This guideline aims to assist the investigation and management of suspected and confirmed PE in adult patients, providing clear standards across SBU Health Board. **Senior clinical advice is essential in the management of these patients.**

Content

Step 1 - Presentation and Initial Investigation

1.1 Common presenting symptoms of PE- patients could present with any of the following:

- Dyspnoea – breathlessness or difficulty breathing
- ☐ Chest pain (pleuritic) and haemoptysis
- ☐ Collapse in patient with poor cardiorespiratory reserve
- ☐ Circulatory collapse in a previously well patient suggestive of massive PE

1.2 Major risk factors for PE (relative risk x 5-20)

Surgery	Major abdominal/pelvic
	Hip/knee replacement
	Postoperative intensive care
Obstetrics	Pregnancy
	Caesarean section
	Puerperium
Lower limb problems	Fracture
	Varicose veins
Malignancy	Abdominal/ pelvic
	Advanced/ metastatic
Reduced mobility	Hospitalisation
	Institutional care
Miscellaneous	Previous proven DVT/ PE
Family History (1st degree relative)	DVT/PE/clotting disorder

1.3 Pulmonary Embolism Rule out Criteria (PERC)

Used **in an emergency department setting** to compliment clinical judgement rather than replace it, with positive criteria helping to form a clinical judgement that would justify a formal evaluation for PE. If all negative, probability of PE is very low.

PERC	Yes	No
Age >50 years	☐	☐
Pulse > 100 bpm	☐	☐
SpO2 < 95%	☐	☐
Unilateral leg swelling	☐	☐
Haemoptysis	☐	☐
Recent trauma or operation	☐	☐
Previous DVT / PE	☐	☐
Hormone usage	☐	☐

1.4 Basic Tests

In assessing patients for suspected PE, clinical judgement is required to determine which tests are appropriate for an individual patient. Markers of poor prognosis include: RV dysfunction/strain, ↑ BNP or ↑ troponin.

Tests on initial assessment include:

- CXR – most often normal, but may be following signs:
  - Linear / wedge-shaped shadows
  - Small pleural effusion
  - Localised subtle paucity of vasculature

- ECG – may be normal, but look for changes:
  - tachycardia
  - S1 Q3 T3 pattern
  - T wave inversion antero-septal leads
  - incomplete/complete RBBB pattern

and can include the following, if clinically indicated and after discussion with a senior clinician:

- ☐ Troponin I or T may be elevated in acute PE [of prognostic value in acute massive PE]
- BNP (if available) – elevation associated with poorer prognosis
- Blood gas on air – if hypoxic/ unwell

Step 2 – Initial Assessment

2.1 Dichotomised Wells Scoring – must involve senior clinician in assessment

Dichotomised Well's Score		
	Score	**Patient's Score**
Clinical DVT	**1**	
Tachycardia >100	**1**	
Immobility > 3 days ***or*** Surgery < 4 weeks	**1**	
Previous PE/DVT	**1**	
Haemoptysis	**1**	
Malignancy within 6 months	**1**	
Alternative diagnosis less likely *(as assessed by senior clinician)*	**1**	
	Total	

If score is ≤ 1, proceed to D-dimer test to exclude PE.

There is **no** benefit from doing D-dimer in those patients with high probability of PE. Therefore if score is **>** 1, proceed straight to clinical differentiation of suspected PE (Step 3).

2.2 Latex Agglutination D-dimer Testing

If D-dimer test result is negative (<500 ug/L), PE can be excluded and an alternative diagnosis should be considered.

Step 3 – Clinical Differentiation and Initial Management

Investigation, management and outcomes of PE are dependent on clinical characteristics of each patient and assessment of haemodynamic stability at an early stage is essential. Defining subgroups of PE is helpful in tailoring management appropriately.

3.1 Suspected Massive PE

Arterial hypotension and cardiogenic shock

- Systolic BP <90 mm Hg for at least 15 mins (or requiring inotropic support) *or* drop in known systolic BP of >40 mm Hg
- Tachycardia, gallop rhythm, pulselessness or persistent profound bradycardia PR < 40 bpm
- Signs of cardiogenic shock: altered level of consciousness, tachypnoea, cool clammy extremities, temp < 36º, SpO2 sat < 90%

Initial management of suspected massive PE

Obtain senior clinical review
Start LMWH (App.2) *or* IV bolus of UFH if considering thrombolysis.
If thrombolysis contraindicated (App.2), consider surgical /cardiology assessment for embolectomy
or
other intervention.

If anticoagulation contraindicated or embolisation continues despite anticoagulation, consider use of IVC filter [see pg 5].

In cardiac arrest situation, when PE is suspected- give 50mg alteplase as bolus stat.

