Investigation and Management of Pulmonary Embolism

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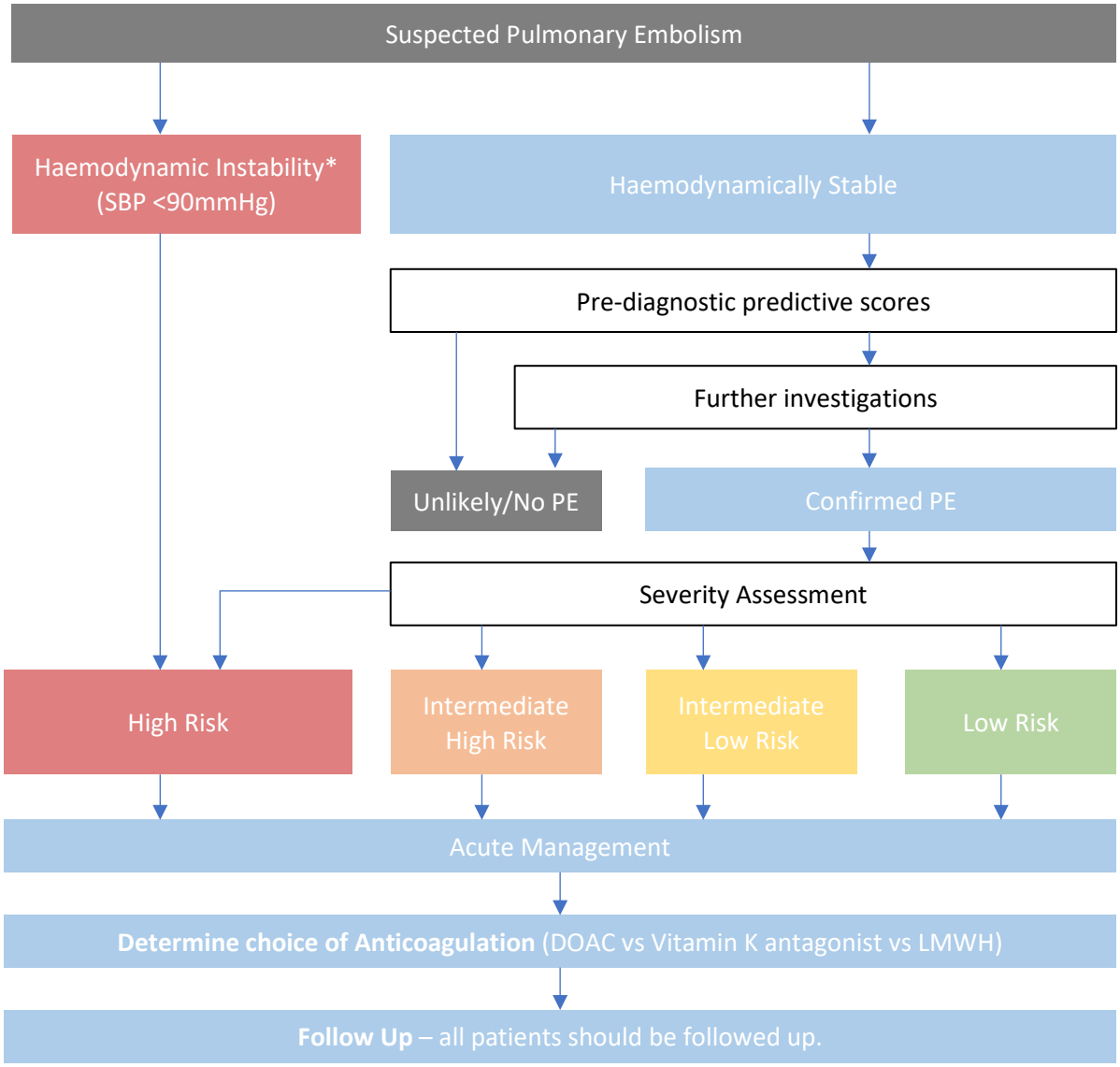
Quick Definitions

	High Risk PE	Haemodynamic instability - sustained hypotension (SBP <90mmHg, for 15 minutes) or requiring inotropic support, that is not related to a cause other than PE (i.e. arrythmia, LV dysfunction, sepsis or hypovolaemia).
	Intermediate-High Risk PE	Haemodynamically stable - but at risk of rapidly deteriorating with evidence of right ventricular dysfunction (on CTPA or TTE) and myocardial injury (i.e. raised troponin).
	Intermediate-Low Risk PE	Haemodynamically stable – lower risk than intermediate high-risk but clinical markers of PE severity and RV dysfunction may still be present.
	Low Risk PE	Haemodynamically stable – no evidence of clinical markers of severity, no RV dysfunction and no myocardial injury.

Introduction

Pulmonary embolism (PE) occurs when emboli, arising from a blood clot in the venous system, obstruct the pulmonary arterial system, leading to respiratory and cardiovascular dysfunction.

