Management of acute pulmonary embolism

The management of pulmonary embolism has changed significantly over recent years (*Figure 1*) with increased importance assigned to risk stratification and the development of outpatient pulmonary embolism management. This article examines these developments in the management of acute pulmonary embolism and discusses several challenging clinical scenarios. The suggested treatment approaches are discussed in more detail in a previous publication by Condliffe et al (2013).

Risk stratification of acute pulmonary embolism

Following diagnosis of an acute pulmonary embolism it is vital that patients are adequately risk stratified in order to guide subsequent management. This article uses the European Society of Cardiology nomenclature, which are comparable to American Heart Association classification (in parentheses): high risk (massive), intermediate risk (sub-massive) and low risk (*Table 1*). High risk is defined as significant hypotension (usually defined as a systemic blood pressure <90 mmHg or >40 mmHg reduction from baseline for >15 minutes) or clinical shock. It is associated with a high mortality and so urgent reperfusion (usually with systemic thrombolysis) is indicated. Non-high-risk patients are further stratified based on prognostic scoring and markers of right ventricular dysfunction and ischaemia.

The most commonly used scoring systems are the pulmonary embolism severity index or simplified pulmonary embolism severity index (*Table 2*). Low risk patients

Figure 1. The changing nature of the management of pulmonary embolism. CTPA = computed tomography pulmonary angiogram.

