UNIVERSITY HOSPITALS DIVISION
ANTITHROMBOTIC GUIDE (ADULTS)

Version 3.1

General advice is provided in this guide on venous thromboembolism (VTE) prophylaxis and treatment. Further information is available in each Clinical Unit's guideline.

The low molecular weight heparin dalteparin (Fragmin®) has been approved for use in:

Prophylaxis of VTE
Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE)

Dalteparin should be administered by subcutaneous (SC) injection, while the patient is lying down, alternately 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.

Heparin injection, 5000 units/0.2ml (25000unit/ml) will continue to be available for subcutaneous use for VTE prophylaxis in Clinical Units where it is considered preferable to dalteparin.

Treatment using 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 standard risk of bleeding.

Every patient admitted to hospital requires a risk assessment for venous thromboembolism. When anticoagulant prophylaxis is indicated the risk of bleeding should also be assessed. Please note the contra-indications and cautions to anticoagulation (Table A).

Table A:	**Contra-indications and cautions to anticoagulation (e.g. heparin, dalteparin, warfarin, alteplase)**
If anticoagulation is contra-indicated prophylaxis with mechanical methods such as graduated elastic compression stockings should be considered.	
Haemorrhagic disorder Coagulopathy Thrombocytopenia <70x 10^9 /L Active peptic ulcer Actual or potential bleeding site Acute bacterial endocarditis Acute stroke - seek advice CNS surgery within 3 months Severe arterial hypertension (uncontrolled) Severe liver disease Renal failure (refer to Table H) Previous history of heparin induced thrombocytopenia (HIT) (refer to Table Q)	

Table B:	**Contraindications and cautions to graduated elastic compression stockings**
Massive leg oedema Peripheral neuropathy Severe peripheral arterial disease Major leg deformity Dermatitis (active/severe) Pulmonary oedema	

Prophylaxis of VTE

- An individual risk assessment for DVT prophylaxis should be carried out for all patients on admission and documented in the clinical case notes. Review all risk factors (Table C) regularly and at the time of discharge.
- Prescribe all prophylaxis including graduated elastic compression stockings (GECS) on the patient's Prescription and Administration Record.
- Hydrate & mobilise all patients as early as possible
- Prophylactic dosage in renal failure and extremes of weight (see Tables H and J).
- Document the reasons in the case notes if thromboprophylaxis is withheld or if there is any deviation from the guideline.

Table C: Risk Factors for VTE	
Risk Factor	**Comments**
Age	Incidence of first VTE rises exponentially with age. In the general population: <40 years – annual incidence of 1/10000 60-69 years – annual incidence of 1/1000 >80 years – annual incidence of 1/100
Obesity	2-3-fold VTE risk if obese (body mass index ≥30 kg/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 recurrent VTE increased 1.6 fold in males v females 5-fold increased risk of postoperative VTE in patients with previous VTE
Family history of VTE	A history of at least one first degree relative having had VTE at age <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. See local protocols.
Other thrombotic states	Heart 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 Paroxysmal nocturnal haemoglobinuria Sickle cell trait and sickle cell disease
Hormone therapy	Combined oral contraceptive pill, oral HRT, raloxifene, tamoxifen, high dose progestogens.
Pregnancy, puerperium	See LUHT obstetric guidelines http://intranet.lothian.scot.nhs.uk/NHSLothian/Healthcare/A-Z/Haematology/policy/Documents/Obstetric%20VTE%20Prophylaxis%20and%20Treatment%20Policy.pdf
Immobility	For example bed rest >3 days, plaster cast, paralysis: 10-fold increased VTE risk; increases with duration.
Immobility during travel	2-3 fold increased risk.
Hospitalisation	Acute trauma, acute illness, surgery: 10-fold increased VTE risk.
Anaesthesia	2-3 fold increased risk of postoperative VTE in general v spinal/epidural.
Central venous catheters	Compared with subclavian access, femoral route 11.5-fold increased risk of VTE.

Table D: Prophylaxis of VTE in Medical Patients	
Low risk	**Prophylaxis**
Minor medical conditions with no risk factors as outlined in Table C	Mobilise early.
High risk	**Prophylaxis**
Major acute medical conditions with any risk factor (as outlined in Table C)	Dalteparin 5000 international units SC once daily for a maximum of 14 days.

