on venous thromboembolism.

For advice regarding thromboprophylaxis and treatment of thrombosis in pregnancy please refer to the Simpson's Centre for Reproductive Health (SCRH) policies and Royal College of Obstetricians and Gynaecologists (RCOG) Green Top Guidance.

http://intranet.lothian.scot.nhs.uk/Directory/reproductivemedicine/policiesandguidelines/documents/maternity%20pan%20lothian/antenatal/thromboprophylaxis%20in%20pregnancy.pdf

https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg37a/

https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg37b/

Please note that this guide is intended as such. Prescribers should take account of local policy within their unit and directorate, and also individual needs of their patient.

Low Molecular Weight Heparin (LMWH) brand on Formulary:
Dalteparin (Fragmin®) is currently the brand of LMWH used in NHS Lothian. It is licensed and approved for use in:
(i) prophylaxis of VTE
(ii) treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE)

LMWH administration technique:
Dalteparin should be administered by subcutaneous (SC) injection, while the patient is lying down, alternatively in the left and right anterolateral or posterolateral abdominal wall. Introduce the whole length of the needle vertically into a skin fold held between the thumb and index finger. Do not release the skin fold until the injection is complete and do not rub the injection site afterwards.
Patients should be advised that local allergies in the form of skin erythema can occur. The patient should be advised to seek medical advice should this occur as a change in the brand of LMWH may be warranted, and the patient may require to have an FBC check to exclude heparin-induced thrombocytopenia.

Intravenous unfractionated heparin (UFH):
In very select circumstances where UFH is used for treatment please note that in NHS Lothian it is available in a ready made concentration of 1000 units/ml. Prescribe as "heparin 1000 units/ml". **DO NOT DILUTE THIS PREPARATION.** An NHS Lothian Adult Heparin Infusion Chart is available on the front page of the intranet for patients with a standard risk of bleeding.

Heparin and LMWH should be prescribed as "units" to avoid prescription errors.

Direct Oral Anticoagulant (DOAC) on Formulary:
Apixaban is currently the DOAC of choice in NHS Lothian.

Section 1: Thromboprophylaxis

General guidance:

- An individual risk assessment for DVT prophylaxis should be carried out for all patients on admission and documented in the clinical case notes. Currently surgical patients at St John's Hospital site are assessed using the Caprini score.

- Decisions regarding anticoagulant thromboprophylaxis in acutely-ill hospitalised patients should be made after consideration of risk factors for both VTE and bleeding (Tables A and B, pages 7 and 8, and Tables F, G and H on pages 11-12).

- Acutely-ill hospitalised medical patients at low risk of VTE, and those who are bleeding or at high risk of bleeding, should not receive anticoagulant thromboprophylaxis. Instead, properly measured and fitted graduated elastic compression stockings (GECS) or intermittent pneumatic compression (IPC) devices should be used. When the bleeding risk subsides, consideration can be given to starting pharmacological thromboprophylaxis.

- Prescribe all prophylaxis including GECS on the patient Prescription and Administration Record.

- Hydrate and mobilise all patients as early as possible.

- Document the reasons in the case notes if thromboprophylaxis is withheld or if there is any deviation from the guideline.

Table A: Risk factors for venous thromboembolism

Risk Factor	Comments
Age	Incidence of first VTE rises exponentially with age. Less than 40 years - annual incidence of 1/10,000. 60-69 years - annual incidence of 1/1000. Greater than 80 years - annual incidence of 1/100.
Obesity	2-3 fold VTE risk if obese (body mass index greater than or equal to 30kg/m^2).
Varicose veins	1.5-2.5 - fold risk after major general/orthopaedic surgery. Low risk after varicose vein surgery.
Previous VTE	Recurrence rate 5% per year after an unprovoked VTE. Risk of recurrence VTE increased 1.6 fold in males vs females. 5-fold increased risk of postoperative VTE in patients with prior VTE.
Family history of VTE	A history of at least one first degree relative having had VTE less than 50 years or more than one first degree relative with VTE history regardless of age is an indicator of increased risk of first VTE (but not of recurrent VTE).
Thrombophilia	Patients with known thrombophilia; no need to routinely perform a thrombophilia screen as part of risk assessment.
Cancer	Active cancer: compared with general population overall 5-7 -fold risk of first VTE and increased risk of recurrent VTE. Risk varies with type of cancer. Further increased risk associated with surgery, chemotherapy, use of erythropoeisis stimulating agents and central venous catheters.
Other thrombotic states	Cardiac failure, recent myocardial infarction Stroke Metabolic syndrome: 2-fold increased risk of VTE Severe acute infection e.g. pneumonia Chronic HIV infection Inflammatory bowel disease Nephrotic syndrome Myeloproliferative disease Paraproteinaemia Bechet's disease Warm autoimmune haemolytic anaemia
Hormone therapy	Combined oral contraceptive pill, oral hormone replacement therapy, raloxifene, tamoxifen, high dose progestogens.
Pregnancy, puerperium	See Royal College of Obstetrics and Gynaecologists (RCOG) guidelines Links given page 5.
Immobility	For example bed rest less than 3 days, plaster cast, paralysis: 10-fold increased VTE risk; increases with duration.
Hospitalisation	Acute trauma, acute illness, surgery: 10-fold increased VTE risk.
Anaesthesia	2-3 fold reduced risk of post operative VTE with spinal/epidural.
Central Venous Catheters (CVC)	Compared with subclavian access, femoral route 11.5-fold increased risk of VTE.