3.2 Suspected Sub-Massive PE

Without systemic hypotension but with RV dysfunction or myocardial necrosis

- RV dysfunction – RV dilation +/*or* RV systolic dysfunction on echo +/*or* ↑ BNP +/*or* ↑troponin
- New ECG changes of complete or incomplete RBBB, anteroseptal ST segment or T wave changes
- Myocardial damage: ↑ BNP; ↑troponin

Initial management of suspected sub-massive PE:

Start LMWH (App.2)
If anticoagulation contraindicated or embolisation continues despite anticoagulation, consider use of IVC filter [see pg 5].

3.3 Non-Massive PE

Absence of clinical markers of adverse prognosis defining massive / sub-massive PE

Some patients with lower risk PEs may still have significant rates of morbidity and mortality that are functions of old age and co morbidities. Therefore important to incorporate risk stratification into clinical decision-making (see Step 5).

Initial management of suspected non-massive PE:
Start LMWH (App. 2).
If anticoagulation contraindicated or embolisation continues despite anticoagulation, consider use of IVC filter [see pg 5].

Step 4 - Radiological Investigations and Management of Proven PE

4.1 Suspected Massive PE

Urgent CTPA is the investigation of choice; if contraindicated discuss with radiologist.
Echo can be done if available – may not be necessary if RV dilatation shown on CTPA.

Management of proven massive PE
Arrange admission to CCU / HDU / ITU.
If diagnosis of PE confirmed, continue LMWH *or* UFH if considering thrombolysis.
If contraindication to anticoagulation / thrombolysis, consider surgical/cardiology assessment for embolectomy or other intervention.

Transfer to low dependency ward when stable.
Warfarin loading protocol unless contraindicated; continue LMWH / UFH until INR in therapeutic range for 2 days.
Perform echo if not already done.

Remain in hospital until condition stable and INR in therapeutic range for at least 2 days.

Thrombolysis
Currently no evidence that thrombolysis improves mortality in patients without shock, hypotension or cardiac arrest compared to LMWH.
Risk of bleeding with thrombolysis and PE is around 10%.

See App.2 for contraindications to thrombolysis.

4.2 Suspected Sub-Massive and Non-Massive PE

CTPA is the investigation of choice where CXR normal. Bilateral duplex scan is of doubtful benefit.

V/Q scan can be considered in patients less than 45 years old after discussion with a radiologist

When there is persisting clinical suspicion of PE with normal V/Q scan or CTPA, continue LMWH a judgement must be made on the basis of the imaging and the clinical information as to what the treatment/management should be.

Management of proven Sub-Massive or Non-Massive PE:
Currently no evidence that thrombolysis improves mortality in PE patients who are not shocked or hypotensive.

If diagnosis of PE is confirmed, proceed to risk stratification for management options. Will require Echo as outpatient if not performed prior to discharge.

All requests for CTPA, VQ/Q scans must be discussed and agreed by duty/on call Consultant Radiologist. All out-of-hours imaging requests to be agreed with on call Consultant Radiologist.

Pre-test probability (i.e. Dichotomised Wells score) to be completed on all requests.

Nuclear medicine (VQ or Q scans) imaging is available weekdays in-hours on all ABMU hospital sites.
There is no out-of-hours availability of VQ or Q scans.

IVC filters are usually deployed as urgent elective procedures; they are rarely done out-of-hours.

See page 9 for imaging in pregnancy.

Note: Use of IVC filters
IVC filters should only be considered in patients with:

i. Proven DVT +/-proven PE who cannot be anticoagulated, with the aim of preventing clot from embolising to the pulmonary circulation
ii. Patients on anticoagulation who continue to embolise (proven on repeat imaging)

A proven PE does **not** need a filter if the veins are clear.

Individual detailed discussions with a vascular Consultant Radiologist on a case by case basis are required to assess factors such as burden of clot, caliber of IVC , venous access etc.

Step 5 – Risk Stratification

Selected patients at low risk of adverse outcome by stratification criteria can be considered for out-patient treatment of PE once diagnosis is confirmed. Patients with a confirmed PE must be:

- **Reviewed by a consultant** who agrees that patient is appropriate for outpatient management.
- Carefully selected for out-patient management according to very strict criteria and protocols.
- Regularly monitored and followed up by senior clinician.
- Informed of the potential risks of ambulatory management - written information for the patient and informed consent are essential.

5.1 Criteria for Suitability for Out Patient Treatment

Patients must have PESI ≤ 85, i.e. lie within Class 1 or 2: see Table 1 below
and
Patients must have **no** additional high risk condition: see Table 2 below

Table 1 - Pulmonary Embolism Severity Index (PESI)

Variable	Points	Patient's Score
Age	1 per year	
Male sex	10	
Cancer	30	
Heart failure	10	
Chronic lung disease	10	
HR 110 bpm	20	
Systolic BP < 100 mm hg	30	
Resp rate ≥ 30 breaths/min	20	
Body temp < 36 ^{0}C	20	
Disorientation, lethargy, stupor, coma	60	
Sa02 < 90% on air	20	
	Total	

Low Risk Classes	Points	30 day all-cause mortality
Class 1 Class 2	<66 66-85	0-1.6% 1.7-3.5%
Intermediate / High Risk		
Class 3 Class 4 Class 5	86-105 106-125 >125	3.2 - 7.1% 4 - 11.4% 10 - 24.5%

Patients must have **PESI ≤ 85** to be managed as an outpatient.