Table E: Prophylaxis of VTE in Surgical Patients PLEASE CHECK YOUR LOCAL UNIT POLICY	
Low risk	**Prophylaxis**
Minor surgery including gynae (<30 min), no other risk factors (as outlined in Table C)	Mobilise early.
Moderate risk	**Prophylaxis**
Minor surgery with any risk factor in Table C, or Major surgery with no risk factors (as outlined in Table C)	Dalteparin 2500 international 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 F),** and thereafter dalteparin 2500 international units subcutaneously each morning until the patient is mobilised, in general 5-7 days or longer.
High risk	**Prophylaxis**
Major pelvic or abdominal surgery with any risk factor (Table C).	Dalteparin 2500 international 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 F)** and dalteparin 2500 international units subcutaneously 8-12 hours later. On the following days, dalteparin 5000 international units subcutaneously each morning. If dalteparin is not given preoperatively, dalteparin 2500 international units should be given as soon as possible (4-6 hours) post operatively followed by 5000 international units each evening. As an alternative, dalteparin 5000 international units is administered subcutaneously the evening before (at least 12 hours) the surgical procedure and 5000 international units subcutaneously the following evenings. Treatment is continued until the patient is mobilised, in general 5-7 days or longer.

Table F:	Spinal and epidural anaesthesia and VTE treatment or prophylaxis

For VTE prophylaxis, spinal or epidural anaesthesia may be preferred to general anaesthesia where appropriate. For elective surgery (seek advice in emergency surgery), the risk of spinal haematoma may be reduced by adhering to the following advice:

Warfarin	Full anticoagulation is an **absolute contra-indication** to spinal or epidural block. If INR ≥1.5 do not perform spinal or epidural anaesthesia
Heparin	Allow 4-6 hours from dose to insertion of block or removal of catheter. Delay 1st dose for 2-4 hours after instituting a block.
LMWH	Allow 10-12 hours from dose to insertion of block or removal of catheter. Delay 1st dose for at least 4 hours after instituting block
Aspirin/NSAIDs	Proceed as normal

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

Table G:	VTE prophylaxis if there are known contraindications to heparin or LMWH

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.

Warfarin with an INR of 2.0 may be a suitable alternative.

For surgical patients	For medical patients
Moderate risk: Intermittent pneumatic compression (IPC) then GECS. Ensure early mobilisation, hydration and patient education. **High risk:** IPC then GECS and seek haematology advice	Use GECS or seek haematology advice.

Table H:	Dalteparin in extremes of weight or renal failure: Prophylaxis of VTE
Low BMI (≤19kg/m^2)	Patients <46kg : NHS Lothian recommends 2500 international units SC daily.
Morbid obesity: BMI ≥ 40kg/m^2	If morbidly obese increase the dose of prophylaxis by 30%.
Renal failure	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	No dose reduction but monitor for bleeding.
CrCl < 30 ml/min	Use unfractionated heparin.

Treatment of VTE

- Before starting treatment consider contraindications to anticoagulation (Table A)
- Check FBC, PT, APTT, U & Es and LFTs.

LOW MOLECULAR WEIGHT HEPARIN

Dalteparin: The therapeutic dose is 200 international units/kg SC once daily.

For VTE, start warfarin and continue dalteparin for at least 5 days and until the INR>2.0 on 2 consecutive days.

Please note for pregnant ladies with VTE refer to RCOG Guidelines for dosing.

Dalteparin daily doses for treatment of VTE			
Patient Body Weight (kg)	Dosage (International units/day)	Syringe (international units/ml)	Injection volume (ml)
<46	7500	25000	0.3
46 – 56	10000	25000	0.4
57-68	12500	25000	0.5
69-82	15000	25000	0.6
>83kg (see Table J)	18000	25000	0.72

- To avoid prescription errors please do not abbreviate international units: please use the term “units”.
- 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 the weight in kilograms recorded in the patient’s case records.
- 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 international units SC once daily.

Table J: Dalteparin in extremes of weight or renal failure: Treatment of VTE *Any concerns please discuss with Pharmacy or Haematology.*	
Low body mass index (≤19kg/m^2)	Patients <46kg with VTE: recommended dose 7500 international units SC daily, but increased risk of bleeding, so monitor clinically for bleeding and consider anti-factor Xa assays.
Morbid obesity: BMI ≥ 40kg/m^2	If morbidly obese (BMI ≥40) discuss with haematology: anti-factor Xa levels may be required.
Renal failure	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 < 30 ml/min	Recommend use of unfractionated heparin.