Table B: Common risk factors for bleeding

Active gastroduodenal ulcer
Previous bleeding (less than 3 months before hospitalisation)
Advanced age greater than 70 years
Renal impairment: CrCl less than 30ml/min
Hepatic failure
Active cancer
Thrombocytopenia (platelet count less than 50 $x10^9$/L)

Graduated Elastic Compression Stockings (GECS):

Graduated compression stockings (GECS) are effective prophylaxis; however education and appropriate fitting are absolutely essential.

Select the correct size, fit carefully, align toe hole under toe, check fitting daily for change in circumference, do not fold down or take off for more than 30 minutes.

Avoid the use of ointment or oily cream on the affected leg.

Table C: Cautions and contra-indications to the use of graduated elastic compression stockings

Massive leg oedema
Peripheral neuropathy
Severe peripheral arterial disease
Major leg deformity
Dermatitis (active/severe)
Pulmonary oedema

Table D: Thromboprophylaxis in hospitalised medical patients

Low risk	**Prophylaxis**
Minor medical conditions with no risk factors (as outlined in Table A, page 7).	Mobilise early.
High risk	**Prophylaxis**
Major acute medical conditions with any risk factor (as outlined in Table A, page 7).	Dalteparin 5000 units SC once daily.

Table E: Thromboprophylaxis in surgical (non-orthopaedic) patients
Note: Surgical patients at St John's site are risk assessed according to the Caprini Score.

Low risk	**Prophylaxis**
Minor surgery including gynae (less than 30 min), no other risk factors (as outlined in Table A, page 7).	Mobilise early.
Moderate risk	**Prophylaxis**
Minor surgery with any risk factor in Table A, page 7, or Major surgery with no risk factors (as outlined in Table A, page 7).	Dalteparin 2500 units **may be** administered subcutaneously 1-2 hours before the surgical procedure (*CHECK YOUR LOCAL POLICY - **this should not be given if spinal or epidural anaesthesia is planned - see Table J***), and thereafter dalteparin 2500 units subcutaneously each morning until patient is mobilised, in general 5-7 days or longer.
High risk	**Prophylaxis**
Major pelvic or abdominal surgery with any risk factor (Table A, page 7).	Dalteparin 2500 units may be administered subcutaneously 1-2 hours before the surgical procedure (*CHECK YOUR LOCAL POLICY - **this should not be given if spinal or epidural anaesthesia is planned - see Table J***) and dalteparin 2500 units subcutaneously 8-12 hours later. On the following days, dalteparin 5000 units subcutaneously each morning. If dalteparin is not given pre-operatively, dalteparin 2500 units should be given as soon as possible (4-6 hours) post operatively followed by 5000 units each evening. As an alternative, dalteparin 5000 units is administered subcutaneously the evening before (at least 12 hours) the surgical procedure and 5000 units subcutaneously the following evenings. Treatment is continued until the patient is mobilised, in general 5-7 days or longer.

Table F:
Thromboprophylaxis if there are known contra-indications to heparin/LMWH

Surgical patients	Medical patients
Moderate risk: intermittent pneumatic compression (IPC) followed by GECS; ensure early mobilisation hydration and patient education. High risk: IPC then GECS and seek haematology advice.	Use GECS and seek haematology advice.

Table G:

Thromboprophylaxis: extremes of weight

In light of a paucity of robust evidence this is a suggested practical approach. Some UK centres use once daily dosing if extended prophylaxis is prescribed for patients over 100kg. These doses are “off-licence”.

	Less than 50kg	50-100kg	100-150kg	Greater than 150kg
Dalteparin	2500 units once daily (off-licence dose)	5000 units once daily	5000 units twice daily (off-licence dose)	7500 units twice daily (off-licence dose)

Table H:

Thromboprophylaxis in renal impairment

- for patients with eGFR less than 30ml/min who may require surgery (elective or emergency) within 24 hours, use low dose unfractionated heparin 5000 units SC twice daily - please refer to local unit policies.
- if weight less than 50 Kg, consider using creatine clearance (e.g. Cockroft-Gault) instead of eGFR for estimation of renal function.
- for patients with the combination of an extreme of body weight and renal impairment, consult with Pharmacy or Haematology.

eGFR 10-30ml/min.	Dalteparin 5000 units SC daily. Monitor LMWH anti-Xa level after 10 days*.
eGFR less than10ml/min or patients on renal replacement therapy.	Consider mechanical measures only. If high thrombosis risk consider Dalteparin 2500 SC daily. Monitor LMWH anti-Xa level after 10 days*.
If weight less than 50 Kg consider using CrCl (e.g.Cockroft-Gault) instead of eGFR for estimation of renal function.	
*Guidance on anti-factor Xa monitoring for thromboprophylaxis Target peak range for thromboprophylaxis is 0.1-0.4 units/ml. Order as “Heparin assay” (click on LMWH-Heparin) on TRAK; no need to call duty haematologist but inform haematology laboratory staff if request is urgent (ext 26093, page 6550/via switchboard out-of-hours). See p25. Level must be checked 3-4 hours post dose. If level is within the appropriate range no need to repeat unless any signs of bleeding or bruising. For patients requiring an invasive procedure/intervention/surgery withhold SC dalteparin the evening before the procedure, and take a “trough” LMWH-heparin level to ensure there is no accumulation (level should be less than 0.1 anti-Xa units/ml).	