Table 2 - Additional High Risk Conditions / Groups	Yes	No
• Coexisting major DVT (high segment femoral and above) in addition to PE	☐	☐
• Severe renal dysfunction (eGFR < 30ml/ min/ 11.73m2)	☐	☐
• Pregnancy	☐	☐
• Bleeding risk: active bleeding, coagulopathy, ICH (ever), GI/GU bleed, trauma, surgery in last month, platelets <50, abnormal coagulation screen: (INR & APTR), FBC and/or Liver Function Test	☐	☐
• Allergy to warfarin/heparin or history of heparin induced thrombocytopenia	☐	☐
• Outpatient unfeasible in terms of: immobility, compliance unlikely, unable to obtain transport to and from hospital, unable to access telephone at home, unaware of adverse symptoms and how to obtain help	☐	☐
• Needing morphine for pain	☐	☐
• Weight >150Kg	☐	☐
• Already on anticoagulation	☐	☐
• Expected poor compliance	☐	☐

NB Patients must have **no** additional high risk condition to be managed as an outpatient.

5.2 Out Patient Treatment

Consideration of the use of Direct oral anticoagulant (DOACS), especially in ambulatory patients as an additional option. DOACs can be used in any patient, whether an IV drug user or not, provided there is no contraindication

With LMWH and anticoagulation as in Appendix 2.

5.3 Review Arrangements for Out Patient Management

If the decision has been made that the patient is suitable for outpatient management, the following steps should be taken:

Senior clinician confirms suitability for outpatient management
Patient informed of the relative benefits and risks of outpatient management
Patient signs informed consent sheet
Patient treated with LMWH (see App 2)
Patient discharged with hospital contact number and written information giving clear advice to return if symptomatic
Patient discharged home
Review in 24-48 hours on acute site by senior clinician to assess clinical condition and commence warfarin (unless CI)
Review every 1-3 days thereafter until INR in therapeutic range and clinically stable for > 2days

Follow up arrangements as in Step 6.

Step 6 – Follow Up Arrangements

Patients with proven PE require follow-up as outpatients at 3 months. The risk of developing chronic thrombotic and/or embolic pulmonary hypertension is approximately 4% at 2 years.

Decisions regarding duration of anticoagulation (lifelong or not) in unselected patients should be made with reference to whether or not a first episode of venous thrombosis was provoked or not, other risk factors such as strong family history, and risk of anticoagulant therapy-related bleeding, regardless of whether a heritable thrombophilia is known.

6.1 Thrombophilia Testing

Thrombophilia testing is not appropriate during an acute episode of VTE, as results will be abnormal as a consequence of the thrombosis and do not impact on management (acute phase or longer term) in most cases.

The need for thrombophilia testing at follow up appointment should be discussed with Consultant Haematologist prior to testing (by phone or referral letter). Only those deemed clinically appropriate by a consultant haematologist will be processed.

6.2 If persistent dyspnoea +/or RV dysfunction at 3 months

Clinical assessment of:

i. **End-organ damage** requiring onward referral.
The following investigations will inform if referral is to cardiologist or respiratory physician:

- Repeat echo: to assess pulmonary artery pressure
- PFTs - for assessment of gas exchange / ? alternative diagnosis
- Repeat CTPA/VQ – to identify ? Recurrent PE or ? alternative diagnosis

ii. **Duration of anticoagulation -** Adult Inpatient Warfarin Chart [see Appendix 3]

		Target INR (range)
1st idiopathic VTE: proximal DVT or PE * *Review by senior clinician after this time to discuss long term anticoagulation	**≥3 months***	**2.5 (2-3)**
1st proximal VTE/PE with precipitating factors e.g. trauma, surgery, pregnancy	**3 months**	**2.5 (2-3)**
1st idiopathic, calf vein DVT	**3 months**	**2.5 (2-3)**
1st calf vein DVT, with precipitating factors e.g. trauma, surgery	**6 weeks**	**2.5 (2-3)**
Recurrent VTE	**Long term**	**2.5 (2-3)**
VTE whilst taking warfarin - Consider changing to alternative anti-coagulant	**Long term**	**3.5 (3-4)**

Appendix 1 - Groups for Special Consideration in Suspected Pulmonary Embolism

1. Pregnancy

In the acute setting, contact the Obstetric Registrar and/or Consultant early to ensure senior input.

When there are clinical signs/symptoms of PE, undertake investigations and treat with LMWH (unless strong contraindication to anticoagulation).

