University Hospitals of Derby and Burton
NHS Foundation Trust

GUIDELINE FOR THE INVESTIGATION AND MANAGEMENT OF ADULT PATIENTS WITH PULMONARY EMBOLISM

Reference No: CG-T/2023/051

Introduction

Acute pulmonary embolism (PE) is a common medical condition with an incidence of 70-80 cases per 100,000 population. Half of patients will develop PE whilst an inpatient, either in hospital or long term care. The remaining 50% develop PE either as a result of recognised risk factors (provoked) or without a clear risk factor identified (unprovoked). In-hospital mortality ranges from 6-15%, with a 30 day mortality of 13%. A high proportion of early deaths are directly due to PE. PE is both under and over diagnosed in practice, leading to inappropriate under and over treatment for this condition.

Purpose

The purpose of this guideline is to provide standards and practical advice for the investigation and management of acute pulmonary embolism in adults.

Aims and Scope

The aim of the guideline is to;

- Describe methods for risk stratifying PE patients and to determine appropriate treatment pathways.
- Summarise options for anticoagulation therapy for PE, including guidance on duration of therapy.
- Determine the appropriate indications and contraindications for thrombolysis in high risk PE patients.
- Discuss specifically the management of submassive PE, incidental PE and cancer-associated thrombosis.
- Describe the follow-up arrangements for PE patients managed in the outpatient setting or discharged following acute PE.

This guideline does not cover;

- Assessment of suspected PE in pregnant patients or children.
- Assessment and management of adult patients with Deep Vein Thrombosis or Superficial Vein Thrombosis.
- Role of anticoagulation in thromboprophylaxis
- A detailed discussion of the role of IVC filters for thromboprophylaxis and interventional radiological procedures for treatment of acute VTE.

Other relevant guidelines

This guideline should be read in conjunction with the following guidelines which cover additional aspects of PE diagnosis and management;

[1]British Thoracic Society Guideline for the initial outpatient management of pulmonary embolism (PE). Thorax 2018.

[2]National Institute for Health and Care Excellence (2020). Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. https://www.nice.org.uk/guidance/ng158

[3]Trust Guideline on Acute Management of Venous Thromboembolism in Pregnancy. ACUTE MANAGEMENT OF VENOUS THROMBOEMBOLISM IN PREGNANCY AND THE PUERPERIUM (koha-ptfs.co.uk)

[4]Trust guideline on Prevention of Contrast Induced Acute Kidney Injury (AKI). opac-retrieve-file.pl (koha-ptfs.co.uk)

Abbreviations

A&E	Accident and Emergency
ACC	Ambulatory Care Centre
BTS	British Thoracic Society
CAT	Cancer-associated thrombosis
CCU	Coronary Care Unit
CTPA	Computed Tomography Pulmonary Angiogram
CXR	Chest x-ray
DOAC	Direct Oral Anticoagulant
DVT	Deep Vein Thrombosis
ED	Emergency Department
HDU	High Dependency Unit
IVC	Inferior vena cava
ICU	Intensive Care Unit
LMWH	Low molecular weight heparin
LV	Left ventricle
MAU	Medical Assessment Unit
NICE	National Institute for Health and Care Excellence
NCEPOD	National Confidential Enquiry into Patient Outcome and Death
OP	Outpatient
PE	Pulmonary embolism
PTT	Prothrombin time
RV	Right ventricle
(s)PESI	(Simplified) Pulmonary Embolism Severity Index
UFH	Unfractionated Heparin
VKA	Vitamin K antagonist
VQ SPECT	Ventilation Perfusion Single Photon Emission Computed Tomography
VTE	Venous thromboembolism (i.e. PE or DVT)

Contents

1. Initial Assessment and Imaging in Suspected Acute PE.

1.1 Principles of assessment

1. A thorough history, careful clinical examination and appropriate use of initial investigations (such as routine bloods, ECG and CXR).
2. Objective assessment of clinical probability using a validated score, such as;
    a. PERC score[5] – excludes PE without requirement for D dimer testing or further imaging if applied to an appropriately selected patient population
    b. YEARS Algorithm[6] - excludes PE without requirement for imaging if applied to an appropriately selected patient population
    c. Two-level Wells score – allows triage of patients with suspected PE into “PE likely” or “PE unlikely “groups.
3. Use of D-dimer testing in “PE unlikely” patients to exclude the diagnosis without the need for further imaging.
4. Appropriate radiological imaging tests for patients with “PE likely”, and those with “PE unlikely” in whom a D dimer test is elevated.
5. An interim therapeutic dose of anticoagulation in patients waiting for definitive imaging (CTPA or V/Q SPECT) if imaging is not available immediately.

1.2 Timing of radiological investigations and use of interim therapeutic anticoagulation

- NICE[6] and NCEPOD[7] recommend patients with suspected PE must be given a dose of interim therapeutic anticoagulation if CTPA or V/Q SPECT is not available immediately, or there is likely to be a wait of more than 4 hours for a D-dimer test result.

- An immediate therapeutic dose of Apixaban, Rivaroxaban or LMWH should be given.

    - A previous history of bleeding is rarely a contraindication for interim anticoagulation.
    - Active major bleeding or major bleeding within the previous 14 days (such as intracranial, gastrointestinal or genitourinary haemorrhage) are absolute contraindications.
    - A platelet count < 50 or clinical evidence of disseminated intravascular coagulation (DIC) may be contraindications.
    - **If there is any doubt about whether interim therapeutic anticoagulation should be given the on call Haematologist should be contacted urgently.**

- Haemodynamically unstable patients with suspected PE, or high clinical probability cases where there is a concern about the safety of interim anticoagulation, should be imaged within 1 hour and the decision for urgent imaging should be made following assessment by a senior clinician and

discussion with the on call Radiologist.

- Stable patients assessed out of normal working hours may be imaged on the first available list the following day, provided they have received appropriate interim therapeutic anticoagulation.

1.3 Clinical evaluation

- Initial investigations should include;
    - Chest x-ray in all patients to exclude other diagnoses with similar clinical presentation to PE, e.g. pneumothorax.
    - ECG to in all patients to exclude myocardial infarction. ECG features of PE are non-specific and may include sinus tachycardia, ST segment or T wave changes, right bundle branch block, right axis deviation or signs of right heart strain.
    - For biochemical risk stratification a troponin should be checked. As an alternative, BNP or NT-pro-BNP can also be used for risk stratification. Other bloods should include U+E, LFT, FBC, INR and PTT
    - A quantitative D dimer may be needed after risk stratification with the two-level Wells score. **If a patient is over the age of 50 then an age-adjusted interpretation of the d-dimer is recommended.**

1.4 Assessing probability of PE

Pulmonary Embolism Rule Out Criteria (PERC rule)

- If clinical suspicion of PE is low (clinician estimates likelihood of PE to be <15% based on overall clinical impression) the PERC criteria can be applied to determine whether any further investigations for PE are needed.
- If all the PERC criteria are negative (see below) PE can be effectively ruled out without the need for D-dimer testing or further imaging. See Appendix 1A.
- If PERC score is positive, proceed to complete a Two-level Wells score.

YEARS Algorithm

- YEARS algorithm uses three clinical criteria in addition to D-dimer testing to exclude PE in certain patients without the need for imaging. See Appendix 1B.

Two-level Wells score

If PE is suspected, use the 2-level PE Wells score to estimate the clinical probability of PE (see Appendix 1C)

If the result of the 2-level Wells score is "PE likely" (score > 4 points);

- Offer CTPA immediately if possible

- CTPA is the first line imaging investigation in patients over 50 or with significant co-morbid cardiorespiratory disease or an abnormal CXR.