Thromboprophylaxis in stroke patients

Patients who have been admitted to hospital with an ischaemic or haemorrhagic stroke, and who are unable to walk without the help of another person should:

a. Have Intermittent Pneumatic Compression (IPC) devices applied for up to 30 days until they can walk, are discharged, refuse IPC or develop adverse effects.
b. Not be fitted with graduated compression stockings.
c. Not routinely be given anticoagulants for VTE prophylaxis unless it is indicated for some co-morbidity e.g. surgery.

:

Spinal/Epidural Anaesthesia

Please check with an anesthetist before giving first dose of dalteparin as regional anaesthesia may have been planned.

Table J

Drug	**eGFR ml/min**	**When to stop to permit spinal or epidural anaesthesia**
Warfarin.	n/a	INR should be equal to 1.4 Full anticoagulation is an **absolute contra-indication** to spinal or epidural block.
Unfractionated heparin.	n/a	Allow 4 hours between last dose and insertion of block or removal of catheter. Delay 1st dose for 2 hours after instituting a block.
Low molecular weight heparin. (prophylactic dose)	n/a	Allow 12 hours between last dose insertion of block or removal of catheter. Delay 1st dose for at least 4 hours after instituting block.
Low molecular weight heparin. (therapeutic dose)	n/a	Allow 24 hours between last dose insertion of block or removal of catheter.
Aspirin	n/a	Proceed as normal.
Clopidogrel	n/a	7 days, last dose day - 8
Apixaban[1,3]	CrCl greater than 30 CrCl less than 30	48h, last dose day - 3 72h, last dose day - 4
Dabigatran [2,3]	CrCl greater than/equal to 50 CrCl 30 - 49	48h, last dose day - 3 96h, last dose day - 5
Rivaroxaban[1,3]	CrCl greater than 30 CrCl less than 30	48h, last dose day - 3 72h, last dose day - 4
Edoxaban[1,3]	CrCl greater than 30 CrCl less than 30	48h, last dose day - 3 72h, last dose day - 4

[1]: Direct factor Xa inhibitor

[2]: Direct thrombin inhibitor

[3]: with these drugs conventional tests of coagulation may be normal despite full therapeutic anticoagulation

Link to guidance on anticoagulation in the peri-operative period

http://intranet.lothian.scot.nhs.uk/Directory/anaestheticsandtheatres/AnaestheticsTheatresDocs/Documents/Perioperative%20Care/Perioperative%20management%20of%20anticoagulants.pdf

Section 2. Therapeutic Anticoagulation

Before starting anticoagulation consider cautions and contra-indications to anticoagulation:

Table K: **Cautions and contra-indications to anticoagulation.**

Inherited bleeding disorder e.g. haemophilia, von Willebrand disease.
Acquired coagulopathy: seek advice from duty haematologist.
Thrombocytopenia, platelet count less than 50 x 10^9/L: dependent on causation of thrombocytopenia, seek advice from duty haematologist.
Acute gastroduodenal ulcer.
Active bleeding of any sort.
Acute stroke.
CNS surgery within the previous 3 months.
Severe uncontrolled arterial hypertension.
Advanced liver disease.
Severe renal impairment – risks increase if eGFR less than 30ml/min.
Previous history of heparin-induced thrombocytopenia - see p27.

Investigation, diagnosis and management of VTE

Policies are maintained on Healthcare A-Z, Haematology, Policies:

NHS Lothian diagnostic algorithm for diagnosis and acute treatment of DVT
http://intranet.lothian.scot.nhs.uk/Directory/haematology/policy/Documents/DVT%20-%20Ambulatory%20Care%20Pathway.pdf

NHS Lothian diagnostic algorithm for suspected PE
http://intranet.lothian.scot.nhs.uk/Directory/Haematology/policy/Documents/DVT%20-%20Ambulatory%20Care%20Pathway.pdf

NHS Lothian diagnostic algorithm for management of confirmed PE
http://intranet.lothian.scot.nhs.uk/Directory/haematology/policy/documents/pe%20-%20confirmed%20-%20ambulatory%20care%20pathway.pdf

Baseline investigations prior to commencing antithrombotic therapy:

All patients should have: FBC, U/Es and liver function test, calcium, PT/INR and aPTT.
A pregnancy test should be performed for women of child-bearing potential.

Investigations for malignancy in patients diagnosed with VTE:

All patients should have a full history and examination. Patients with any concerning symptoms or signs should have targeted further investigations to investigate for an underlying cancer.

A recent large randomised controlled trial has demonstrated that routine screening with CT of the abdomen and pelvis did not provide a clinically significant benefit.

The following further investigations are recommended:

• chest X-ray,

and if not performed in the past year

• breast examination

• ensure cervical smear up to date

• PSA in men over 40 years of age

Selection of an anticoagulant for treatment of VTE:

• In NHS Lothian treatment of VTE can be either with (i) Apixaban or (ii) LMWH and warfarin.