Choice of investigations will depend on local availability and should be made through discussion between clinician, radiologist and mother. Involvement in the care of the patient by a physician and obstetrician is essential and of a haematologist may be helpful.

- All pregnant women with suspected PE should have a Chest xray.
- Management of PEs in pregnancy is a complex clinical problem
- Senior clinicians should be directly involved in the care at the earliest.
- Best imaging option will depend on the clinical context, pre-test probability and patient's previous medical history
- Patient should be actively involved in the decision making process. Patient information leaflet should be included in trust policy so that clinicians can have an informed discussion.
- Appropriate modality for imaging is to be decided after discussion with duty or on call consultant radiologist.

Diagnosis of DVT may indirectly suggest a diagnosis of PE and, since anticoagulation therapy is the same in both conditions, further investigation may not be necessary. This would limit radiation doses to mother and foetus.

In terms of the risks of radiation from investigations in pregnancy, these vary for foetus and mother depending on the investigation:

- CTPA gives a significantly greater radiation dose to the mother particularly if the mother is very young and has very large breasts , (especially to the breast), and this gives her a higher risk of developing breast cancer later in life than other women her age but lower foetal dose. Average foetal radiation dose is <10% of V/Q scan in all trimesters of pregnancy. (This must be offset by relatively higher risk of breast cancer in mother). See 1.1 consent form for CTPA scan during pregnancy.
- VQ (Q) scans administer a greater dose to foetus, but less to mother than CTPA.
- Both tests are well within the safe levels of radiation which can be given to a fetus. Usually what is best for the foetus is considered paramount, but when feasible women should be involved in the decision to undergo CTPA or V/Q scanning. Ideally, informed consent is obtained before these tests are undertaken.

- The use of D-dimer in pregnancy is not appropriate.
- If **initial imaging** is normal with low level of clinical suspicion, can stop LMWH.
- If **initial imaging** confirms diagnosis, continue anticoagulation.
- If **initial imaging** is negative but clinical suspicion of PE is high, continue LMWH then repeat imaging (or another diagnostic test) within 1 week; if repeat testing is negative and clinical review suggests low risk of PE, discontinue anticoagulation.

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1.1 Consent form for CTPA Scan during Pregnancy

Consent form for CTPA scan during Pregnancy

(to be retained in patient's notes)

Name:.....

Hospital Number:.....

Date of birth:.....

Consultant:.....

Pregnancy is associated with up to a tenfold increase in clots (thrombosis) in the leg veins which can travel to the lungs causing pulmonary embolism (PE). This is one of the leading direct causes of maternal death in the UK and may present with breathlessness, chest pain or collapse. Untreated PE in pregnancy has a death rate of 15-30%. The diagnosis of PE is therefore important not to miss. A scan called a CT pulmonary angiogram (CTPA) is used to detect the PE in the form of clots in the arteries supplying the lungs. The scan involves radiation and intravenous contrast or 'dye'. There are risks associated with radiation and to avoid this you will have already had ultrasound (involving no radiation) to look for deep vein thrombosis (DVT) in both your legs. The treatment for clot is similar whether it is found in your legs or lungs. Unfortunately, in your case, despite your leg scans being negative we are still concerned that you may have a PE and a CTPA is required to detect this.

The radiation exposure from having a CTPA may affect you and your baby. There is an extremely slight increase (1 in 1,000,000) risk of childhood cancer in your unborn baby. Studies suggest the greater risk is to you as the mother, with a lifetime risk of breast cancer following radiation exposure with the CTPA increased by 13.6%. With newer CT scanners and lower doses of radiation now being used the risk of breast cancer is likely to be lower than originally thought.

The contrast or 'dye' injected into a vein is used to make the clots visible on the CTPA scan. There is no reported risk to an unborn child, however if you are breastfeeding a child you should express enough milk to cover a 24 hour period after your CTPA when it is advised not to breastfeed. Please tell us if you've had a previous reaction of any type to contrast dye or iodine.

An alternative (VQ) scan which is not available at , involves lower doses of radiation to your breast tissue but higher risks of childhood cancer in your unborn baby. The VQ scan also is less accurate at detecting PE compared with the CTPA. The VQ scan, unlike the CTPA, is unable to detect other chest problems that may be causing your symptoms.

Statement of health professional:

I have explained the intended benefits and the risks associated with the CTPA scan during pregnancy as detailed above to the patient named above. I confirm that the patient has the capacity to consent.

Signed..... Job title..... Date..... Name (PRINT).....

Statement of patient:

I agree to the CTPA scan and understand the information given to me.

Signed..... Date.....

Name (PRINT).....

2. Oncology patients

PE may present in 2 ways in patients with a known diagnosis of cancer:

- With clinical suspicion of PE – follow pathway as for non-cancer patients
- PE diagnosed on routine staging CT scan – continue pathway after diagnosis

Management of PE in oncology patients

- Following assessment, involvement of the patient's oncologist is essential within 24 hours of diagnosis/clinical suspicion of PE. LMWH can be commenced until a definitive management plan is agreed by oncologist.