- PE should be systematically stratified and managed according to the risk of haemodynamic compromise.
- Patients with suspected PE with haemodynamic compromise should be treated urgently, as for High Risk PE.
- In patients with suspected PE who are haemodynamically stable, pre-diagnostic predictive scores should be used to assess the need for further investigations.
- Patients with confirmed PE should undergo severity assessment to determine the management and bed allocation.
- All patients with PE should have a follow up in a PE clinic
- The following algorithm outlines the general approach to a patient with suspected PE. For details see relevant sections below.



*Haemodynamic instability - sustained hypotension (SBP <90mmHg, for 15 minutes) or requiring inotropic support, that is not related to a cause other than PE (e.g. arrythmia, LV dysfunction, sepsis or hypovolaemia)

Pre-Diagnostic Scores and Diagnosis

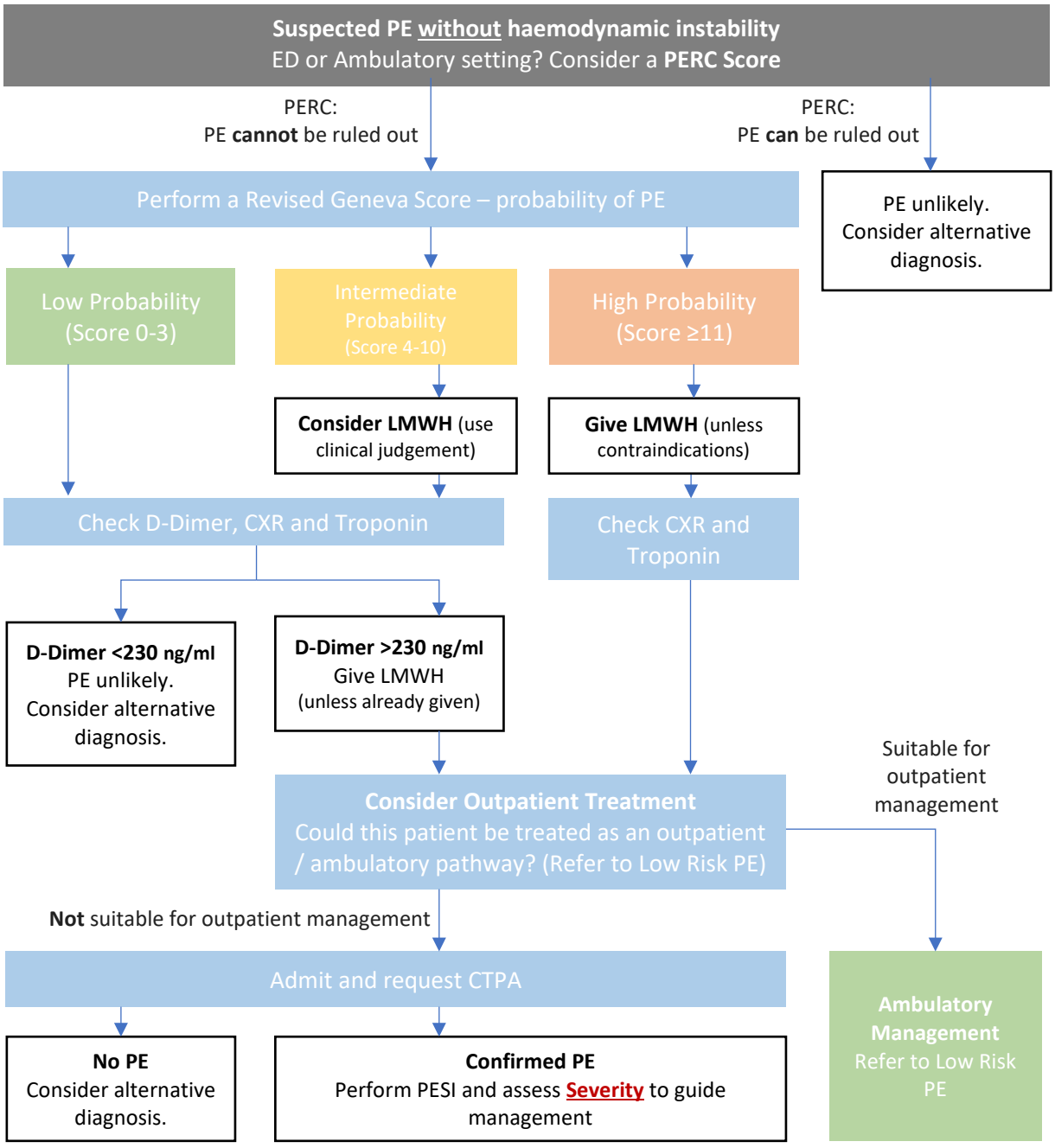
- If a patient has a suspected PE with haemodynamic instability (SBP<90) refer to High Risk PE.
- Patients who are stable should have PE considered based on predictive scores and consideration for further testing.

Signs and Symptoms

- Chest pain (often pleuritic), cyanosis, dyspnoea, haemoptysis, syncope
- Tachycardia, hypotension, raised JVP, hypoxaemia, tachypnoea

Assess Predictive Score

- If the patient is haemodynamically unstable go straight to High Risk PE.
- Consider use of the PERC score for low-risk patients to rule out PE
- Perform a pre-predictive calculation (such as the revised Geneva score or the Wells score) to assess the probability of PE and inform investigations.