• An individual decision should be made for each patient based on the following recommendations:

Selecting an anticoagulant:
(i) warfarin should be used if weight greater than 120kg
(ii) LMWH should be chosen if the patient has active cancer
(iii) DOACs are renally eliminated and should not be used if eGFR less than 30 ml/min

If the above are not applicable, the choice of anticoagulant should be discussed with the patient; some may opt for a drug with a longer history of use or have warfarin again if they have been on it before.

The efficiency of apixaban is similar to that of warfarin. If there is no medical reason to favour warfarin and if there is no patient preference for warfarin then apixaban should be chosen. Compared to warfarin, apixaban is significantly less likely to cause clinically relevant non-major bleeding. There is also a dose reduction after 6 months for apixaban, making this the direct oral anticoagulant (DOAC) of choice.

If a once daily DOAC is felt to be beneficial (for example for compliance reasons) then a non-formulary request for rivaroxaban should be made. Note that in clinical trials, rivaroxaban had an increased risk of gastrointestinal bleeding compared with warfarin, and that when compared with placebo for long-term secondary prevention, rivaroxaban had a significantly increased risk of bleeding, and apixaban did not have this risk.

Use of graduated compression stockings in acute DVT for prevention of post-thrombotic syndrome:

Initial studies from 1997-2004 suggested that stockings with 30-40 mmHg compression at the ankle can half the incidence of post-thrombotic syndrome. However, the randomised SOX Trial (Kahn, et al 2013) was much larger and blinded doctors and patients by comparing stockings with 30-40 mmHg pressure with placebo stockings giving negative results.

Stockings do not require to be prescribed routinely but only used selectively in patients to treat symptoms.

Absolute contra-indications are advanced peripheral arterial occlusive disease, decompensated heart failure, septic phlebitis, and phlegmasia caerulea dolens (DVT leading to severe swelling of the whole leg).

Relative contra-indications are suppurative dermatoses, intolerance of compression stocking fabric, advanced neuropathy, and chronic arthritis.

Thrombophilia testing please refer to policy document, Healthcare A-Z, Haematology, Policies:

http://intranet.lothian.scot.nhs.uk/Directory/Haematology/policy/Documents/Thrombophilia%20Testing.pdf

Duration of Anticoagulation

A full advisory document can be found on the Healthcare A-Z, Haematology, Policies page:
http://intranet.lothian.scot.nhs.uk/Directory/Haematology/policy/Documents/Venous%20Thromboembolism%20-%20Duration%20of%20anticoagulation.pdf

The following table is taken from the advisory document and offers a summary.
Please note that all recommendations should be based on clinical judgement, and a longer course of anticoagulation may be preferred if : (i) the DVT or PE was very large or very symptomatic; or (ii) the symptoms of the initial DVT or PE persist; or (iii) the patient is not ready (confident) to stop anticoagulant therapy; and (iv) the patient does not have a high risk or bleeding.

Categories of VTE	Duration of Treatment
First provoked VTE	minimum 3 months (please see caveats in full guidance as patients may require up to 6 months or longer)
First unprovoked VTE* Low/moderate bleeding risk High bleeding risk	Minimum of 3 months and then reassess to consider long-term anticoagulation Indefinite therapy with periodic review 3 months
Isolated distal DVT (calf)	3 months (please see caveats in full guidance as patients may require longer duration of anticoagulation if remaining symptomatic)
Central Venous Catheter (CVC) - related venous thrombosis	3 months
Second provoked VTE	3 months and then assess on case-by-case basis
Second unprovoked VTE	Same as for first unprovoked VTE
Cancer-associated VTE	Minimum 3 months, then reassess and continue if active cancer or continuing to receive chemotherapy

***Absence of a transient risk factor or active cancer**

Definition of “transient risk factor”:
Transient risk factors include: surgery, hospitalisation or plaster cast immobilisation, all within the past 3 months; oestrogen therapy (combined contraceptive pill, hormone replacement therapy), pregnancy and puerperium, flight greater than 8 hours, recent leg injuries/trauma (e.g. fracture) or immobilsation (within 6 weeks).
The stronger the provoking risk factor is (e.g. recent major surgery), the lower the expected risk of recurrence after stopping anticoagulant therapy.
Note that temporary immobility (e.g. confined to bed up to 3 days or a flight of less than 6 hours are weak risk factors).

Thrombolysis

(i) Massive Pulmonary Embolism and systemic thrombolysis: refer to PE pathway.

http://intranet.lothian.scot.nhs.uk/Directory/CriticalCare/Catheter%20directed%20thrombolysis%20for%20DVT/Acute%20pulmonary%20embolism%20risk%20stratification%20and%20management%20plan.pdf

(ii) Catheter-directed thrombolysis for phlegmasia caerulea dolens/limb-threatening DVT.

Patients should be discussed with the on call vascular surgeon to access this service.

Incidentally discovered asymptomatic VTE

In patients who are unexpectedly found to have asymptomatic DVT or PE, the same initial and long-term anticoagulation is recommended as for comparable patients with symptomatic VTE.

Upper limb DVT

All suspected cases should have an ultrasound examination; pre-test probability assessment and D-dimers are not used.