- Assess suitability for V/Q SPECT if:
    - Age under 50, no significant co-morbid cardiorespiratory disease and a normal CXR, **or**
    - Allergy to contrast media, severe renal impairment (estimated creatinine clearance < 30 ml/min) or a high risk from irradiation.

- If CTPA or V/Q SPECT cannot be completed within 1 hour, offer immediate therapeutic anticoagulation (Apixaban, Rivaroxaban or LMWH).

- Note that V/Q SPECT is not available out of hours and if a patient with suspected PE presents between Friday morning and Sunday evening, V/Q imaging within 24 hours cannot be guaranteed.

In patients with suspected massive or submassive PE, CTPA is the preferred imaging modality.

- CTPA requires venous access in the right arm for optimal contrast dynamics, preferably a 20G (pink) cannula or larger in the right antecubital fossa.

- Renal function should be considered before ordering CTPA. If eGFR < 60, read the section on renal impairment below.

If PE is not identified by CTPA, V/Q SPECT or V/Q planar scan:

- Consider proximal leg vein ultrasound scan if DVT is suspected clinically.

- Note that leg vein ultrasound is performed by the Clinical Measurement department and not the Radiology department.

If the result of the 2-level Wells score is "PE unlikely" (4 points or less):

- Offer D-dimer testing with the result available within 4 hours if possible **or**

- If the D-dimer result cannot be obtained within 4 hours, offer interim therapeutic anticoagulation whilst awaiting the result.

- If the D-dimer is normal PE is as unlikely as with a negative CTPA or V/Q SPECT, and no further thoracic imaging for PE is warranted. Alternative diagnoses should be considered.

- If the D-dimer is abnormal then image for suspected PE as above.

<u>Patients presenting with signs or symptoms of both DVT and PE</u>

- If a patient presents with symptoms compatible with both DVT and PE, consider proximal leg vein ultrasound, with a presumptive clinical diagnosis of PE made if the leg ultrasound is positive for DVT.

- This diagnostic strategy should not be applied to higher risk patients with suspected PE such as those with adverse features including;
    - haemodynamic instability,

- raised troponin or BNP,
- new ECG changes,
- sPESI score >0
- clinical features including haemoptysis, presyncope/syncope, palpitations or ischaemic-sounding chest pain.

1.5 Interpretation of imaging results

- A PE is confirmed by a positive report from either a CTPA or V/Q scan. Acute PE can resolve in as little as 2 days resulting in a negative scan. There is a small false positive rate with both tests.

- All indeterminate V/Q scans should be followed by further imaging, usually CTPA. A small proportion of CTPAs may be indeterminate due to incomplete opacification of pulmonary vessels or respiratory motion. Thus, CTPA may not be sufficient to exclude the diagnosis, unless the scan shows clear evidence of another diagnosis. In cases with an indeterminate CTPA result the clinical probability and scan result should be reviewed by a senior clinician with expertise in pulmonary embolism. If any doubt remains a decision should be made either to re-image with the alternative test or treat empirically.

1.6 Additional investigations

Cardiac Troponins / BNP / NT pro-BNP

May be raised in some PE patients with more severe disease reflecting right ventricular myocardial damage due to RV strain. In this case they give prognostic information but used in isolation their role in clinical decision making remains unclear. They may allow recognition of a lower risk cohort of PE patients suitable for outpatient management, but only when used in conjunction with an appropriate risk score such as the Pulmonary Embolism Severity Index (PESI), simplified (s)PESI or Geneva score.

Echocardiogram

An echocardiogram is the bedside test of choice for patients who are too ill to be transferred to the Radiology department for urgent imaging. Right ventricular dilatation and hypokinesis in the appropriate clinical setting can strongly suggest the diagnosis of massive PE. The decision for bedside echocardiography should be made in conjunction with the consultant responsible for the patient's care.

Malignancy screening

NICE guidance was updated in 2023[3]. Patients with confirmed *unprovoked* PE or DVT should have the following assessment:

- Careful history and examination looking for occult malignancy
- FBC, U+E, LFT, calcium, coagulation
- The following tests may be appropriate **only if clinical signs / symptoms are suggestive of underlying malignancy**.
    - PSA and digital rectal examination if male

- Breast examination if female
- CT or USS imaging of abdomen / pelvis
- Endoscopy

Thrombophilia testing

There is a limited role in the acute setting. Thrombophilia testing can be requested in the outpatient setting in specialist clinics when it may have an impact on length of anticoagulation treatment or further risk stratification.

1.7 Renal impairment

Please refer to the Trust guideline on Prevention of Contrast Induced Acute Kidney Injury (AKI). opac-retrieve-file.pl (koha-ptfs.co.uk)

In patients with severe renal dysfunction in whom V/Q scan is not helpful, a positive Doppler ultrasound may avoid the need for CTPA. Advanced renal failure is not an absolute contraindication for CTPA, particularly in the acutely unstable patient if a diagnosis is needed, but discussion with the renal team is essential to ensure an appropriate management/escalation plan in the event of worsening renal function post-contrast.

1.8 Appendix 2 summarises the pathway for risk assessment of patients with suspected PE presenting via ED (page 28).

2. Management of Pulmonary Embolism by Risk Stratification

2.1 Risk stratification for Acute PE

- The clinical classification of severity of acute PE is based on assessment of in-hospital or 30 day mortality associated with PE and is derived from the patient's clinical status at presentation.

HIGH risk
 	
(includes Massive PE)
	• Evidence of shock / sustained hypotension;
	  ○ Systolic BP ≤90 mmHg for at least 15 minutes,
	  ○ **or** a fall in SBP ≥40 mmHg from baseline,
	  ○ **and** hypotension not due to an alternative cause (new arrhythmia, sepsis, dehydration, LV dysfunction).
	• Consider suitability for thrombolysis.

INTERMEDIATE risk
 	
(includes Submassive PE)
	• Normotensive PE with;
	  ○ Raised Troponin T, BNP or NT-pro BNP (not due to a primary cardiac cause such as myocardial infarction)
	  ○ **or** evidence of RV dysfunction on echocardiogram / CT
	• Admission usually required.
	• Consider need for level 2 (HDU) monitoring.

LOW risk	• All other presentations of PE (i.e. without hypotension or evidence of RV dysfunction). • Consider admission for observation if not suitable for outpatient management.

Appendix 3 summarises the pathway for risk assessment of patients with suspected PE presenting via Ambulatory Care or MAU (page 29).

2.2 HIGH risk PE (aka PE with haemodynamic instability or 'massive' pulmonary embolism)

- PE with hypotension (either systolic BP < 90mmHg or a systolic pressure drop ≥40 mmHg from baseline for more than 15 minutes) that is *not* caused by a cardiac arrhythmia, hypovolaemia or sepsis.

- The diagnosis of PE should be confirmed by CTPA or, if patients are too unstable to transfer to CT, an urgent bedside echocardiogram showing either acute right ventricular dysfunction (where there is no other explanation for RV dysfunction) or a free-floating thrombus in the right atrium or right ventricle.

- NOTE: in patients with a confirmed PE but small clot burden (for example, subsegmental PE), haemodynamic instability is unlikely to be due to acute clot

and alternative explanations should be sought.

- Thrombolysis should be *considered* in all patients presenting with massive PE as the mortality is >30%.

- All decisions regarding thrombolysis should be discussed with a senior clinician - usually the ED Consultant or Respiratory Consultant on call - *before* thrombolysis is given, unless time critical e.g. cardiac arrest or peri-arrest scenario.