PERC Score (Pulmonary Embolism Rule Out Score)
This is used for patients with a low likelihood of PE, who demonstrate low-risk features, and can be used to rule out PE in the Assessment Unit or the Emergency Department.
A score of ≥1 means PE **cannot** be ruled out.

Age ≥ 50	1
Heart Rate ≥ 100	1
Peripheral oxygen saturation ≤95%	1
Unilateral leg swelling	1
Haemoptysis	1
Surgery or trauma ≤4 weeks ago requiring general anaesthetic	1
Previous PE or DVT	1
Hormone Use e.g. oral contraceptive, hormone replacement or oestrogen containing hormones	1

Revised Geneva Score
Assesses the probability of PE in order to inform investigations.

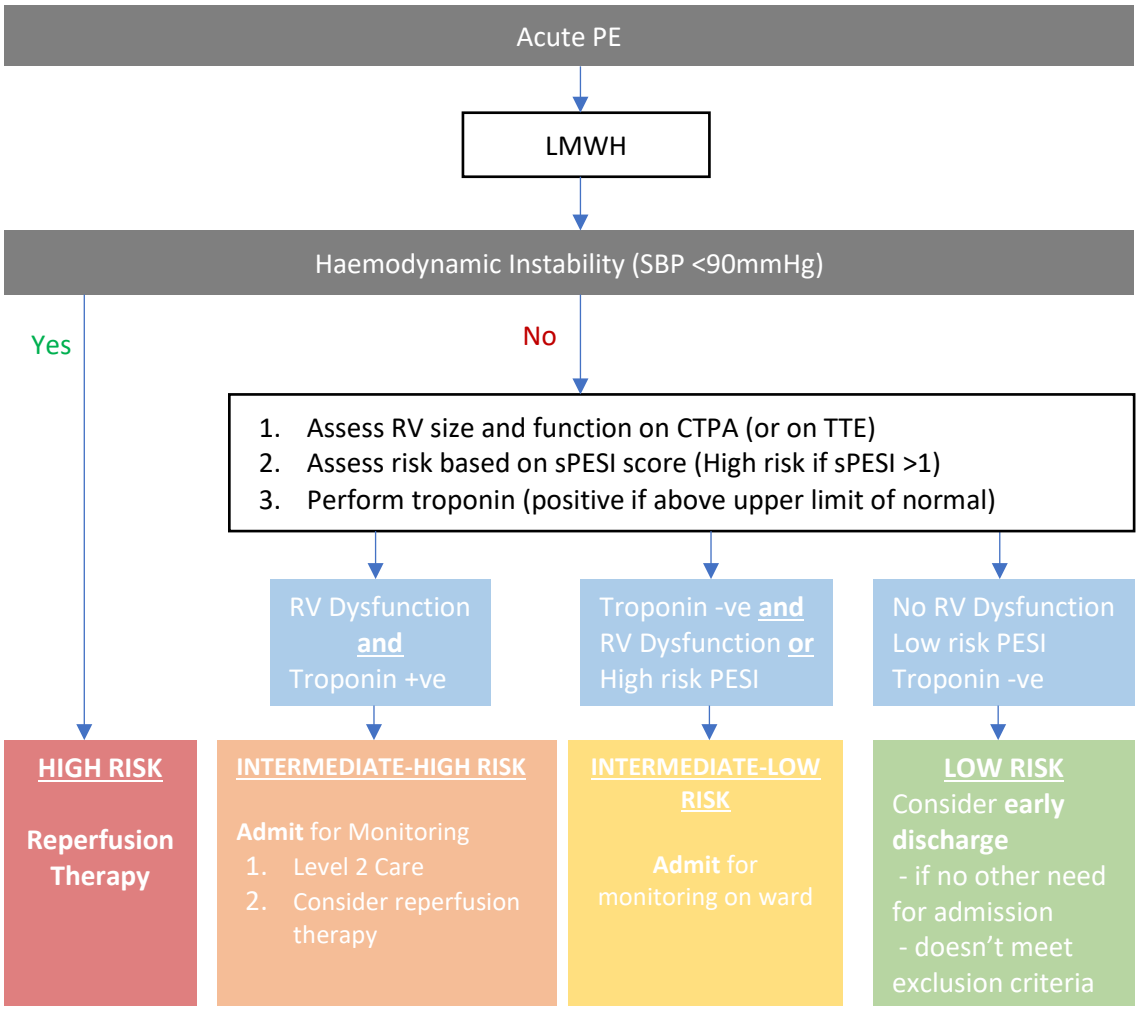
Age ≥ 65 years	1
Previous DVT/PE	3
Recent surgery or lower limb fracture (≤ 1 month)	2
Malignant disease (active or cured ≤ 1 year)	2
Unilateral lower limb pain	3
Haemoptysis	2
Heart rate 74 – 94 bpm	3
Heart rate ≥ 95 bpm	5
Pain on deep venous palpitation of leg and unilateral oedema	4