Initial treatment is the same as for lower limb DVT; recurrence rates for upper limb DVT after treatment for 3-6 months are low and it is likely that prolonged anticoagulation is not required for most patients. Further investigation is required to exclude thoracic outlet obstruction and individual cases should be discussed with radiology regarding further imaging.

Superficial thrombophlebitis (SVT)

The most commonly affected superficial veins are the long (great) and short saphenous veins of the leg. Referral for investigation should not normally be necessary for a short segment of below knee SVT unless concomitant DVT is suspected.

Patients referred for suspected DVT should be assessed in the usual way for an underlying DVT: if during this investigation the SVT is adjacent to (within 3 cm of) the saphenofemoral junction (SFJ) then therapeutic anticoagulation is required for a 3 month period as there is a high risk of progression to DVT.

Otherwise SVT is a benign and self-limiting condition and in the past has been treated with NSAIDs. Although reasonable for mild cases, it has become recognised that for more symptomatic cases there is a better response to anticoagulation.

It is suggested that mild SVT (less than 5 cm in length) can be treated with non-steroidal anti-inflammatory drugs (NSAIDs). If there is no improvement after a week, then it may be better to switch to prophylactic dose dalteparin (5000 units SC daily) for 4 weeks.

If more than 5 cm in length, or treating a large distended thrombosed varicosity, it may be better treated with low molecular weight heparin for 4-6 weeks. In NHS Lothian it is advised to prescribe a treatment dose of dalteparin (200 units/Kg subcutaneously daily) for 4-6 weeks duration.

It is important to offer a 1 week review to the patients after commencing treatment to ensure no worsening or extension.

Compression therapies:
Patients should be examined for foot pulses and, if present, patients may be offered Class 1 compression stockings, which may help symptoms. Patients without detectable foot pulses do not need compression. ABPI measurement is not required.

Patients with two or more episodes of thrombophlebitis of the proximal long or short saphenous veins should be referred to the Vascular Service electively.

Treatment of VTE

Apixaban

All patients must be counselled carefully at the time of commencing therapy with apixaban.

Patients adhere to the guidance given at the following link, and use the counselling sheet to document discussions held with the patient.

http://intranet.lothian.scot.nhs.uk/NHSLothian/Healthcare/A-Z/Haematology/policy/Documents/Apixaban%20-%20Prescribing%20Guidance%20and%20Counselling.pdf

Guidance on the interpretation of laboratory tests in the presence of DOACs, peri-operative advice for patients on DOACs and the management of bleeding in patients on DOACs can be found on the Healthcare A-Z, Haematology, polices intranet web page and are updated annually.

http://intranet.lothian.scot.nhs.uk/NHSLothian/Healthcare/A-Z/Haematology/policy/Documents/Apixaban%20-%20Switching%20anticoagulants%20and%20peri-operative%20guidance.pdf

Low Molecular Weight Heparin (LMWH)

Dalteparin is the brand of LMWH currently on the NHS Lothian Formulary.

- The therapeutic dose is 200 units/kg SC once daily.
- It is imperative that the patient is weighed and that the weight is documented on TRAK in the EPR section, observations and measurements.
- For VTE, start warfarin and continue dalteparin for at least 5 days and until the INR is greater than 2.0 on 2 consecutive days.
- For pregnant women with VTE refer to RCOG Guidelines and local obstetric guidelines for dosing, and the patient must be referred to the on-call obstetric team. Links are given on p5.

Dalteparin daily doses for treatment of VTE

Note: All pre-filled syringes listed below contain 25,000 units/mL

Patient Body Weight (kg)	Dosage (units/day)	Volume of Pre-filled syringe (ml)
Less than 46	7500	0.3
46-56	10000	0.4
57-68	12500	0.5
69-82	15000	0.6
Greater than 83	18000	0.72

- These are fixed-dose pre-filled syringes. Determine the required dose (dependent on patient's weight and assuming normal bleeding risk) and select the appropriate pre-filled syringe. All patients should be weighed and weight in kilograms recorded in the patient's case records/electronically on TRAK.
- Administer the full syringe contents by subcutaneous injection.
- Do not expel the air bubble from these pre-filled syringes before administration.
- The maximum dose: 18000 units SC daily.

Note: in certain situations of acute life-threatening thrombosis, patients weighing over 120 Kg can be given a weight-based dose of dalteparin. This is an off-label approach and must be discussed with haematology.

- Patients receiving low molecular weight heparin (or unfractionated heparin) may require platelet monitoring. See p27.

Table L: Recommendations for therapeutic dalteparin dosing in extremes of body weight and in renal impairment. If advice required please contact Haematology.

Body weight less than 46 Kg	Patients less than 46 Kg with VTE: recommended dose 7500 units SC daily, but increased risk of bleeding, so monitor clinically for bleeding and check LMWH assay - see p25.
BMI greater than/equal to 40 Kg/m^2	If morbidly obese (BMI greater than/equal to 40) discuss with haematology: LMWH anti-Xa levels may be required, and depending on clinical circumstances, a decision may be made to use an off-label dose of dalteparin.
Renal Impairment	Dalteparin is eliminated via the kidneys so the half-life is prolonged in renal impairment, leading to dalteparin accumulation and increased bleeding risk.
CrCl 30-50 ml/min	Recommend no dose reduction but monitor for bleeding.
CrCl less than 30ml/min	Recommend use of unfractionated heparin. If the use of unfractionated heparin is felt impractical consider the use of a lower dose band of dalteparin for the patient's weight. LMWH monitoring will be necessary. Seek advice from haematology.