- When PE is diagnosed opportunistically on imaging, the radiologist will refer the patient to the on-call medical team for assessment. The medical team will then contact the patient's Consultant Oncologist for involvement in management.

- Evidence indicates LMWH is usually superior to warfarin in cancer patients in terms of bleeding risk, recurrence/progression of thrombosis and potential interaction with chemotherapeutic agents. Therefore continue LMWH unless oncologist decides to switch to warfarin.

- Some cancer patients may be suitable for management of their PE on an ambulatory pathway, especially when detection has initially been made through routine CT scanning.
  Management of these patients may differ from standard practice for PE in that PESI of Class 3 or 4 may not prevent their outpatient management (see page 6 for standard practice). Discussion with the patient's Consultant Oncologist, with consideration of relative risk/benefits, is essential.

3. IV Drug Abusers

On presentation with suspected PE, septic emboli should be considered as a cause and additional investigations with blood cultures / infection screens undertaken.

These patients may be poorly compliant, making it difficult to control their INR with warfarin. They can be treated with longer term LMWH, if appropriate.

Patients receiving longer term LMWH should have a full blood count and creatinine checked when periodically, for example when a new prescription is issued.

4. Patients with Alcoholism

Alcoholics with diagnosed thromboembolic disease may present problems if treated with oral anticoagulants - they may be poorly compliant and binge-drinking may interfere with control of their INR. Furthermore, accidental falls or altercations pose a risk of bleeding whist on anticoagulants. Thus a team approach which may involve senior clinicians, nurses, social workers, carers and the patient is often appropriate.

Appendix 2 – Treatment of PE

1. Tinzaparin for the treatment of pulmonary embolism

In the treatment of pulmonary embolism, tinzaparin should be administered subcutaneously as a single daily injection of 175 anti-Factor Xa IU/kg bodyweight once daily, for a minimum of 5 days and until the INR is in target range for two consecutive days, whichever is longer.

Tinzaparin (innohep®) for treatment of DVT/PE is available as 20,000 anti-Factor Xa IU/ml in 0.5ml,0.6ml, 0.7ml, 0.8ml and 0.9ml in colour-coded syringes and as a multi-dose vial. (See page 14)

The dosing chart below indicates the volume of tinzaparin that needs to be administered when treating pulmonary embolism, and the most convenient and cost-effective formulation to use in each case (figures rounded to the nearest 0.05ml).

e.g. a 70kg patient will require 12,000 units (0.6ml) tinzaparin (20,000 anti-Factor Xa IU/ml) given via a yellow 0.7ml syringe.

Renal impairment

Caution is recommended when treating patients with renal impairment. Monitoring of anti-factor Xa activity should be considered in patients with severe renal impairment (creatinine clearance < 30 ml/min); however, available evidence suggests that no dose reduction is needed in patients with creatinine clearance levels down to 20 ml/min.

Monitoring

Risk assessment and clinical monitoring are the best predictors of the risk of potential bleeding. Routine anti-Xa activity monitoring is usually not required (see above). However, anti-Xa activity monitoring might be considered in those patients treated with LMWH who also have either an increased risk of bleeding (such as those with renal impairment, elderly and extremes of weight) or are actively bleeding.

There is a small risk of antibody-mediated heparin-induced thrombocytopenia with low molecular weight heparin. A baseline platelet count should be measured before treatment and then 2-3 times between day 4 and 14. If a patient has received any type of heparin within the preceding 100 days, the platelet count should also be check 24 hours after starting treatment. Patients who develop thrombocytopenia whilst receiving heparin should be discussed urgently with a haematologist.

Further information to aid prescribing is available by viewing the Summary of Product Characteristics at:
http://www.medicines.org.uk/emc/medicine/5176/SPC/Innohep+20%2c000+IU+ml+and+Innohep+syringe+20%2c000+IU+ml/

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innohep®
tinzaparin sodium

DVT and PE Treatment Dosage

For 20,000 anti-Factor Xa IU/ml variable dose syringe or multi-dose vial

Dosage: 175 anti-Factor Xa IU/kg bodyweight once daily for at least 6 days and until adequate oral anti-coagulation is established. Syringe (only): Extended treatment of symptomatic VTE and prevention of its recurrence in patients with solid tumours: 175 IU anti-Xa/kg once daily for a recommended treatment duration of 6 months.

	Bodyweight (kg)	Injection Volume subcutaneous inj. (ml)	Prescribed Dose anti-Factor Xa IU
innohep® 0.4 ml syringe 	*35	0.30	6,000
	40	0.35	7,000
	45	0.40	8,000
innohep® 0.5 ml syringe 	50	0.45	9,000
	55	0.50	10,000
innohep® 0.6 ml syringe 	60	0.55	11,000
	65	0.60	12,000
	70		
innohep® 0.7 ml syringe 	75	0.65	13,000
	80	0.70	14,000
innohep® 0.8 ml syringe 	85	0.75	15,000
	90	0.80	16,000
	95	0.85	17,000
innohep® 0.9 ml syringe 	100	0.90	18,000
innohep® Multi-dose vial  For patients above 103 kg in weight, the multi-dose vial can be used**	>103	Based on Weight	175 IU/kg

* No experience with children.