Score	Probability of PE	Incidence of PE
0-3	Low	~7-9%
4-10	Moderate	~20-30%
≥11	High	>60%

Severity Assessment

All confirmed PE should be stratified and managed according to the severity. This is judged by;

- Haemodynamic instability (shock) - hypotension
- Myocardial damage – troponin biomarkers
- Right ventricular strain – RV size and function on CTPA or TTE
- Risk of early mortality – PESI score



sPESI Score Simplified Pulmonary Embolism Severity Index

Age ≥ 80	1
History of cancer	1
History of cardiorespiratory disease	1
Heart rate ≥110 bpm	1
Systolic BP ≤100 mmHg	1
Peripheral O2 saturations ≤90%	1

Management of High-Risk PE (Massive PE)

- High-risk PE is defined as an acute PE with sustained hypotension (SBP <90mmHg, for 15 minutes) or requiring inotropic support, that is not related to a cause other than PE (e.g. arrythmia, LV dysfunction, sepsis or hypovolaemia).
- Death occurs as increased right ventricle afterload leads to strain placed on the right ventricle, causing a reduction in cardiac output, hypotension and hypoxaemia.

Investigations

- Confirmation by CTPA is preferable and also allows assessment of pulmonary vascular anatomy and RV assessment
- If not possible due to clinical condition (e.g. intubated) urgent bedside TTE should be performed to assess for RV size and dysfunction

Management

- Move to level 2 or level 3 area (resus, HDU, CCU, ITU) for monitoring and treatment
- Give resuscitation care which may include appropriate oxygen therapy, invasive blood pressure monitoring, fluid resuscitation and inotropic support.
- If PE confirmed, or felt highly likely, give **reperfusion therapy**, which in most centres will currently consist of systemic thrombolysis.
- Full-dose Systemic thrombolysis should the first consideration, but if there are concerns of a high bleeding risk, or systemic thrombolysis has been unsuccessful, other modalities should be considered.

Reperfusion Therapy			
Systemic Thrombolysis (Full Dose)	Systemic Thrombolysis (Low Dose)	Catheter-directed Thrombolysis (CTD)	Surgical Embolectomy
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Systemic Thrombolysis (Full Dose)

- Systemic thrombolysis **is** safe to give if LWMH has already been administered.
- Consider contra-indications to thrombolysis;

Absolute*	Relative*
Haemorrhagic stroke (at any time)	TIA in last 6 months
Ischaemic stroke in last 6 months	Pregnancy or within 1-week post-partum
CNS damage or neoplasia	Advanced liver disease
Major trauma/surgery/head injury in last 3 weeks	Infective endocarditis
GI Bleeding within the last month	Active peptic ulcer

*In massive PE, even in the presence of contra-indications, it may be that thrombolysis is still considered and given, due to the high risk of death.

If possible, **consent** that patient for thrombolysis. Relative risks are shown below.

	Thrombolysis + Anticoagulation	Anticoagulation alone
Major Bleeding	~10-15%	~4%
Intracranial Haemorrhage	~2%	~0.2%
Death from all causes	~2%	~4%

Clearly these risks need to be taken in the context of patient's clinical condition. We would strongly advocate systemic thrombolysis if the criteria for High-Risk PE are met.

1. **Alteplase**

- **10mg Alteplase IV over 2 minutes**
- Followed by **90mg Alteplase IV over 2 hours**
- If under 65kg – maximum dose is 1.5mg/kg
- In a peri-arrest, consider a stat dose of 50mg Alteplase IV, followed by 50mg as an IV infusion over 2 hours
- If alteplase is not available, consider other lytics such as Tenecteplase or follow local MI thrombolysis regimen (note these are unlicensed for use in PE).

2. **Unfractionated Heparin (UFH)**

- Upon completion with alteplase, commence UFH*. Only use 1000units/ml concentration.
- If the patient has had treatment with LMWH within 12 hours, do not give a bolus dose.
- If no LWMH within 12 hours, give a **bolus of 5000 units UFH IV over 5 minutes**.
- Followed by **maintenance infusion of UFH** at a rate of 18units/kg/hour
  e.g. usually ~ 1,200units per hour for a 70kg patient.
  If patient is at high risk of bleeding, start at 1000units/hour.
- Check APTT ratio after 6 hours – aiming 1.8-2.8. Adjust as per table below. If an adjustment is made, recheck APTT ratio after 4 hours. If no change, check APTT ratio daily.
- *If there are concerns with UFH, subcutaneous LMWH may be considered.

UFH Dose Adjustment	
APTT Ratio	**UFH Infusion Rate Change**
>4	Stop for 60 minutes and recheck APTT ratio, before recommencing at a rate reduced by 300–500units/hour
3.5–4	Stop for 60 minutes and reduce heparin by 200units/hour
2.9–3.4	Stop for 30 minutes and reduce heparin by 100units/hour
1.8–2.8	TARGET - No change
1.2–1.7	Increase heparin by 200units/hour
<1.2	Increase heparin by 400units/hour and consider further bolus of 5,000units heparin
- Check APTT ratio every 4 hours after any adjustment in infusion rate. - Patients rarely require rates >1.6-2ml/hour. If target APTT ratio is not achieved at this rate, monitor anti-Xa levels (target 0.35-0.7units/ml). - Routine platelet monitoring for HIT is not required unless <3 months from recent surgery.	