Table K:	Discharge of patients on LMWHs

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

- Indication for anticoagulation with LMWH
- Anticipated duration of anticoagulation
- Dose (units), frequency
- Weight (kg)
- Renal function
- Frequency of FBC monitoring (usually weekly following discharge for first month)

This is to ensure safe prescribing of LMWH following the patient's discharge.

UNFRACTIONATED HEPARIN

Unfractionated Heparin infusion: 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 <30ml/min.

When prescribing unfractionated heparin use the NHS Lothian Adult Heparin Infusion Chart (available on the front page of the intranet). 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 haematology.

Unfractionated Heparin infusion treatment schedule

Use the ready-made concentration of heparin 1000 units/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 APTT 6 hourly until stable in the therapeutic range and adjust rate to achieve a therapeutic range of **2.0-3.0**. Monitor platelets on daily basis.

Adjust heparin infusion as follows:

APTT Ratio	Infusion adjustment	Recheck APTT
>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 infusion rate 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 100 units (0.1 ml)/hr	6 hrs
1.2 – 1.4	Increase infusion rate by 200units (0.2ml)/hr	6 hrs
<1.2	Increase infusion rate by 400units (0.4ml)/hr	6 hrs

Table L:	Massive PE and Alteplase

See Table A prior to administration.

Alteplase 10mg IV in 1-2 min then 90mg over 2 hours (max 1.5mg/kg if weight <65kg). After Alteplase, once APTT ratio <2.0, heparin infusion should be started to maintain APTT ratio between **2.0-3.0. Do not give a bolus of heparin at the time of starting heparin infusion after thrombolysis as this may increase the risk of bleeding.**

Warfarin - Initiation of warfarin
STANDARD FENNERTY REGIMEN

This 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	>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 1day then give 2mg
	Greater than 4.5	Miss 2 days then give 1mg

Full NHS Lothian Guidelines for managing patients on Warfarin can be found on the Intranet – click on link below.

http://intranet.lothian.scot.nhs.uk/NHSLothian/Healthcare/A-Z/Warfarin/Pages/Warfarin.aspx

Another guideline "Guideline for Initiating Warfarin in Primary Care" can be found on Intranet (click on link below) but please note this is only suitable for patients with atrial fibrillation. It is not suitable for the initiation of warfarin in patients with VTE.

http://intranet.lothian.scot.nhs.uk/NHSLothian/Healthcare/A-Z/Warfarin/Documents/warfarin%20appdx.pdf

Recommended Target INRs for Warfarin

Clinical State		Target INR	Duration
Atrial fibrillation/paroxysmal AF		2.5	Long-term
Cardioversion		2.5	4 weeks prior
Cardiomyopathy		2.5	Long-term
Symptomatic antiphospholipid syndrome		2.5	Long-term
Mechanical prosthetic heart valve	mitral aortic	3.5 3.0	Long-term Long-term
DVT		2.5	3-6 months
Pulmonary embolism		2.5	6 months
Recurrent DVT/PTE (off warfarin)		2.5	Long-term
Recurrent DVT/PTE (on warfarin)		3.5	Long-term

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

Management of bleeding

Haemorrhage is the main adverse effect of all anticoagulants. Management depends on whether there is major or minor bleeding. Please seek advice from a haematologist if appropriate.

Reversal of warfarin

Protocol for the reversal of warfarin
http://intranet.lothian.scot.nhs.uk/NHSLothian/Healthcare/A-Z/Haematology/policy/Documents/Warfarin%20Reversal.pdf

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

Table M: Major bleeding irrespective of INR	
Irrespective of INR	STOP warfarin. Give vitamin K 5mg (0.5ml) of Konakion MM injection 10mg/ml by slow IV bolus and prothrombin complex concentrate (PCC) 25-50units/kg. **Check PT and APTT screen immediately** after PCC.
Minor or no bleeding	
INR ≥ 7.0	Omit warfarin. Give vitamin K 2mg PO; consider IV vitamin K if patient at increased risk of bleeding. Withold warfarin dose. Check INR at 24 hours
INR 4.5-6.9	Reduce warfarin dose or withhold on dose Consider vitamin K 1mg PO if at high risk of bleeding. Check INR at 24 hrs, or earlier if clinical deterioration.