** **The innohep® multi-dose vial should not be used in pregnancy.**

This document has been coated with an Antimicrobial Finish which reduces levels of bacteria by up to 99.9%.

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2. UFH – dosage and schedules

ABERTAWE BRO MORGANNWG UNIVERSITY HEALTH BOARD
HEPARIN INFUSION PRESCRIPTION CHART

HOSPITAL NO: _____
SURNAME: _____
FIRST NAMES: _____
ADDRESS: _____
DATE OF BIRTH: _____

PATIENT'S WEIGHT (Kgs)

INTRAVENOUS HEPARIN THERAPY TARGET APTT 1.5-2.5

1. HEPARIN LOADING DOSE: (See guidelines)

Date	Dose	Dr's Sig	Given by	Checked by	Date & Time Infusion started	Pharm
	Units	Bleep No.				

2. HEPARIN INFUSION DOSE INITIATION: (See guidelines)
Infusion strength 20,000 units in 20ml (1000 units per ml)

Date	Date & Time APTT sample taken	APTT	Dr's Sig	Infusion rate	Given by	Checked by	Date & Time Infusion started	Pharm
			Bleep No.	ml/hour				

3. HEPARIN INFUSION MAINTENANCE DOSE: (See guidelines)
Infusion strength 20,000 units in 20ml (1000 units per ml)

Date & Time APTT sample taken	APTT	Dr's Sig	Date	Infusion Rate	Given by / Checked by	Date & Time Infusion started/changed	Pharm
		Bleep No.		ml/hour	Given by / Checked by		
		Bleep No.		ml/hour	Given by / Checked by		
		Bleep No.		ml/hour	Given by / Checked by		
		Bleep No.		ml/hour	Given by / Checked by		
		Bleep No.		ml/hour	Given by / Checked by		
		Bleep No.		ml/hour	Given by / Checked by		
		Bleep No.		ml/hour	Given by / Checked by		
		Bleep No.		ml/hour	Given by / Checked by		

Heparin Infusion Schedule – Guidelines

Before starting heparin a coagulation screen and baseline APTT should be done:

1. HEPARIN LOADING DOSE:

Give Loading Dose: Heparin 5,000 units iv over 5mins
(Patients below 65Kg = 4,000 units)
(in severe pulmonary embolism 10,000 units may be used)

2. COMMENCE HEPARIN INFUSION:

USE INFUSION STRENGTH 20,000 UNITS IN 20ML (= 1,000 units per ml) only.
Start on an initial infusion rate of 18 units/kg/hour (= 0.018ml/kg/hr)
Due to the limitations of some syringe drivers round to the nearest 0.1ml.

3. HEPARIN INFUSION MAINTENANCE DOSE:

Check APTT ratio after SIX hours

Adjust dose according to APTT ratio as follows:-

APTT Ratio	Infusion Rate Change	Recheck APTT
>7.0	Stop infusion for 3 hours and seek medical opinion, THEN **REDUCE BY 0.5ml/hr (500 units/hr)**	3 hours
5.1-7.0	Stop infusion for 60 mins and seek medical opinion, THEN **REDUCE BY 0.5ml/hr (500 units/hr)**	4 hrs
4.1-5.0	Stop infusion for 30-60 mins, THEN **REDUCE BY 0.3ml/hr (300 units/hr)**	6 hrs
3.1-4.0	Stop infusion for 30-60 mins, THEN **REDUCE BY 0.2ml/hr (200 units/hr)**	6 hrs
2.6-3.0	Stop infusion for 30-60 mins, THEN **REDUCE BY 0.1ml/hr (100 units/hr)**	6 hrs
1.5-2.5	**NO CHANGE**	**Within 24hrs**
1.2-1.4	Consider further IV loading dose of 2500 i.u. **INCREASE BY 0.2ml/hr (200 units/hr)**	12 hrs
<1.2	Consider further IV loading dose of 5000 i.u. **INCREASE BY 0.4ml/hr (400 units/hr)**	6hrs

Platelet counts should be monitored in patients receiving heparin for more than 4 days. **APTT must be checked a minimum of every 24 hours for every heparin patient.** After every dose change check APTT ratio as per "Recheck APTT" column.