Systemic Thrombolysis (Low Dose)

Low Dose Systemic Thrombolysis should be considered when;

- High Risk PE or Intermediate-High Risk PE – where it is felt the bleeding risk outweighs the benefit of full dose systemic thrombolysis

It is administered by;

1. **Alteplase 10mg IV bolus over 2 minutes**,
2. Followed by **40mg Alteplase IV infusion over 1 hour**
3. Commence UFH as for High Risk PE. Aim for the same APTT target of 1.8-2.8

Catheter Directed Thrombolysis (CDT)

CDT should be considered when;

- Systemic thrombolysis has been unsuccessful
- High Risk and Intermediate-High Risk PE – where it is felt the bleeding risk outweighs the benefit of either full-dose or low-dose systemic thrombolysis

CDT uses a lower dose of thrombolysis and has a safer bleeding risk profile than systemic thrombolysis. However, it takes time to set-up and may not be available immediately.
Direct clot retrieval is not currently available, but may become available in the future.

This technique is organised through contacting Interventional Radiology. A pulmonary artery catheter is placed into the right and left Pulmonary artery and alteplase is infused at 10mg/24 hrs into each. If CDT is felt to be the most suitable therapy, but is not available at your site, site transfer should be considered.

Surgical Embolectomy

Surgical embolectomy should be considered when;

- Systemic thrombolysis has been unsuccessful
- High Risk and Intermediate-High Risk PE – where it is felt the bleeding risk outweighs the benefit of either full-dose or low-dose systemic thrombolysis
- Transient clot in the RA, RV or traversing a PFO to reduce the risk of rapid deterioration or stroke (in the case of a PFO).

Surgical embolectomy requires a careful MDT approach including ITU, anaesthetics, cardiothoracic surgery and haematology. Recent thrombolysis is not a contra-indication to potential surgery.

Management of Intermediate-risk PE

Intermediate-risk PE patients may present with significant symptoms and/or large volume clot on CTPA whilst not meeting high risk criteria. These patients may have a positive troponin (indicating myocardial damage), a high risk sPESI or evidence of RV dysfunction on imaging. Intermediate-risk patients have a higher mortality than low-risk patients and can deteriorate rapidly, warranting consideration for level 2 monitoring and admission for observation.

Management

- If hypotensive (SBP <90mmHg) refer to the High-risk PE guideline

Intermediate-High Risk

Patients with Intermediate-High Risk PE are at risk of rapidly deteriorating, most often within 48 hours of admission. Therefore;

- Monitor in a level 2 bed (e.g. HDU, CCU or an acute care environment with cardiac monitoring and adequate nursing provision)
- Monitor as an inpatient for a minimum of 48 hours
- Treat with LMWH for a longer period (i.e. 2-3 days) before converting to DOAC

- If at presentation patients appear critically unwell (e.g. marked hypoxaemia, high lactate, signs of right heart failure) but not meeting criteria for High Risk PE, **reperfusion therapy** should still be considered.
- If clinically deteriorating (e.g. progressive hypoxaemia, rising heart rate, high or rising lactate, clinical features of circulatory compromise e.g. cold, clammy, cyanosis), consider **reperfusion therapy** in any modality.
  - ➔ *See the details on these treatment options under High Risk PE*
- Whilst all modalities should be considered and be appropriate to the patient, low-dose thrombolysis perhaps provides the lowest chance of dying from PE whilst simultaneously reducing the bleeding risk.