2.2.1 Thrombolysis in Massive PE

Appendix 4 summarises the pathway for thrombolysis in patients with confirmed PE (page 30).

Appendix 5 summarises the relative and absolute contraindications for thrombolysis in acute PE (page 31).

Appendix 6 contains a checklist to be completed in any patients who are to receive thrombolysis (page 32)

- In massive PE **but not** in cardiac arrest or imminent cardiac arrest, give a 10mg IV bolus of Alteplase over 1-2 minutes, followed by an infusion over 2 hours (see dosing table below).

- If the patient is taking LMWH or UFH this should be discontinued prior to thrombolysis.

- Following thrombolysis, the patient's APTT should be checked immediately.

- Monitoring requirements for patients receiving Alteplase:

    - Patients should be monitored during and for several hours after the infusion for signs of orolingual angioedema. If such reactions occur, the patient should receive appropriate treatment with corticosteroids and anti-histamines; and consideration should be given to discontinuing Alteplase treatment.

    - Anaphylactic reactions require discontinuation of the infusion immediately and initiation of appropriate treatment.

    - Monitor for injection site haemorrhage (puncture site haemorrhage, catheter site haematoma and catheter site haemorrhage). If severe, discontinuation of Alteplase should be considered.

2.2.2 Dosing regimen of Alteplase for the treatment of massive PE

Weight	IV bolus dose (over 1-2 minutes)	Subsequent IV infusion dose (over 2 hours)
40kg	10mg	50mg
45kg	10mg	55mg
50kg	10mg	65mg
55kg	10mg	70mg
60kg	10mg	80mg
≥65kg	10mg	90mg

2.2.3 Thrombolysis in cardiac arrest or imminent cardiac arrest secondary to massive PE

- Thrombolysis is the first line treatment for a massive PE and may be instituted on clinical grounds alone if cardiac arrest is imminent.

- In cardiac arrest occurs or is imminent (in confirmed or suspected acute PE) give Alteplase 50mg IV injection (the on-call pharmacist can be fast bleeped to assist with this).

- Reconstitute each 50mg vial of Alteplase with 25ml of water for injection (provided in the drug pack) using a syringe. The mixture should only be agitated gently until complete dissolution. Avoid vigorous shaking to prevent foam agitation.

- In cardiac arrest, consider continuing CPR for 60 - 90 minutes after thrombolysis.

2.2.4 IV Heparin post Thrombolysis

- Following thrombolysis, the patient's APTT should be checked immediately.

- If the APTT ratio is <2, commence IV unfractionated heparin (UFH) infusion (no loading bolus dose should be given; start at 18units/kg/hr using the patient's actual body weight). However, avoid starting an UFH infusion within 8 hours of administration of a therapeutic dose of LMWH.

- If the APTT ratio is >2, wait and repeat after 4 hours. Continue to repeat 4 hourly until APTT ratio is <2, then start the IV UFH infusion

- Check APTT 6 hours after starting IV heparin, and aim for ratio of 1.5-2.5.

2.2.5 Thrombolysis consent

- Written consent for thrombolysis is not required, however, verbal consent must be obtained where possible, prior to the administration of any thrombolytic drugs, and documented in the case notes. Benefits and risks should be discussed including:

    - Intracerebral bleed – incidence around 1-2 in 100.

    - Gastrointestinal bleed - incidence of more than 1 in 100, but less than 1 in 10.

    - Bleeding from intravascular lines and attempted venepuncture sites (common).

2.2.6 Place of care

- Thrombolysis may be carried out in the emergency scenario whenever the patient presents. However, if time / clinical stability allows, it is preferable for the patient to be transferred to respiratory HDU, medical HDU or ICU prior to thrombolysis.

2.2.7 Additional management

- Oxygen therapy
    - Oxygen therapy should be administered to target saturations of 94-98% unless a lower target is required in patients at risk of hypercapnic respiratory failure. Severe hypoxaemia or haemodynamic collapse should prompt consideration of intubation and mechanical ventilation and such patients should be discussed promptly with ICU.

- IV access and fluid resuscitation
    - A fluid bolus of 250-500ml 0.9% ‘normal’ saline may be appropriate in a patient with hypotension and PE in whom the hypotension is thought possible to be due to a non-PE cause.

    - Further administration of IV fluids should be carefully titrated to the patient’s volume status. Aggressive fluid resuscitation is not beneficial, and may in some cases be harmful, in patients with RV dysfunction / failure.

- Vasopressors
    - Persistent hypotension despite adequate fluid resuscitation either before or after thrombolysis (if given) can occasionally require vasopressor support but this should be discussed directly with ICU.

- Anticoagulation
    - Patients are frequently started on UFH after thrombolysis, but ongoing anticoagulation will usually be with LMWH, with a switch to an oral agent (DOAC or VKA) when haemodynamically stable and bleeding risk acceptable (see section 3).

2.3 INTERMEDIATE risk PE (aka 'submassive' pulmonary embolism)

- Patients with intermediate risk PE are haemodynamically stable but have evidence of RV dysfunction;
    - Raised Troponin T, BNP or NT-pro BNP (not due to a primary cardiac cause such as myocardial infarction)
    - RV dysfunction on echocardiogram

- Patients in this group can vary substantially from the clinically stable patient with PE and a mildly raised troponin T, to the patient with a large PE, borderline hypotension (e.g. systolic BP of 105), raised TnT/BNP and high oxygen requirement. Clinical judgment must be exercised when deciding optimal treatment.

- Current evidence does not support thrombolysis for patients intermediate risk PE as it does not appear to influence either short term mortality, or reduce the risk of longer term complications such as chronic thromboembolic pulmonary hypertension (CTEPH).

- Some 'intermediate-high risk' patients with PE may be considered for thrombolysis on the basis of perceived risk of clinical deterioration. Markers such as; rising oxygen requirement, rising lactate / acidosis, large clot burden (e.g. saddle embolism) or evidence of peripheral hypoperfusion may guide the clinician.

- All decisions regarding thrombolysis for submassive PE should be discussed with a senior clinician - usually the ED Consultant or Respiratory Consultant on call.

- ‘Intermediate-high risk' PE patients should be admitted to respiratory HDU for haemodynamic monitoring. Other intermediate risk PE patients will require admission to a respiratory ward for at least 48 hours observation (the highest risk period for PE mortality) to monitor for clinical deterioration.

- Consider managing intermediate-high risk PE patients on ultra-fractionated heparin in case of clinical deterioration necessitating thrombolysis. Lower risk patients can be started on LMWH, or directly on to a DOAC without LMWH bridging given the speed of onset of action of most DOACs.

2.4 LOW risk PE (including outpatient management of PE)

- Low risk PE patients are normotensive with no adverse features for poor outcomes and absence of RV dysfunction on biomarkers or RV imaging (CT or echo). Some will be suitable for outpatient management.

2.4.1 Outpatient management of PE

- **Appendix 3 summarises the pathway for risk assessment of patients with suspected PE presenting via Ambulatory Care or MAU (page 29).**

- Studies suggest that up to 37-44% of patients with suspected / diagnosed PE can be safely managed in the outpatient setting.

- Patients with suspected / confirmed PE should be risk stratified and assessed for suitability for outpatient management with results of clinical risk scores documented in the patient notes.