Table M: Advice for continuing LMWH in patients with cancer and VTE

Patients with an underlying malignancy should be considered for continuation of LMWH rather than oral anticoagulation. However in those who do not want to inject, an oral Xa inhibitor (either apixaban or rivaroxaban) is a reasonable alternative. Edoxaban has recently been shown to be efficacious in this setting but may hold an increased risk of bleeding in gastro-intestinal and urological cancers, and drug-interactions with chemotherapy are unclear. Edoxaban is currently not yet on Formulary for this indication.

Compared to warfarin, LMWH carries a similar risk of bleeding but halves the recurrences in patients with cancer.

Full dose dalteparin (200 units/Kg) is given for the first month; if continuing dalteparin after the first month the dose is reduced to 150 units/Kg as detailed in the box below, unless the patient weighs less than 46 Kg, or over 98 Kg, when the dose is left unaltered. For patients with BMI greater than or equal to 40, discuss with haematology as LMWH anti-Xa levels may be required.

First month		Second month and onwards	
Weight (Kg)	Dose (units)	Weight (Kg)	Dose (units)
Less than 46	7500	Less than 46	7500
46-56	10000	46-56	7500
57-68	12500	57-68	10000
69-82	15000	69-82	12500
Greater than 83	18000	83-98 99	15000 18000
		Greater than 98 Kg	18000

At 3 months, review the patient to decide on subsequent management. If cancer is not cured some form of continuing anticoagulation is recommeded. If this is with LMWH, there is no date to support if the dose can be reduced to a prophylactic dose.

Link to Edinburgh Cancer Centre protocol:
Dalteparin for extended treatment and prophylaxis of Venous Thromboembolism (VTE) in patients with solid tumours within the Edinburgh Cancer Centre.

http://intranet.lothian.scot.nhs.uk/Directory/ooqs-theoncologyonlinequalitysystem/Documents/Dalteparinforcancerclots.pdf

Safe prescribing of LMWH at time of discharge

If a patient is being discharged from hospital on LMWH the following information **MUST** be provided to the general practitioner:

- Indication for anticoagulation with LMWH.
- Anticipated duration of anticoagulation.
- Dose (units), frequency.
- Weight (Kg).
- Renal function.

This is to ensure the safe ongoing prescription of LMWH after discharge.

Table N

LMWH anti-Xa monitoring

LMWH does not require routine laboratory monitoring since weight-adjusted dosing for treatment, or thromboprophylaxis, provide a predictable clinical response.

Dosing may be unreliable in patients:

- at extremes of body weight: BMI less than/equal to 19 or BMI greater than/equal to 40
- with severe renal impairment (creatinine clearance less than 30ml/min)

(see footnotes, Table H, p12 for thromboprophylaxis, and Table L, p23 for therapeutic dosing).

- during pregnancy (see RCOG guidelines and SCRH protocol) - links on p5.

In these situations there may be some merit in assessing LMWH activity.
LMWH activity should be measured if there is unexpected bleeding.

How to arrange a LMWH anti-Xa level:
LMWH anti-Xa levels are ordered on TRAK as “heparin assay” and click on LMWH; samples are sent in a green citrated tube filled adequately to the level marked on the tube. Samples must be couriered to the RIE haematology laboratory if the patient is being managed at other NHS Lothian sites.
A 24-hour service is available for this automated test and all requests should be discussed with the duty laboratory haematology biomedical scientist: extension 26093 or page 6550/via switchboard out-of- hours.

When to take a LMWH level:
A peak LMWH anti-Xa level should be taken after the third dose of LMWH has been administered, 3-4 hours following the administration of the drug.

Interpretation:
For patients on once daily dosing (therapeutic), the expected peak plasma concentration is about 1.0 anti-Xa units/mL with a range of 0.5-1.5 anti-Xa units/mL for twice daily dosing).

For patients receiving thromboprophylaxis the expected peak plasma concentration is between 0.1-0.4 anti-Xa units/mL.

The duty haematologist can assist with dose adjustment if the level is sub-or supra-therapeutic.

Unfractionated Heparin (UFH)

Indications:

- an infusion of unfractionated heparin should be considered if immediate anticoagulation is required or if urgent reversal may be needed e.g. known potential bleeding site.

- unfractionated heparin should be used if the creatinine clearance less than 30ml/min if surgery is required within 24 hours.

When prescribing unfractionated heparin use the NHS Lothian Adult Heparin Infusion Chart (available on the front page of the intranet).
http://intranet.lothian.scot.nhs.uk/Directory/Haematology/policy/Documents/Heparin%20Infusion%20Chart.pdf

This chart has been designed for use in a patient with standard bleeding risk, so consider if a bolus of heparin is required prior to starting the infusion. Also consider carefully the infusion starting rate if the patient has a risk of bleeding. If in doubt ask the on call duty haematologist.