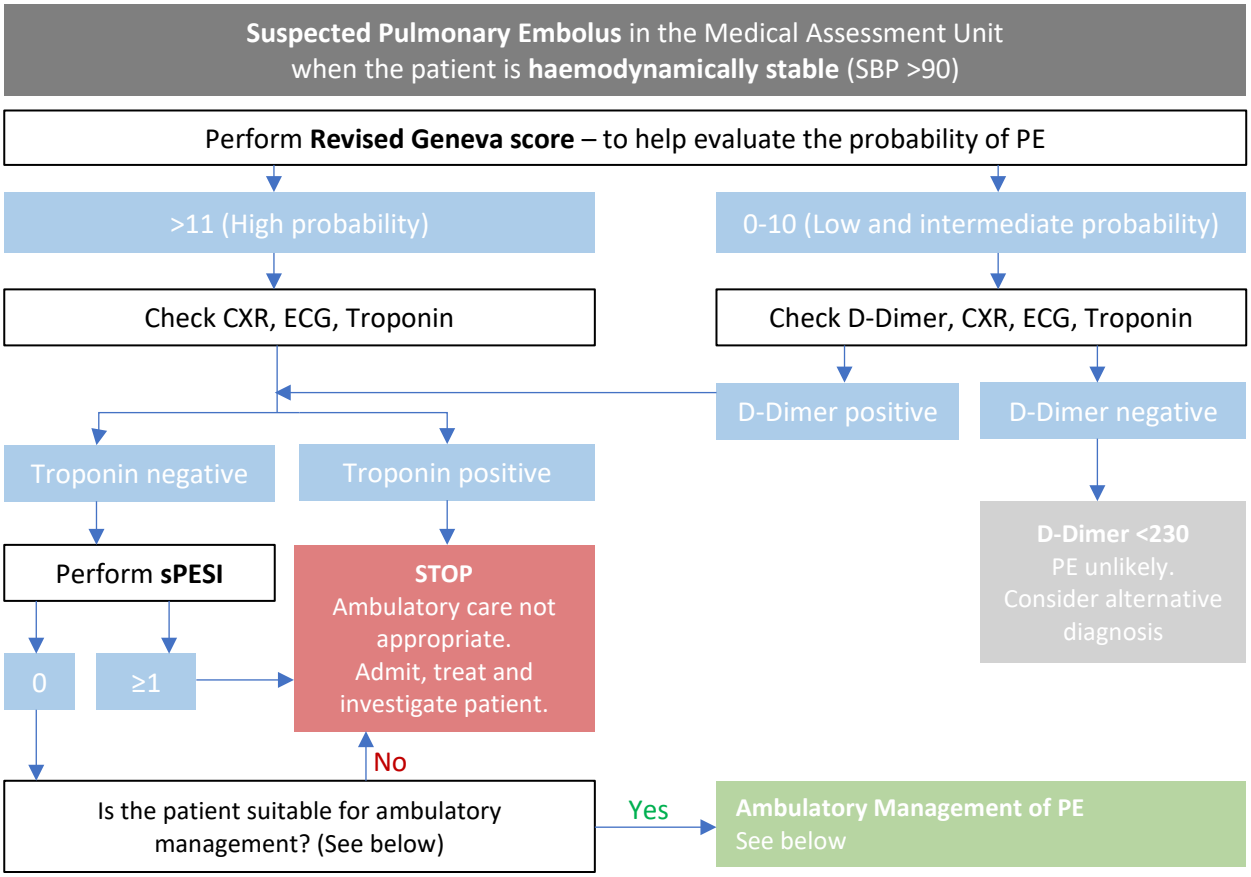
Intermediate Low-Risk

These patients should be monitored on a ward.

- Once PE is confirmed on CTPA, LMWH can be stopped and a DOAC commenced for acute and ongoing treatment (see Anticoagulation section).
- Patients should be monitored as an inpatient for a minimum of 24 hours, yet discharge within 48 hours of presentation should be guided by senior clinical judgement.

Management of Low-Risk PE

- Patients with low risk PE should be assessed for early discharge.
- Use the below flowchart to assess suitability for outpatient management.
- Further guidelines for ambulatory care management of patients with suspected PE exist on the GGC Intranet and on the QEUH Ambulatory care pathways.



Suitable for Early Discharge/Ambulatory Care

- No suspicion of PE whilst already therapeutically anticoagulated
- No severe chest pain
- No significant co-morbidity that may complicate acute PE and/or it's treatment
  e.g. significant renal/liver/cardiac dysfunction
- No other requirement for admission
- Patient is mobile and able to return to hospital
- Patient is happy for ambulatory management
- Patient is aware of the need to return to hospital earlier if they become more unwell at home (should be warned of presyncope symptoms, becoming more breathless, etc.)
- Patient is **not** pregnant (see Special Cases)
- Bleeding risks and contra-indications to LWMH have been ruled out
- Patient does not live alone
- Patient has a working telephone

Ambulatory Management of PE

- Give treatment dose LWWH or DOAC– teach the patient how to administer using this dose.
- Ensure they have enough doses of LMWH to administer at home until CTPA.
- Explain plan to patient and give advice leaflet – ensure they understand follow-up/CTPA/LWMH
- Request CTPA
- Request follow-up as per local protocol e.g. hot clinic, ambulatory care pathway

Patient Categories

Diagnosis and/or management of PE in the following categories of patients varies to a greater or lesser extent to that described above. Please use the following links to access the relevant guidelines available on the GGC Therapeutics Handbooks (link) and/or the GGC Clinical Guidelines (link), and use alongside this guideline, to ensure these special categories receive the appropriate care

Pregnancy	Link
Active Malignancy	Link
Superficial Thrombophlebitis	Link
COVID and VTE Prophylaxis	Link

PE whilst on anticoagulation (treatment failure)

- Check adherence to anticoagulation
- Address other sources of hypercoagulability e.g. cancer
- Consider increasing the dose of anticoagulant, or change to a different class of anticoagulants
- Seek haematology advice

Anticoagulation

Subcutaneous Low Molecular Weight Heparin (LMWH)

Dalteparin is the LMWH of choice across NHSGGC for the initial treatment of VTE unless the patient is pregnant, has specific contraindications to dalteparin, or is to be treated with apixaban.