- Patients with sPESI class 0 or PESI class I or II are considered low risk and may be appropriate for outpatient management.

sPESI criteria	**Score**
Age >80 years	1
Cancer*	1
Chronic cardiopulmonary disease	1
Heart rate >110 bpm	1
Systolic BP <100 mmHg	1
Arterial Oxygen saturations <90%**	1

Score = 0 equates to low risk cohort (low 30 day mortality)
Score = 1 or more equates to high risk cohort
*Defined as active cancer (diagnosed within last 12 months or undergoing treatment)
**With or without the administration of supplemental oxygen

- Further exclusion criteria (Hestia criteria) should be applied before deciding upon an outpatient management strategy.Hestia criteria can be applied to patients with active cancer for suitability for outpatient management.

- HAS-BLED score[9] can be used to assess bleeding risk in patients deemed suitable for outpatient management for PE.

- Measurement of RV:LV ratio on CT or RV function on echo is not obligatory for identification of low risk patients for OP management.

- In patients where RV dilatation has been identified on echo/CT, check either troponin or BNP – if negative biomarkers these patients can be considered low risk. If biomarkers are elevated patients should be admitted for observation.

Hestia criteria
Haemodynamic instability (HR >110 bpm, systolic BP <100 mmHg, requirement for inotropes or critical care, requirement for thrombolysis or embolectomy
Oxygen required to maintain saturations > 90%
Active bleeding or risk of major bleeding (e.g. Recent gastrointestinal bleeding or surgery, previous intracranial bleeding, uncontrolled hypertension)
On full dose anticoagulation at the time of the PE
Severe pain (e.g. requiring opiates)
Other medical comorbidities requiring hospital admission
Chronic kidney disease (stage 4 or 5) or severe liver failure
Heparin-induced thrombocytopenia within the last year where there is no alternative to repeating heparin treatment
Social reasons (e.g. Inability to return home, inadequate home care, lack of telephone communication, concerns over compliance etc.)

If no Hestia criteria apply then patient may be suitable for outpatient management

- Patients considered suitable for discharge should have senior review by Consultant or senior trainee (ST3+ in Medicine or ST4+ in ED) prior to final discharge decision on an outpatient pathway.

- Patients discharged on an OP pathway should have verbal and written information on the following;
    - Signs and symptoms of PE recurrence
    - Signs and symptoms of bleeding and other relevant complications.
    - Information about the anticoagulant therapy they are prescribed.

- Patients should be referred to the PE clinic for follow-up and the Anticoagulation service (dhft.anticoagulationclin@nhs.net). Most routine PE patients do not require referral to Haematology. unless com

- **Please refer to BTS guideline for the Initial Outpatient Management of Pulmonary Embolism for additional information[1].**

- Low risk PE patients not suitable for outpatient management are admitted to the respiratory ward with the aim to discharge them within 24-48 hours if other barriers (such as social care needs) are not encountered.

2.5 Other scenarios

2.5.1 Incidental Pulmonary Embolism

- Incidental PE is a frequent finding on CT, for example identified in 1.1% of coronary CT scans and 3.6% of CT scans in Oncology patients.

- Observational studies (mainly in cancer patients with incidental PE) suggest the natural history of incidental PE is similar to that of symptomatic PE with regard to risk of recurrence and mortality.

- In patients at high risk of bleeding, in whom anticoagulation is relatively contraindicated, bilateral leg ultrasound to look for DVT may be a helpful investigation. The presence of DVT in addition to incidental PE increases the

risk of recurrent VTE if the patient is not anticoagulated.

- Choice of anticoagulation, duration of anticoagulation and whether a patient is suitable for outpatient therapy should be decided as for any patient with symptomatic PE.

2.5.2 Subsegmental Pulmonary Embolism

- Choice of anticoagulation, duration of anticoagulation and whether a patient is suitable for outpatient therapy should be decided as for any patient with symptomatic PE for reasons similar those discussed above for incidental PE.

2.5.3 Cancer associated thrombosis (CAT)

- 5-10% of all cancer patients will have their clinical course complicated by VTE.

- Active cancer is defined as;
    - Any diagnosed cancer (except for basal cell carcinoma or squamous cell carcinoma of the skin) within the previous 6 month period,
    - Any treatment for cancer within the previous 6 month period,
    - Recurrent or metastatic cancer.

- Until recently, first line treatment for most patients with CAT was LWMH but following recent studies, DOACs are being increasingly used in selected patients with cancer and PE. DOACs can also be offered to patients intolerant of LMWH (either due to side effects or not able / willing to have subcutaneous administration).

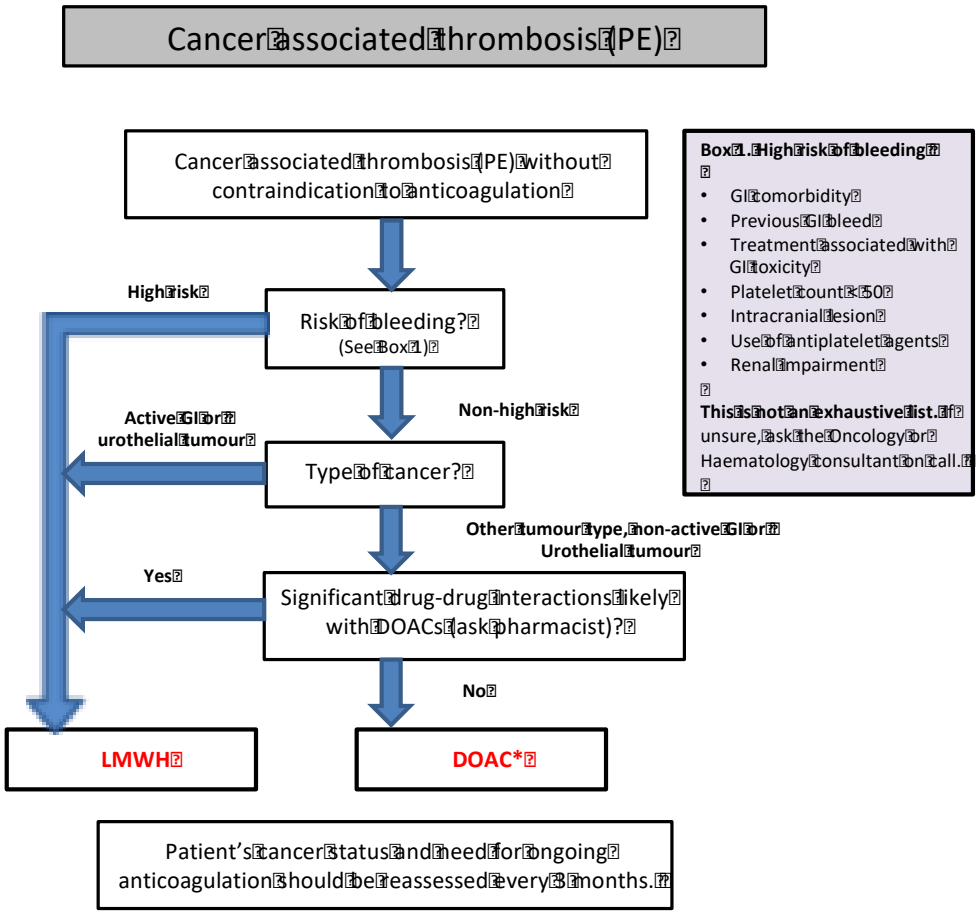
- DOACs appear to be as effective as LMWH in preventing VTE recurrence, with a similar rate of major bleeding, but a higher rate of clinically relevant non-major bleeding, particularly in patients with intraluminal gastrointestinal tumours or active urothelial tumours.