Please note that in NHS Lothian UFH is available in a ready-made concentration of 1000 units/ml. Prescribe as "heparin 1000 units/ml". **DO NOT DILUTE THIS PREPARATION.**

UFH infusion treatment schedule & nomogram

Use the ready-made concentration of heparin 1000units/ml. This concentration **must not be diluted.** For a patient of average weight, with normal renal function and no bleeding risk, give a loading dose of 5000 units (5ml). Start the infusion at a rate of 1200 units (1.2ml)/hr. Check the APTTr 6 hourly until stable in the therapeutic range and adjust rate to achieve a therapeutic range of **2.0-3.0.** Monitor platelets on a daily basis.

APTT ratio	Infusion adjustment	Recheck APTT
greater than 5.0	Stop for 1 hr and decrease rate by 500units (0.5ml)/hr	2 hrs
4.1-5.0	Decrease infusion rate by 300units (0.3ml)/hr.	6 hrs
3.1-4.0	Decrease infusuion by 200units (0.2ml)/hr	6 hrs
2.0-3.0	No change in infusion rate	Next day AM
1.5-1.9	Increase infusion rate by 100units (0.1ml)/hr	6 hrs
1.2-1.4	Increase infusion rate by 200units (0.2ml)/hr	6 hrs
less than 1.2	Increase infusion rate by 400units (0.4ml)/hr	6 hrs

Reversal of unfractionated heparin and LMWH

As the half-life of unfractionated heparin is about 1 hour, it is usually sufficient to stop the heparin infusion without administration of a specific reversal agent. If bleeding is severe, consider protamine sulphate (1mg for every 100 units heparin given in previous hour). Give slowly at rate not exceeding 5 mg/min, maximum single dose of 50 mg. The anticoagulant effect of LMWH dalteparin can be partially reversed by protamine sulphate. One mg of protamine sulphate inhibits the effect of 100 units (anti-Xa) of dalteparin. The usual maximum dose is 50 mg given by slow IV injection at a rate not exceeding 5 mg per minute.
Note - there is a risk of anaphylaxis with protamine administration.

Heparin-induced thrombocytopenia (HIT)

HIT is a serious complication of heparin/LMWH therapy. Please refer to the diagnostic and management pathway at
http://intranet.lothian.scot.nhs.uk/Directory/Haematology/policy/Documents/Heparin-induced%20Thrombocytopenia%20Clinical%20Guideline.pdf

Argatroban management guidelines:

http://intranet.lothian.scot.nhs.uk/NHSLothian/Healthcare/A-Z/Haematology/policy/Documents/Argatroban%20Management%20Guidelines.pdf

Argatroban infusion chart:

http://intranet.lothian.scot.nhs.uk/NHSLothian/Healthcare/A-Z/Haematology/policy/Documents/Argatroban%20Infusion%20Chart.pdf

Platelet count monitoring in patients receiving unfractionated heparin (UFH) or LMWH:

Clinically important HIT is rare with LMWH except in patients receiving the drug in some post-operative settings. Evidence suggests the risk of developing HIT with LMWH is greatest in patients who have undergone cardiac surgery, and that other patients do not require monitoring. The most common type of HIT is immune-mediated and does not normally develop until 5-10 days after starting unless the patient has been exposed to heparin in the previous 100 days. Prior to commencing heparin or LMWH a baseline platelet count should be checked.

Post-operative patients including obstetric cases receiving UFH should have platelet count monitoring performed daily from days 4-14 or until UFH is stopped.

Post-cardiopulmonary bypass patients receiving LMWH should have platelet count monitoring performed daily from days 4-14 (if an in-patient) or until LMWH is stopped. If an outpatient, then FBC checks every 2-3 days is advised until day 14 post-operatively.

Post-operative patients (other than cardiopulmonary bypass patients) receiving LMWH do not need routine platelet monitoring.

All post-operative patients including cardiopulmonary bypass patients who have been exposed to heparin in the previous 100 days and are receiving any type of heparin should have a platelet count determined 24 hours after starting heparin.

Orthopaedic, surgical and gynaecology patients discharged on LMWH should be advised of the small risk of HIT, and advised that in the event of general malaise, development of signs and symptoms of venous thrombosis, and development of erythematous or necrotic areas at the site of injection, they should have an urgent FBC check to ensure there has not been a 30% fall in the platelet count from the pre-operative baseline.

If HIT is strongly suspected or confirmed, dalteparin should be stopped and an alternative anticoagulant such as fondaparinux, argatroban or danaparoid should be given.

Warfarin

Initiation of Warfarin

The Fennerty regimen is only for rapid initiation of warfarin (caution in elderly) and is valid for the first 4 days of warfarin treatment only.