- Patients with an incidental finding of PE on imaging can start anticoagulation with a treatment dose DOAC and do not need initial anticoagulation with LMWH.

Continue dalteparin until:

- The diagnosis is disproved
- The diagnosis is confirmed and either apixaban (or other direct oral anticoagulant) is commenced or dalteparin has been over-lapped with warfarin for at least 5 days and the INR has been ≥2 for two consecutive days.

Dalteparin Dose

Actual weight (kg)	Dalteparin once daily dose (units)	Pre-filled syringe colour
34-35	7,500	Green
46-56	10,000	Red
57-68	12,500	Brown
69-82	15,000	Purple
≥83	18,000 (maximum dose)	Grey

Renal Impairment and Extremes of Body Weight

- Guidance on dose adjustment for patients with significant renal impairment or weighing >120kg are available in the GGC Therapeutic Handbook (link).
- If there is concern about efficacy in patients with significant renal impairment or who are underweight or weighing >95kg, anti-factor Xa activity can be checked after 2–3 consecutive doses of dalteparin, at 4 hours after a dose (target 0.5-1units/ml).
- Lower doses of dalteparin should be considered in patients with significant liver and/or renal failure (CrCl <30ml/minute).

Unfractionated Heparin (UFH)

See guidance under High Risk PE.

Used in treatment of DVT / PE if rapid anticoagulation is deemed appropriate (e.g. high-risk PE) or patients thought to be at particularly high bleeding risk (e.g. recent surgery/trauma)

Warfarin

- While it is becoming less common to use warfarin, it may still be used in patients who have a ongoing high risk of bleeding and may benefit from rapid reversal of anticoagulation. It may also be used to monitor patient's compliance or for patients with recurrent VTE whilst taking a DOAC.
- Warfarin should always be used for patients who have had a PE and who are diagnosed with triple positive antiphospholipid syndrome.
- It is used as a follow-on from LMWH to treat PE. It may not be suitable for patients who are unable to comply with changes in dosage or regular INR checks.
- Induction treatment with warfarin should always follow a validated induction dosing algorithm; there are induction protocols available on the GGC Clinical Guideline platform (link)
- Warfarin should be administered orally, once daily at 6pm.

Direct Oral Anticoagulants (DOACs)

Apixaban is the DOAC of choice across NHSGCC for acute treatment and long-term secondary prevention of PE.

Rivaroxaban, Edoxaban and Dabigatran remain on formulary for special cases when they may be preferable. All DOACs are as effective as warfarin for the treatment and prevention of PE yet do not require monitoring. Reversal agents for life-threatening haemorrhage are available in GGC (after discussion with haematology) for dabigatran (idarucizumab [Praxbind]), apixaban and rivaroxaban (andexanet alfa [Ondexxya]) and off-licence for edoxaban (andexanet alfa).

Apixaban Exclusions

- Apixaban should not be used if the Creatinine Clearance is <15ml/minute and used with caution if 15-29mls/min. Further information can be found on the GGC Clinical Guideline platform (link).
- Liver disease, associated with cirrhosis and/or coagulopathy
- Pregnancy or breast feeding
- Concurrent treatment with azoles (except fluconazole), protease inhibitors, or other cytochrome P450 inducers (e.g. Rifampicin, Phenytoin, Carbamazepine, Phenobarbitol)

Treatment Regimen

- Treat with LMWH until the diagnosis is objectively confirmed.
- If the diagnosis has already been confirmed, e.g. an incidental finding on a CT scan, then treatment can immediately start with a DOAC.
- Start Apixaban 22-24 hours after the last dose of LWMH
- Loading dose – **Apixaban oral, 10mg twice daily, for 7 days**
- Maintenance dose – **Apixaban oral, 5mg twice daily** for duration of anticoagulation
- **If** long term anticoagulation, after 3-6 months reduce to Apixaban oral 2.5mg twice daily.

Discharging on Apixaban

- Dispense 21 days of acute treatment from the hospital pharmacy
- A timely letter to the GP informing of anticoagulation therapy. A template letter is available on the GGC Clinical Guideline platform (link).
- Issue the patient with a Patient Alert card for Apixaban
- Counselling of the patient on the risks and benefits of anticoagulation

Renal impairment and DOACs

- Renal impairment affects the use and dosage of DOACs.
- Creatinine clearance (CrCl) must be calculated as eGFR is not reliable for DOAC dosing.
- For Creatinine Clearance <15mls/min, DOACs cannot be used and LMWH or Warfarin should be used.
- Apixaban should be used first line for all patients, if Creatinine Clearance is >15mls/min

Creatinine Clearance (ml/min)	**Apixaban**	**Rivaroxaban**	**Dabigatran**	**Edoxaban**
30-50	No dose adjustment	Reduce dose to 15mg OD	Consider 110mg BD	Reduce dose to 30mg OD
15-30	Use with caution		Contraindicated	
<15	Contraindicated	Contraindicated		Contraindicated

Discharge and Follow Up

Discharge Check-list

- ◯ The patient is aware of the diagnosis of PE
- ◯ The patient is aware of the importance of continuing to take anti-coagulation for the treatment of acute PE and to prevent further PE
- ◯ The patient has been referred for follow-up (see below)
- ◯ The patient is aware that they will be seen in a follow-up clinic
- ◯ The patient has an adequate supply of anticoagulant
- ◯ The GP is informed of the PE and anticoagulation on the discharge letter

Follow Up

Follow-up should be performed for all patients with PE, regardless of severity and risk.