- Deciding whether DOACs are suitable for patient with CAT, and if so, which agent, requires assessment of a variety of factors including;
    - Type of cancer
        - Avoid in active GI cancer and some urothelial cancers
    - Risk of bleeding (HIGH risk includes);
        - Previous GI bleed or recent life threatening GI bleed
        - GI comorbidity
        - Treatment associated with GI toxicity
        - Thrombocytopenia (platelet count <50)
        - Use of antiplatelet therapy
        - Renal impairment
        - Intracranial lesion
    - Body weight (weight >120 Kg, BMI >40)
    - Other relevant comorbidities
    - Significant GI surgery or risk of malabsorption
    - Potential drug interactions (e.g. Chemotherapy)
    - Patient preference

- If uncertainty exists as to whether a patient with cancer is suitable for DOAC therapy they should be discussed with Oncology / Haematology.

- Patients with recurrent CAT already on anticoagulation despite good adherence should always be discussed with Oncology / Haematology to provide a specialist anticoagulation plan.

- **See below for a decision aid to assess use of DOACs in patients with PE and malignancy.**



*DOACs currently used in this Trust for cancer associated pulmonary embolus are Rivaroxaban and Apixaban. Other DOACs may be appropriate but should be discussed with Oncology / Haematology before use.

Other factors which may influence prescriptions of a DOAC include;

- Patient preference
- Body weight (particularly if BMI >40 or weight >120Kg)
- Renal impairment
- Significant GI surgery or malabsorption
- Pre-existing conditions and co-medication

3. Anticoagulation for Pulmonary Embolism

3.1 Direct oral anticoagulants (DOACs)

- Several DOACs are licensed for treatment of VTE; Apixaban and Rivaroxaban are commonly used for VTE treatment in this trust; both drugs have a rapid onset of action with peak effect by 2-4 hours after administration.

- Apixaban – Initial dose of 10mg twice daily orally for 7 days then 5mg twice daily thereafter for continuation phase.

- Rivaroxaban – initial treatment phase – 15mg twice daily orally for 21 days, 20mg once daily thereafter for continuation phase. Take with food to increase bioavailability.

- Edoxaban/Dabigatran required a 5 day heparin lead-in (LMWH) prior to starting the oral anticoagulant.

- DOACs can be used as first line treatment (both for suspected and confirmed PE) in a variety of settings including A&E, medical SDEC, inpatient wards and in patients deemed suitable for outpatient management of suspected/confirmed PE.

- DOACs can be used in certain patients with malignancy and may be an appropriate first line choice (see section on cancer-associated thrombosis).

- When deciding between different DOACs consider;
    - If patient convenience is important: Rivaroxaban or Edoxaban are once daily dosing in the maintenance phase whilst Apixaban is a twice daily dosing schedule.
    - If patient has renal impairment: Edoxaban can be used if CrCl > 30ml/min, Rivaroxaban and Apixaban can be used if CrCl > 15ml/min.
    - If patient is high risk for bleeding (e.g. previous GI bleed) and DOAC is necessary: Apixaban or Edoxaban.

3.2 Low molecular weight heparin (LMWH)

- Commence patient on Enoxaparin 1.5mg per kg of body weight subcutaneously once daily on suspicion of PE.

- An alternative dose of Enoxaparin at 1mg / Kg subcutaneously twice daily *may* be appropriate, particularly if;
    - Obesity (BMI > 40) or weight > 150kg
    - Active malignancy
    - Extensive clot burden on CTPA or V/Q scan

- LMWH is discontinued when;
    - Diagnosis of PE is excluded (consider whether prophylactic dose LMWH may still be required).
    - Following 5 days treatment with LMWH and patient has commenced

Warfarin with **two** INR values >2.

- Patient has been started on appropriate direct oral anticoagulant – for Rivaroxaban or Apixaban (the most commonly used DOACs in this Trust) this is following the first dose of the DOAC.

3.3 Unfractionated heparin (UFH)

- Certain patients may be more appropriately managed initially with unfractionated heparin (UFH) with dose adjustments based on the APTT ratio;
    - Severe renal impairment (eGFR < 30)
    - Submassive PE, at risk of bleeding, in whom thrombolysis may be considered if haemodynamic collapse – these patients must be managed in medical or respiratory HDU, or ICU.
    - Any patient with PE, at risk of bleeding in whom anticoagulation may need to be reversed in a timely fashion (e.g. patients with concurrent GI bleeding).

3.4 Warfarin

- Warfarin remains an option particularly in patients with poor renal function (CrCl < 15ml/min), concerns regarding compliance or drug absorption, extremes of body weight.

- If starting inpatients on warfarin please refer to relevant trust guideline:

- If starting outpatients on warfarin use an evidence based protocol such as the Fennerty protocol (for rapid warfarinisation in VTE).
    - British Medical Journal, 1984; 288, 1268-70

- Please refer all patients discharged on warfarin to the anticoagulation service by choosing the ‘warfarin – discharge only’ option on the discharge summary. The anticoagulation team can be contacted on x89414 or via email on dhft.anticoagulationclinic@nhs.net

- Provide a ‘Yellow book’ and counseling re: interactions and side effects of warfarin.

3.5 Summary of anticoagulation options

Agent	Consider	Avoid	Dose
DOAC	• No GI malignancy • Low risk of major bleeding • Ease of treatment for patient is a priority • No strong drug-drug interactions*	• Active GI malignancy (oesphageal/gastric) • History of GI bleeding • Extremes of weight (<50kg or > 150kg) • Renal failure (depending on eGFR)	• RIVAROXABAN - 15mg bd for 3 weeks then 20mg od thereafter. • VTE prophylaxis dose (after 6 months) 10mg od. • APIXABAN – 10mg bd for 7 days then 5mg bd thereafter. • VTE prophylaxis dose (after 6 months) 2.5mg bd.
LMWH	• Difficulty with oral route • Concerns re: GI absorption • Drug-drug interactions with DOAC or VKA • Motivated patient • Known increased bleeding risk • Recurrent cancer-associated VTE whilst on anticoagulation	• Patient aversion to injectable therapy • Renal failure (depending on eGFR) • Extremes of weight (<50kg or > 150kg)	• ENOXAPARIN – 1.5 mg/kg OD (max 150mg) or 1mg/kg BD
VKA	• Close anticoagulant monitoring needed • Concerns re: absorption or metabolism • Advanced chronic kidney disease • Extremes of weight <50kg or >150kg	• Patent unable to engage with anticoagulation monitoring service	• WARFARIN – as per INR • Follow loading protocol such as Fennerty.

*****Discuss with pharmacy if concerns about potential drug interactions or check online at https://about.medicinescomplete.com/publication/stockleys-drug-interactions/

4. Discharge planning and follow-up

4.1 Early discharge cohort

- Some PE patients initially identified as intermediate risk and admitted for treatment may be suitable for early discharge. This decision is based on clinical criteria and by recalculating the PESI score (not the sPESI score) at 48 hours (the so called PESI-48 criteria)[6].

4.2 Follow-up

- All PE patients commencing anticoagulation for VTE should be referred to the anticoagulation team who will arrange a telephone follow-up 7 days after discharge from hospital. The anticoagulation team can be contacted on x89414 or via email on dhft.anticoagulationclinic@nhs.net.

- All PE patients - with either provoked or unprovoked PE - should be referred to the PE clinic.

- Patients with cancer-associated thrombosis who are known to Oncology may be

more appropriately followed up in the Oncology clinic.

- Do not routinely request an echocardiogram post-discharge for all patients with PE.

- Do not routinely request thrombophilia screening for all patients diagnosed with PE.