3. Warfarin

Please refer to the warfarin inpatient chart (Appendix 3)

Patient Characteristics	Warfarin loading dose
All patients with organ dysfunction / sepsis	Treat as an inpatient. Discuss loading dose with senior clinician
All patients < 70 years old and > 60kg body weight and not taking potentiating drugs.	Follow rapid initiation of warfarin (Fennerty scale) see appendix 3 Adult in-patient warfarin chart.
Any patient who is either > 70 years old, or < 60 kg body weight or who is receiving Potentiating drugs.	Follow low dose loading in high risk patients, see appendix 3 Adult in-patient warfarin chart.
When adopting the rapid initiation of warfarin for under 70 years or low dose loading for over 70 yea obtain a baseline INR and daily INR's for the first four days as per the loading protocol. Please follow induction of warfarin guidance as per the Adult in-patient warfarin chart (appendix 3)	
See BNF Appendix 1. for details of potential drug reactions	

4. Thrombolysis

Alteplase can be given to patients with massive PE who fulfil criteria for administration of thrombolysis. There is no evidence for positive effects on mortality and late morbidity related to pulmonary embolism.

Risk-benefit analysis of thrombolysis
As with all thrombolytic agents, the expected therapeutic benefit should be weighed up particularly carefully against the possible risk.

In **Pulmonary Embolism**, a total dose of 100 mg of alteplase should be administered in 2 hours. Most experience is available with the following dose regimen:

	Concentration of alteplase 1 mg/ml	2 mg/ml
	ml	ml
10 mg as an intravenous bolus over 1 - 2 minutes	10	5
followed by an intravenous infusion of 90 mg over 2 hours	90	45

The total dose should not exceed 1.5 mg/kg in patients with a body weight below 65 kg.

Adjunctive therapy:

After treatment with alteplase (Actilyse), heparin therapy should be initiated (or resumed) when aPTT values are less than twice the upper limit of normal. The infusion should be adjusted to maintain aPTT between 50 - 70 seconds (1.5 to 2.5 fold of the reference value).

Contraindications to Thrombolysis

Hypersensitivity to the active substance or to any of the excipients.

Alteplase (Actilyse) is contraindicated in cases where there is a high risk of haemorrhage such as:

- significant bleeding disorder at present or within the past 6 months
- known haemorrhagic diathesis
- patients receiving oral anticoagulants, e.g. warfarin sodium
- manifest or recent severe or dangerous bleeding
- known history of or suspected intracranial haemorrhage
- suspected subarachnoid haemorrhage or condition after subarachnoid haemorrhage from aneurysm
- any history of central nervous system damage (i.e. neoplasm, aneurysm, intracranial or spinal surgery)
- recent (less than 10 days) traumatic external heart massage, obstetrical delivery, recent puncture of a non-compressible blood-vessel (e.g. subclavian or jugular vein puncture)
- severe uncontrolled arterial hypertension
- bacterial endocarditis, pericarditis
- acute pancreatitis
- documented ulcerative gastrointestinal disease during the last 3 months, oesophageal varices, arterial-aneurysm, arterial/venous malformations
- neoplasm with increased bleeding risk
- severe liver disease, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis
- major surgery or significant trauma in past 3 months.
- any known history of haemorrhagic stroke or stroke of unknown origin
- known history of ischaemic stroke or transient ischaemic attack (TIA) in the preceding 6 months, except current acute ischaemic stroke within 3 hours.

Special warnings and precautions in acute pulmonary embolism

Thrombolytic/fibrinolytic treatment requires adequate monitoring. Actilyse should only be used by physicians trained and experienced in the use of thrombolytic treatments and with the facilities to monitor that use. It is recommended that when Actilyse is administered standard resuscitation equipment and pharmacotherapy be available in all circumstances.

The risk of intracranial haemorrhage is increased in elderly patients, therefore in these patients the risk/benefit evaluation should be carried out carefully.

As with all thrombolytic agents, the expected therapeutic benefit should be weighed up particularly carefully against the possible risk, especially in patients with:

- small recent traumas, such as biopsies, puncture of major vessels, intramuscular injections, cardiac massage for resuscitation
- conditions with an increased risk of haemorrhage

The use of rigid catheters should be avoided.

A dose exceeding 100 mg of alteplase must not be given because it has been associated with an additional increase in intracranial bleeding.

There is limited experience with readministration of Actilyse. Actilyse is not suspected to cause anaphylactic reactions. If an anaphylactoid reaction occurs, the infusion should be discontinued and appropriate treatment initiated.

The expected therapeutic benefit should be weighed up particularly carefully against the possible risk, especially in patients with systolic blood pressure > 160 mm Hg.

Further information, including special warnings and precautions for use, is available by viewing the Summary of Product Characteristics at:
http://www.medicines.org.uk/EMC/medicine/308/SPC/Actilyse/

Appendix 3 – Adult inpatient warfarin chart

ADULT INPATIENT WARFARIN CHART

Prescribe warfarin on the in-patient chart, write **"see warfarin treatment chart"** and attach this sheet securely to the chart. All doses must be given between 14.00 – 1800 hours. If warfarin temporarily withheld write **"OMIT"** on this chart.