Follow-up should be performed at 3-6 months by a PE specialist. This is performed to help identify patients who are at risk of a post-PE syndrome, which includes pulmonary hypertension, and to help clarify duration of anticoagulation. Follow up includes an assessment of patient's symptoms and their risk factors for developing CTEPH. Other investigations, such as an echocardiogram, NT-proBNP and V/Q scan may then be performed.

How to Follow Up

Currently, post-PE follow up will vary at each hospital across Greater Glasgow & Clyde. We suggest forwarding the discharge letter to the nominated respiratory consultant including pertinent information such as the risk status at diagnosis, the method of anticoagulation and whether thrombolysis was given.

Duration of Anticoagulation

Duration of anticoagulation should be assessed at a PE follow-up clinic; however, the below guidance may be used to inform patients of their likely duration at the time of discharge.

The aim of anticoagulation is to complete the treatment of the acute PE and prevent recurrence of VTE over the long-term.
The length of ongoing anticoagulation should depend on the patient's VTE recurrence risk, taking into account the individual risk of bleeding. Clinical judgement should be used to assess an individual's bleeding risk, although the HAS-BLED and VTE-BLEED score may be useful.

Recommendations
The following are recommendations only and, in each case, clinical judgement and an individual's bleeding risk should be taken into consideration.

Scenario	Duration of Anticoagulation
All patients with PE	A minimum of 3 months
First episode of PE and active cancer	Indefinite or until cured
First episode of PE and single/dual positive Antiphospholipid syndrome	Indefinite (with apixaban)
First episode of PE and triple positive Antiphospholipid syndrome	Indefinite (with warfarin)
First episode of PE with no identifiable risk factor	Consider indefinite*
First episode of PE with a persistent risk factor	Consider indefinite*
First episode of PE with a minor transient risk factor	Consider indefinite*
First episode of PE secondary to a major transient/reversible risk factor	3 months
Recurrent VTE (more than one episode) not related to a transient/reversible risk factor	Indefinite*

*If using anticoagulation for > 3 months, and the patient doesn't have active cancer, continue anticoagulation with a DOAC at prophylactic dose (i.e. Apixaban 2.5mg BD, Rivaroxaban 10mg OD).

Risk of VTE Recurrence

Estimated risk for long-term recurrence	Risk factor category for index PE	Examples
Low (<3% per year)	Major transient or reversible factors associated with >10-fold increased risk for the index VTE event (compared to patients without the risk factor)	• Surgery with general anaesthesia for >30 min • Confined to bed in hospital (only "bathroom privileges") for ≥3 days due to an acute illness, or acute exacerbation of a chronic illness • Trauma with fractures
Intermediate (3-8% per year)	Transient or reversible factors associated with ≤10-fold increased risk for first (index) VTE	• Minor surgery (general anaesthesia for <30 min) • Admission to hospital for <3 days with an acute illness • Oestrogen therapy/contraception • Pregnancy or puerpium • Confined to bed out of hospital for ≥3 days with an acute illness • Leg injury (without fracture) associated with reduced mobility ≥3 days • Long-haul flight
	Non-malignant persistent risk factors	• Inflammatory bowel disease • Active autoimmune disease
	No identifiable risk factor	
High (>8% per year)		• Active cancer • One or more previous episodes of VTE in the absence of a major transient or reversible factor • Antiphospholipid antibody syndrome

Frequently Asked Questions (FAQ)

Should thrombolysis be given to prevent Chronic Thromboembolic Pulmonary Hypertension (CTEPH)?
There is no evidence to suggest that thrombolysis decreases the subsequent risk of CTEPH. This is based on multiple studies and the European Respiratory Society 2019 guidelines.

Should thrombolysis be given if a patient has clot in the RA or RV at the time PE is diagnosed?
For transient clot in the RA and RV or traversing a PFO, surgical embolectomy should be considered to reduce the risk of rapid deterioration or stroke (in the case of PFO).

If the patient is haemodynamically stable there is no evidence that systemic thrombolysis improves outcomes.

The patient is haemodynamically unstable, but has already been treated with LMWH. Can I still proceed with thrombolysis?
Systemic thrombolysis should still be given if the patient has already been treated with LMWH. Note that the bolus dose of UFH should be omitted if the patient has already been treated with LMWH.

A PE has been detected as an incidental finding on a CT scan; should I still treat the patient with LMWH or can I commence treatment with a DOAC?
A severity assessment should be performed;

- If the patient is in a High Risk or Intermediate-High Risk category, please refer to individual guidance.
- For patients with Intermediate-Low Risk or Low Risk PE, and have do not have active cancer, they can be treated with a treatment-dose DOAC and do not require initial LWMH.