4.3 Length of anticoagulation

- Length of anticoagulation depends on variety of clinical factors including;
    - Nature of the PE (provoked vs unprovoked) and any ongoing risk factors
    - Bleeding risks associated with prolonged anticoagulation.
    - Patient preference

- Treatment duration decisions should usually be made by a clinician with a specialist interest in managing VTE anticoagulation (such as Respiratory medicine, Haematology or Oncology).

- Several validated risk scores[7,8] exist to guide decision-making regarding length of anticoagulation in unprovoked VTE but should be applied to each patient recognising the clinical context.

- Suggested duration of treatment by category of PE;

Provoked PE with temporary risk factor	6 weeks to 3 months
First unprovoked PE	3 months minimum Consider long term anticoagulation if high risk of recurrence
Provoked PE with ongoing risk factor Previous PE or DVT	Long term anticoagulation
Incidental PE	3 months minimum
Subsegmental PE	Initial 3 month treatment duration followed by consideration of long term treatment if risk of recurrence is high.
Cancer-associated thrombosis (CAT)	6 months minimum Consider long term anticoagulation if persistent / metastatic malignancy or ongoing treatment with VTE risk (e.g. chemotherapy)

4.4 Patient information

- On discharge all patients should be provided with the Trust patient leaflet entitled “Pulmonary embolism”. Printed copies are available on MAU / Ambulatory Care and on all Respiratory wards. The information is also available via the Trust website.

- All patients should be provided with a medication leaflet and Patient Alert Card specific to the anticoagulant drug they are taking.

- Patients should be informed of potential side effects of anticoagulant medication and the symptoms of recurrent PE. They should contact their GP or attend ED if they develop bleeding or symptoms suggestive of recurrent PE.

- Patients discharged from Medical SDEC should be provided with information on opening hours and contact details upon discharge.

5. References

1) Howard L, Barden S, Condliffe R et al. British Thoracic Society Guideline for the initial outpatient management of pulmonary embolism (PE). Thorax (2018); 73 (Suppl 2):ii1-ii29.

2) National Institute for Health and Care Excellence (2020). Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. https://www.nice.org.uk/guidance/ng158

3) Trust guideline on Acute management of Venous Thromboembolism in Pregnancy and the Puerperium. ACUTE MANAGEMENT OF VENOUS THROMBOEMBOLISM IN PREGNANCY AND THE PUERPERIUM (koha-ptfs.co.uk)

4) Trust guideline on Prevention of Contrast Induced Acute Kidney Injury (AKI). opac-retrieve-file.pl (koha-ptfs.co.uk):

5) Kline JA, et al. Prospective multicenter evaluation of the pulmonary embolism rule-out criteria. J Thromb Haemost 2008; 6: 772–80.

6) van der Hulle T, Cheung WY, Kooij S, et al. Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study. Lancet 2017;390:289-297.

7) The National Confidential Enquiry into Patient Outcome and Death. Know the Score. 2019. London https://www.ncepod.org.uk/2019pe/PE_Full%20report.pdf

6) Moores L, Zamarro C, Gomez V et al. Changes in PESI score predict mortality in intermediate-risk patients with acute pulmonary embolism. Eur Resp J. (2013); 41(2):354-9

7) Tosetto A, Iorio A, Marcucci M et al. Predicting disease recurrence in patients with previous unprovoked venous thromboembolism: a proposed prediction score (DASH). J Thromb Haemost (2012); 10(6):1019-25

8) Rodger MA, Kahn SR, Wells PS et al. Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. CMAJ (2008); 179(5):417-26

9) Pisters R, Lane DA, Nieuwlaat R et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest (2010);138(5):1093-100

Documentation Controls

Development of Guideline:	Dr James Donaldson
Consultation With:	Radiology, Oncology, Haematology
Approved By:	Medicine division
Approval Date:	**December 2023**
Review Date:	December 2026
Key Contact:	Dr James Donaldson

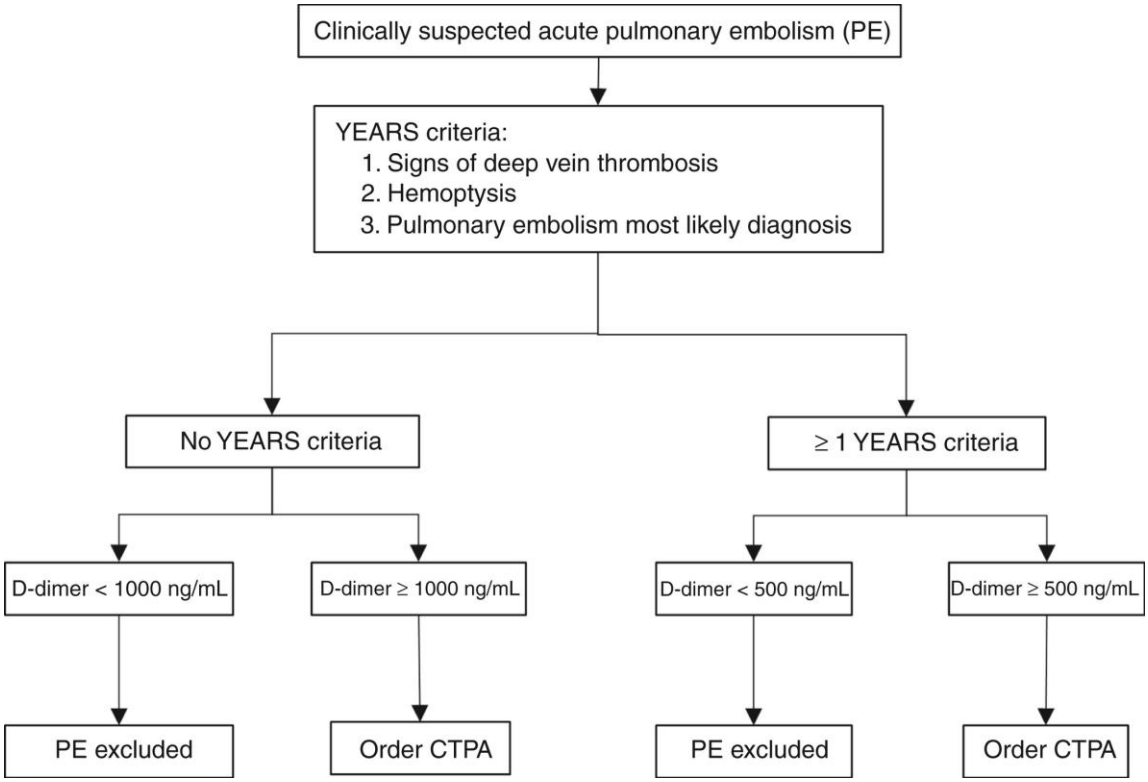
6.1 Appendix 1 - Clinical prediction rules for PE.