Note: if bleeding occurs whilst the INR is within the therapeutic range investigation should be undertaken for other underlying causes

Table N:	Reversal of unfractionated heparin and dalteparin

As the half life of unfractionated heparin is about 1 hour, it is usually sufficient to stop the heparin infusion. If bleeding is severe, consider protamine sulphate (1mg for every 100 units heparin given in previous hour). Give slowly at rate not exceeding 5mg/min, maximum single dose of 50mg. Protamine is less effective at reversal of dalteparin (please consult haematologist for advice).

Monitoring Low Molecular Weight Heparins (LMWH) (including Dalteparin)

FBC, PT and aPTT and renal function must be checked prior to commencing therapeutic treatment with LMWH.

Table P:	Anti-Xa monitoring

LMWH does not require routine laboratory monitoring since weight-adjusted dosing used for treatment, or a fixed dose used for thromboprophylaxis, provide a predictable clinical response.
Dosing may be unreliable in patients :

- at extremes of weight BMI ≤19 or BMI ≥40
- with severe renal impairment (Creat Cl <30ml/min)
- during pregnancy (see RCOG guidelines)

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

Peak levels can be measured around 3-4 hours after a subcutaneous dose of LMWH. The APTT assay is unsuitable for this purpose, and therefore a chromogenic anti-Xa assay using a LMWH standard is recommended, although such assays also have their limitations. Please discuss with Haematology to arrange anti-Xa assays. The target range for **therapeutic** anticoagulation is 0.5-1.0 anti-Xa units/ml.

Table Q:	FBC monitoring (for patients receiving unfractionated heparin or LMWH)

All patients who are receiving treatment doses of UFH or LMWH, and all surgical and medical patients who are receiving unfractionated heparin or LMWH for thromboprophylaxis, should be monitored for the development of thrombocytopenia.

Heparin-induced thrombocytopenia (HIT) is a condition that is associated with a high risk of serious arterial and venous thrombosis and may be life-threatening.

- All patients who are to receive unfractionated heparin or LMWH for prophylaxis or treatment of VTE should have a platelet count performed beforehand.
- Monitoring patients for the development of HIT should be by performing serial platelet counts.
- Patients who have previously received unfractionated heparin or LMWH within 100 days or in whom the history of recent exposure to heparins is not clear should have a platelet count performed within 24 hours of receiving the first dose of treatment.
- All other patients for whom monitoring is indicated should have platelet counts performed every 2 to 3 days from day 4 to day 14 of exposure or until treatment stops.
- Patients who are at highest risk such as those receiving UFH in treatment doses or after cardiac or orthopaedic surgery should be considered for more frequent monitoring.
- HIT should be suspected if the platelet count falls by 30% or more or if there is thrombocytopenia (<140 x 10^9/l).
- HIT should be considered in patients who develop a new thrombosis or in whom thrombosis extends and in patients who develop typical skin lesions or features of a systemic response such as fever, chills, shivering or cardiovascular collapse whilst receiving any form of heparin.
- In cases where HIT is suspected please stop heparin or LMWH and immediately call Haematology for urgent advice about further investigation and management. The patient should be evaluated using a clinical scoring system to assess the pre-test probability of having the condition. Management will be directed by the haematology service and may involve the administration of danaparoid or lepirudin as alternative anticoagulants to heparin.
- This should be followed where appropriate by laboratory testing for anti-HIT antibodies. The combined information should be used to assess the probability of having HIT.
- Where warfarin therapy is proposed it should not be introduced until the platelet count has normalised
- When warfarin therapy is introduced it should be at low dose (5 mg daily) and danaparoid or lepirudin should be withdrawn only after the INR has been >2 on two consecutive days.

Table R:	Oral Direct Factor Xa Inhibitors
Rivaroxaban is an oral factor Xa inhibitor licensed for the prevention of venous thromboembolism in adults undergoing elective hip or knee replacement. 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 replacement 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.**	

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

The Antithrombotic Guide was produced by the
NHS Lothian - University Hospitals Division Thrombosis Committee
and ratified by the Drug & Therapeutics Committee

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