Day	INR (check at 9-11am)	Warfarin (mg)(give at 5-7pm)
1	Less than 1.4	10
2	Less than 1.8	10
	1.8	1
	Greater than 1.8	0.5
3	Less than 2.0	10
	2.0-2.1	5
	2.2-2.3	4.5
	2.4-2.5	4
	2.6-2.7	3.5
	2.8-2.9	3
	3.0-3.1	2.5
	3.2-3.3	2
	3.4	1.5
	3.5	1
	3.6-4.0	0.5
	Greater than 4.0	0
		Predicted maintenance dose
4	Less than 1.4	Greater than 8
	1.4	8
	1.5	7.5
	1.6-1.7	7
	1.8	6.5
	1.9	6
	2.0-2.1	5.5
	2.2-2.3	5
	2.4-2.6	4.5
	2.7-3.0	4
	3.1-3.5	3.5
	3.6-4.0	3
	4.1-4.5	Miss 1 day then give 2mg
	Greater than 4.5	Miss 2 days then give 1mg

Reversal of Warfarin

Secondary care NHS Lothian Guidelines for reversal of patients on warfarin and for the use of Beriplex can be found on the Intranet - click on the links below.

http://intranet.lothian.scot.nhs.uk/Directory/Haematology/policy/Documents/Warfarin%20Reversal.pdf

http://intranet.lothian.scot.nhs.uk/NHSLothian/Healthcare/A-Z/Haematology/policy/Documents/Beriplex%20Administration.pdf

Primary Care Guidelines for Warfarin

Another guideline “Prescribing guidelines for the management of patients on warfarin in primary care, February 2018” is available in full, and summary format:

Full guideline
http://intranet.lothian.scot.nhs.uk/Directory/unscheduledcareservice/all%20files/Prescribing%20Guidelines%20for%20the%20Management%20of%20Patients%20on%20Warfarin%202018.pdf

Summery guideline
http://intranet.lothian.scot.nhs.uk/Directory/unscheduledcareservice/all%20files/Guidelines%20for%20the%20management%20of%20patients%20on%20warfarin%20Feb18.pdf

Safe prescribing of warfarin at time of discharge:

Before discharge ensure the patient is given a completed yellow anticoagulant booklet, counselled about warfarin (contact pharmacist), and ensure timely notification to GP. Please ensure that the appropriate section on the immediate discharge summary is completed.

Indication	INR Range (Target INR)	Duration
Venous thrombosis acute treatment and secondary prevention.	2.0-3.0 (target INR: 2.5)	See Duration of Anticoagulation p18.
Non-valvular Atrial Fibrillation (AF) Paroxysmal or permanent AF		
All patients with AF who have $CHADS_2$ or CHA_2DS_2-VASc of equal to 1	2.0-3.0 (target INR: 2.5)	Long term.
AF associated with a) clinical thyrotoxicosis b) non-cerebral thromboembolism	2.0-3.0 (target INR: 2.5)	a) Until controlled b) Long term
Elective cardioversion.	2.0-3.0 (target INR: 2.5)	Minimum 3 weeks pre procedure Minimum 4 weeks post procedure Ongoing requirement as directed by cardiologist.
Valvular Atrial Fibrillation		
Rheumatic mitral valve disease and mitral stenosis.	2.0-3.0 (target INR: 2.5)	Long term.
Mechanical heart valves Target INR depends on site of valve replacement, position and manufacturer.	See recomendations from Cardiothoracic Surgery RIE p31	Lifelong - follow guidance from cardiac unit.
Patients requiring anticoagulation and antiplatelet therapy.	2.0-3.0 (target INR 2.5)	As prescribed by consultant cardiologist/stroke physician/ haematologist.
Intracardiac thrombus.	2.0-3.0 (target INR 2.5)	At least 3 months as prescribed by cardiology.

Target INR for Mechanical Prostheses

Prosthesis Thrombogenicity	Patient related risk factors: Mitral or tricuspid valve replacement Previous thromboembolism Atrial fibrillation Mitral stenosis of any degree LVEF less than 35%	
	No risk factors	1 risk factor or more
Low (Carbomedics, Medtronic Hall, ATS, Medtronic Open-Pivot, St Jude Medical, On-X, Sorin Bicarbon)	Target INR 2.5 (2.0-3.0)	Target INR 3.0 (2.5-3.5)
Medium (Other bileaflet valves with insufficient data)	Target INR 3.0 (2.5-3.5)	Target INR 3.5 (3.0-4.0)
High (Lillehei-Kaster, Omniscience, Starr- Edwards (ball-cage), Bjork-Shiley and other tilting-disc valves)	Target INR 3.5 (3.0-4.0)	Target INR 4.0 (3.5-4.5)

Direct Oral Anticoagulants (DOACs)

Rivaroxaban and Dabigatran are non-formulary, with the exception of rivaroxaban for thromboprophylaxis in elective hip and knee arthroplasty.

Advice for the management of patients on DOACs, including advice on the reversal of Dabigatran using the antidote Idarucizumab can be found using the following links:

http://intranet.lothian.scot.nhs.uk/Directory/Haematology/policy/Documents/Rivaroxaban%20-%20Switching%20anticoagulants%20and%20peri-operative%20guidance.pdf

http://intranet.lothian.scot.nhs.uk/NHSLothian/Healthcare/A-Z/Haematology/policy/Documents/Dabigatran%20Management%20Guidelines.pdf

Rivaroxaban for thromboprophylaxis in elective hip and knee arthroplasty:

A dose of 10mg once daily is started 6-10 hours after surgery, provided haemostasis has been established. Treatment duration is 5 weeks for hip replacaenent and 2 weeks for knee replacement. **Any patient being discharged from hospital will be given the required amount to complete the course of treatment and the GP should not be required to prescribe rivaroxaban.**

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