A) PERC criteria

PERC criteria	Score
Age ≥50 years	1
Heart rate ≥110 bpm	1
Oxygen saturations on air <95%	1
Unilateral leg swelling	1
Haemoptysis	1
Recent surgery or trauma (within 4 weeks and requiring general anaesthesia)	1
Previous PE or DVT	1
Use of oral contraceptive, HRT or oestrogen-containing hormones	1

If any criteria are positive, the PERC rule CANNOT be used to rule out PE in this patient

B) YEARS algorithm



C) Two-level Wells Score

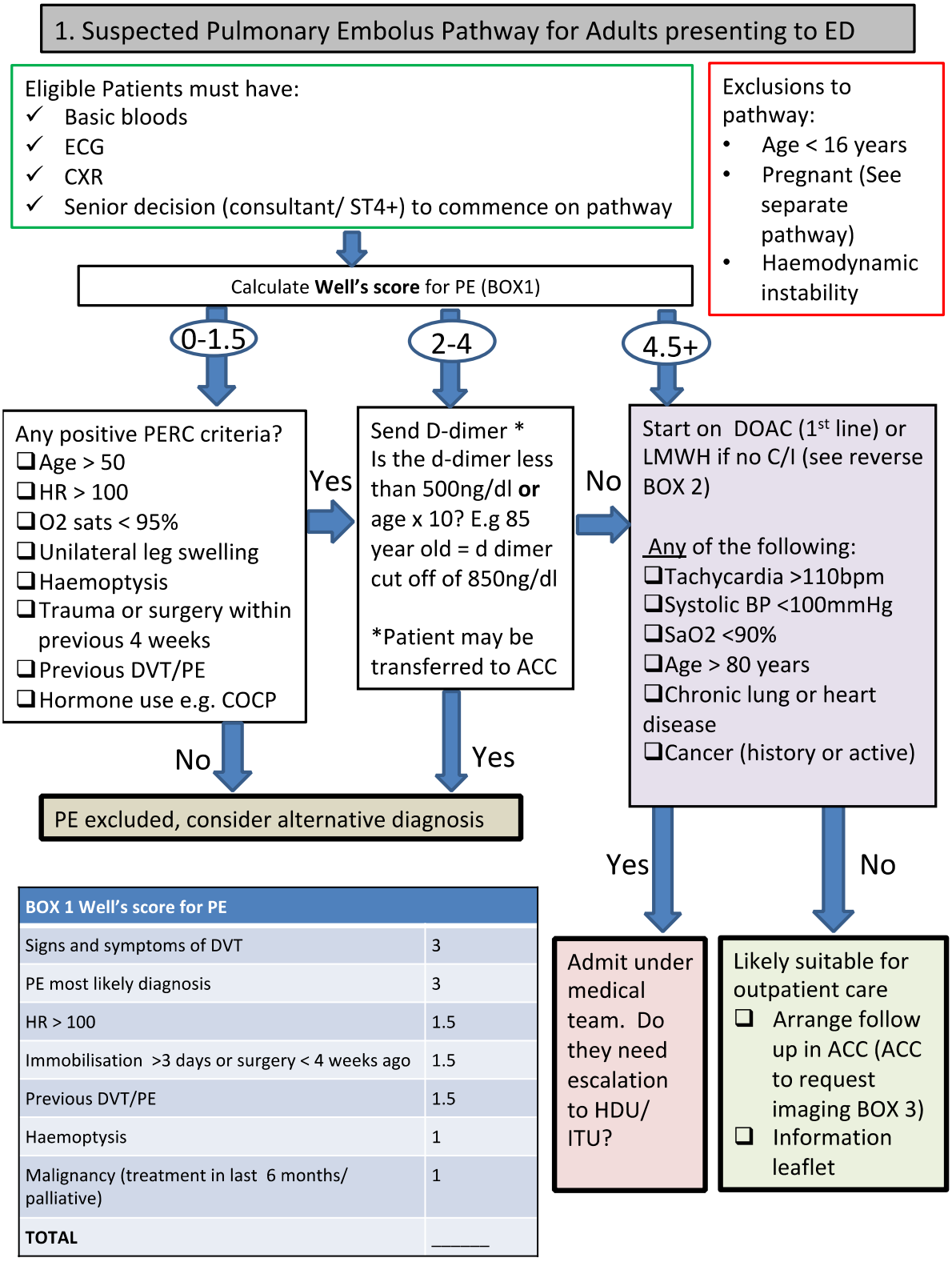
Pulmonary embolism (PE)

Table 2 Two-level PE Wells score[a]

Clinical feature	*Points*
Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	3
An alternative diagnosis is less likely than PE	3
Heart rate > 100 beats per minute	1.5
Immobilisation for more than 3 days or surgery in the previous 4 weeks	1.5
Previous DVT/PE	1.5
Haemoptysis	1
Malignancy (on treatment, treated in the last 6 months, or palliative)	1
Clinical probability simplified score	
PE likely	**More than 4 points**
PE unlikely	**4 points or less**

[a] Adapted with permission from Wells PS et al. (2000) Derivation of a simple clinical model to categorize patients' probability of pulmonary embolism: increasing the model's utility with the SimpliRED D-dimer. Thrombosis and Haemostasis 83: 416–20