Affix addressograph label here Name: ..... Hospital Number: ..... Date of birth:	**Ward:** **Consultant:**	☐ New Treatment	☐ Continuing Treatment
		INR before starting warfarin	Warfarin dose on admission
		Follow induction nomogram below	Follow maintenance dosing overleaf
		Patient educated	☐ Patient educated
		Yellow booklet given	☐ Patient has yellow booklet

Interacting drugs:

Duration of warfarin for specific clinical indications	✓	Duration	Target INR (range)
1st idiopathic VTE : proximal DVT or PE* *Review by senior clinician after this time to discuss long-term anticoagulation		≥ 3 months*	2.5 (2-3)
1st proximal VTE / PE, with precipitating factors eg trauma, surgery, pregnancy		3 months	2.5 (2-3)
1st idiopathic, calf vein DVT		3 months	2.5 (2-3)
1st calf vein DVT, with precipitating factors eg trauma, surgery		6 weeks	2.5 (2-3)
Recurrent VTE		Long-term	2.5 (2-3)
VTE whilst taking warfarin		Long-term	3.5 (3-4)
Atrial fibrillation		Long-term	2.5 (2-3)
Prosthetic heart valve		Long-term	Seek specialist advice
Pre-cardioversion		> 3 weeks	2.5 (2-3)
Post-cardioversion		4 weeks	2.5 (2-3)
Other (specify)			

Induction of warfarin for atrial fibrillation

Where atrial fibrillation is the sole indication, rapid loading with warfarin (using the nomograms across) is not required. Consider using a local low dose loading regime.

Induction of warfarin – Nomogram for target INR of 2.5

- Obtain a baseline INR and daily INRs for the first 4 days.
- If baseline INR ≥1.4 do not use the nomogram below. Review the indication for warfarin / seek haematological advice.
- If the patient is unstable (heart failure / liver disease / sepsis) consider using a therapeutic dose of low molecular weight heparin until the patient is stabilised.
- Give low molecular weight heparin for a minimum of 5 days (see BNF for special precautions) or until the INR is in the target range for 2 consecutive days (whichever is longer)

Nomograms for the loading and reloading of warfarin (See overleaf for maintenance dosing)

Date	INR result	Warfarin dose (mg)	Prescriber (Signature)	Next test (date)	Given by	Time & Date

Rapid initiation of warfarin for under 75 years (Fennerty scale)

Day	INR (Best taken 0900-1000)	Warfarin dose (mg) (Best given 1700-1800)
Day 1	<1.4	10
Day 2	<1.8	10
	1.8	1
	>1.8	0.5
Day 3	<2.0	10
	2.0 to 2.1	5
	2.2 to 2.3	4.5
	2.4 to 2.5	4
	2.6 to 2.7	3.5
	2.8 to 2.9	3
	3.0 to 3.1	2.5
	3.2 to 3.3	2
	3.4	1.5
	3.5	1
	3.6 to 4.0	0.5
	>4	Omit dose
Day 4 and predicted dose for days 5-7. Check INR on day 8 and dose as overleaf.	<1.4	>8
	1.4	8
	1.5	7.5
	1.6 to 1.7	7
	1.8	6.5
	1.9	6
	2.0 to 2.1	5.5
	2.2 to 2.3	5
	2.4 to 2.6	4.5
	2.7 to 3.0	4
	3.1 to 3.5	3.5
	3.6 to 4.0	3
	4.1 to 4.5	Miss one dose then 2mg
	>4.5	Miss two doses then 1 mg

Rapid initiation of warfarin for over 75 years, cardiac failure or liver failure

Day	INR (Best taken 0900-1000)	Warfarin dose (mg) (Best given 1700-1800)
Day 1	<1.4	10
Day 2	<1.8	5
	1.8 to 2.0	1
	>2.0	Omit
Day 3	<2.0	5
	2.0 to 2.5	4
	2.6 to 2.9	3
	3.0 to 3.2	2
	3.3 to 3.5	1
	>3.5	Omit
Day 4 and predicted dose for days 5-7. Check INR on day 8 and dose as overleaf	<1.4	>7
	1.4 to 1.5	7
	1.6 to 1.7	6
	1.8 to 1.9	5
	2.0 to 2.3	4
	2.4 to 3.0	3
	3.1 to 3.2	2
	3.3 to 3.5	1
	>3.6	Omit

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COIN ID.	CID726
Document Title.	Guidance for the Management of Suspected Pulmonary Embolism (PE) in Adults
Name of Author.	Kieron Power, Principal Pharmacist, Thrombosis and Anticoagulation AGPU
Name of Lead Pharmacist.	As above.
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Equality Statement. *(All policies and procedures need to comply with CID76 Policy for the Management of Heath Board Wide Policies, Procedures and other Written Control Documents (WCD).*	N/A
Published Date.	March 2013
Last Reviewed Date.	October 2023
Next Review Due/Expiry Date.	October 2025