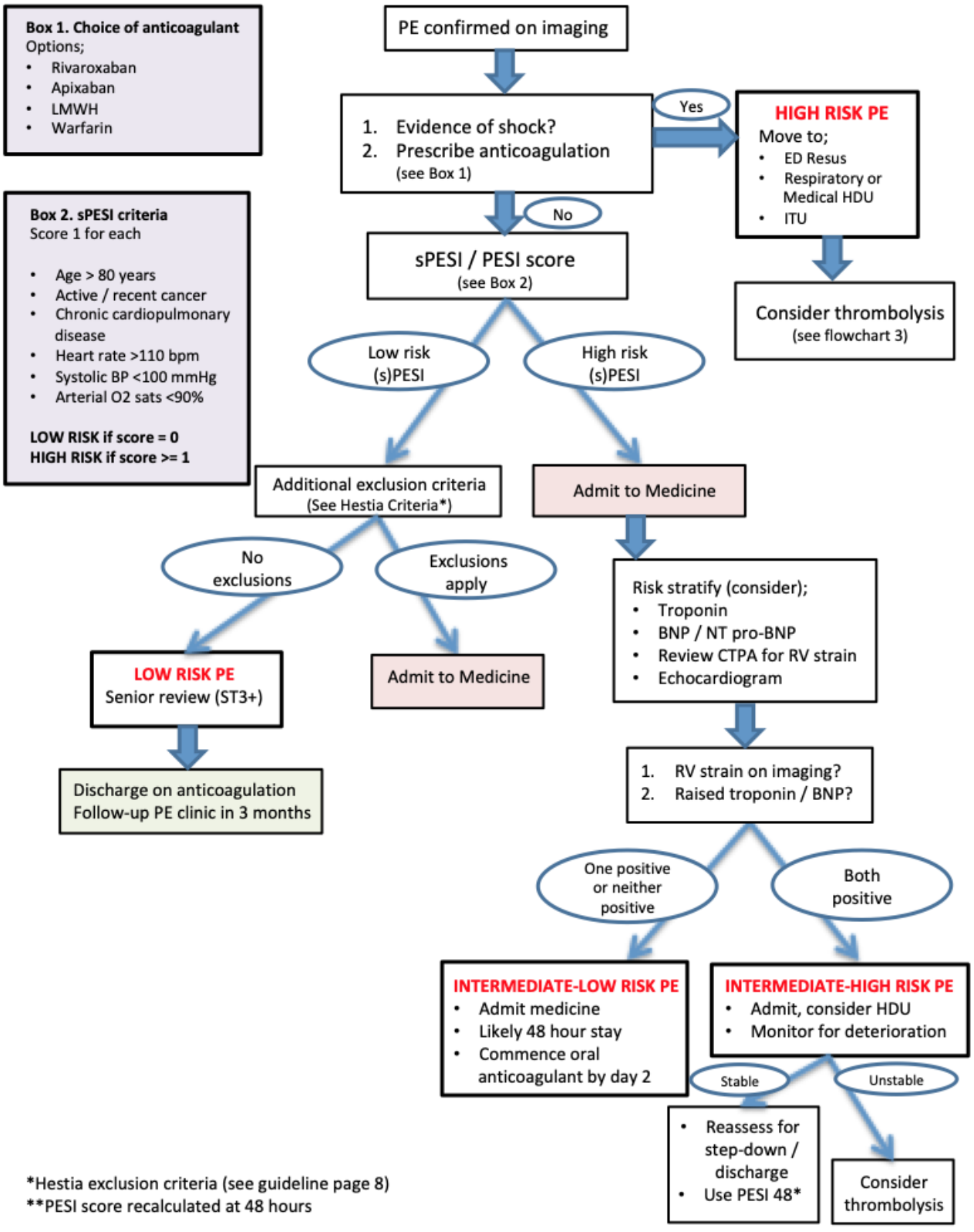
6.2 Appendix 2



BOX 1 Well's score for PE	
Signs and symptoms of DVT	3
PE most likely diagnosis	3
HR > 100	1.5
Immobilisation >3 days or surgery < 4 weeks ago	1.5
Previous DVT/PE	1.5
Haemoptysis	1
Malignancy (treatment in last 6 months/ palliative)	1
TOTAL	_____

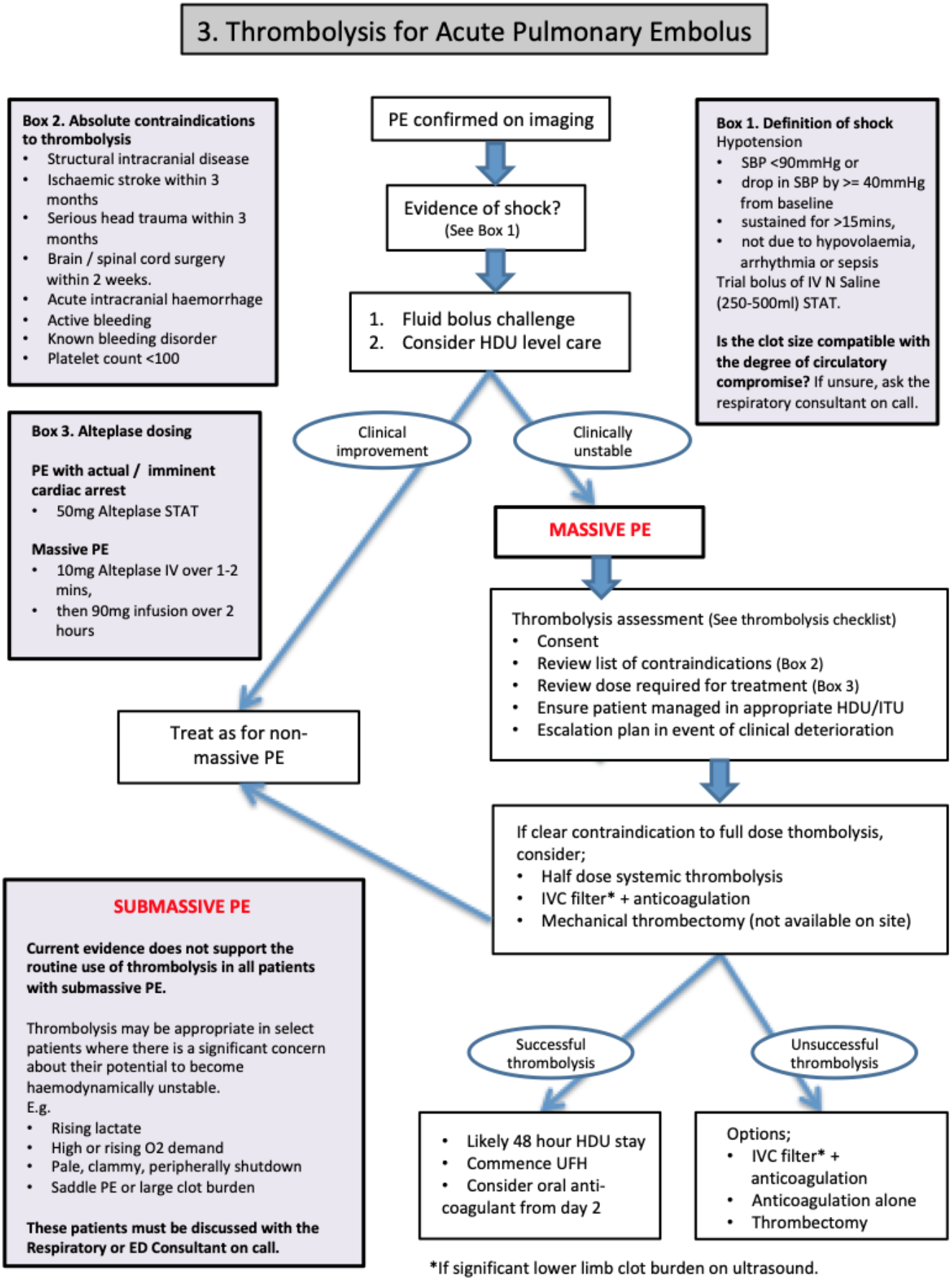
6.3 Appendix 3

2. Management of Acute Pulmonary Embolus



*Hestia exclusion criteria (see guideline page 8)
**PESI score recalculated at 48 hours

6.4 Appendix 4



6.5 Appendix 5. Absolute and Relative Contraindications to Systemic Thrombolysis

Absolute*	Relative†
Structural intracranial disease (CNS neoplasm, AV malformations or aneurysms)	Recent bleeding (< 4 weeks)
Ischemic stroke within 3 months	Recent surgery (within 3 weeks) or invasive procedure of non-compressible vessel
Active bleeding	Ischemic stroke > 3 months previously
Recent brain or spinal surgery (within 2 weeks)	INR >1.7 (discuss with Haematology)
Recent serious head trauma within last 3 months (e.g. fracture or brain injury)	Traumatic cardiopulmonary resuscitation
Known bleeding disorder or coagulopathy	Pericarditis or pericardial effusion
Acute intracranial haemorrhage	Pregnancy or 1 week post-partum
Platelet count <100	Previous intracranial haemorrhage (*the timing, site, cause and treatment of haemorrhage are important factors, and specialist discussion is needed*)
	Acute pancreatitis
	Acute peptic ulceration

*Thrombolysis could cause a life-threatening complication.
†Caution is required. Thrombolysis is acceptable if the benefits outweigh the risks.

If there is uncertainty in any of the above situations, please discuss with the Respiratory or ED consultant on call.

6.6 Appendix 6. Checklist for Patients receiving Thrombolysis

	Tick the box for a positive response		**If unable to tick, comment and explain the reason (s) for this**
1	Patient meets criteria for 'Massive Pulmonary embolism'?	☐	
2	Senior physician (Consultant level) has been involved in Thrombolysis decision-making process?	☐	
3	HDU or ICU bed available for patient requiring Thrombolysis for PE? (*If bed not available, <u>do not delay</u> Thrombolysis if clinically indicated, but perform in adequately monitored area*)	☐	
4	Relative and absolute contraindications have been reviewed? *See 'Systemic Thrombolysis contraindications'*	☐	
5	Written consent obtained (if time allows)? *See 'PE Thrombolysis consent'*	☐	
6	Weight-adjusted Alteplase dose checked and prescribed? *See 'Thrombolysis in Massive PE'*	☐	
7	Post thrombolysis monitoring has been stated and appropriate IV Heparin instruction/regime followed? *See 'IV Heparin Post PE Thrombolysis'*	☐	