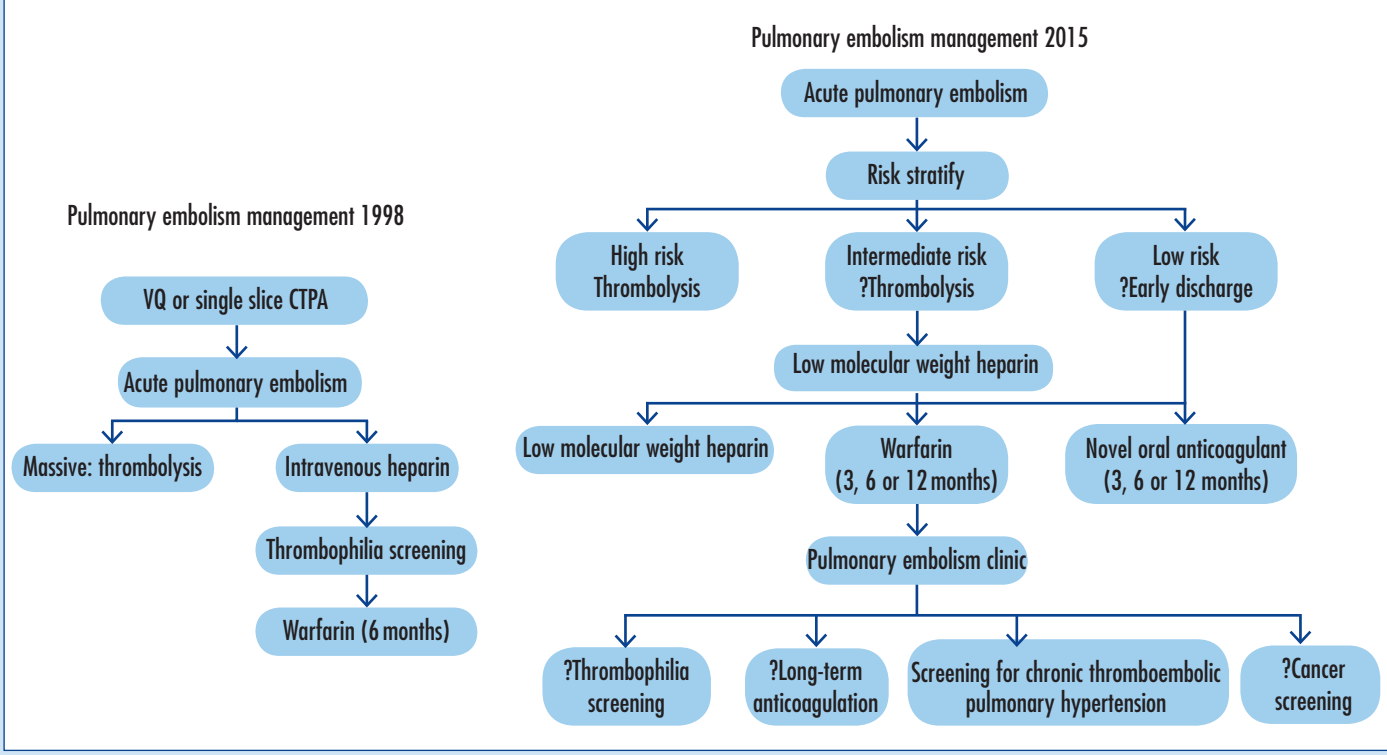

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Table 1. Risk stratification in acute pulmonary embolism: European Society of Cardiology 2014 guidelines

		Risk parameters and scores			
Early mortality risk		Shock or hypotension	PESI class III–V or simplified PESI >1*	Signs of right ventricular dysfunction on an imaging test†	Cardiac laboratory biomarkers‡
High		+	(+)§	+	(+)§
Intermediate	Intermediate–high	–	+	Both positive	
	Intermediate–low	–	+	Either one (or none) positive¶	
Low		–	–	Assessment optional; if assessed, both negative¶	

* Pulmonary embolism severity index (PESI) class III–V indicates moderate to very high 30-day mortality risk; simplified PESI ≥1 point indicate high 30-day mortality risk. † Echocardiographic criteria of right ventricular dilation and/or an increased end-diastolic right ventricular:left ventricular diameter ratio (in most studies the reported threshold value was 0.9 or 1.0); hypokinesia of the free right ventricular wall; increased velocity of the tricuspid regurgitation jet; or combination of the above. On computed tomographic angiography (four-chamber views of the heart), right ventricular dysfunction is defined as an increased end-diastolic right ventricular:left ventricular diameter ratio (with a threshold of 0.9 or 1.0). ‡ Markers of myocardial injury (e.g. elevated cardiac troponin I or -T concentrations in plasma), or of heart failure as a result of (right) ventricular dysfunction (elevated natriuretic peptide concentrations in plasma). § Neither calculation of the PESI (or simplified PESI) nor laboratory testing are considered necessary in patients with hypotension or shock. ¶ Patients in PESI class I–II, or with simplified PESI 0, and elevated cardiac biomarkers or signs of right ventricular dysfunction on imaging tests, are also classified into the intermediate–low risk category. This might apply to situations in which imaging or biomarker results become available before calculation of the clinical severity index. From Torbicki et al (2014)

are defined by pulmonary embolism severity index class I or II or simplified pulmonary embolism severity index of 0.

Patients in pulmonary embolism severity index class ≥ III or a simplified pulmonary embolism severity index of ≥ 1 are considered intermediate and high risk groups. Within this category, further risk assessment focuses on the status of the right ventricle in response to the pulmonary embolism-induced acute pressure overload. Patients who have evidence of both right ventricular dysfunction (on echocardiography or a right ventricular diameter ≥ left ventricular diameter on computed tomography pulmonary angiogram) and elevated cardiac biomarker levels in the circulation are classified into an intermediate–high risk category while patients with none or only one feature of right ventricle strain belong to an intermediate–low risk group (Torbicki et al, 2014). In clinical practice a right ventricle equal or greater in size than the left ventricle or an elevated level of N-terminal pro B-type natriuretic peptide (NT-proBNP) are useful indicators of right ventricular dysfunction while an elevated troponin level is an indicator of right ventricular ischaemia. Patients with evidence of both right ventricular dysfunction and ischaemia are at intermediate–high risk of early mortality.

Role of thrombolysis in intermediate risk pulmonary embolism

In the context of an elevated simplified pulmonary embolism severity index, right ventricular dysfunction, right ventricular ischaemia and the presence of a deep vein thrombosis cumulatively increase the risk of deterioration, with a 25% risk of a complicated outcome (mortality or deterioration requiring intensive care and/or thrombolysis) when all features are present. Data also suggest that the risk of deterioration increases with increasing lactate levels (Vanni et al, 2013). This raises the question of thrombolysis in patients with intermediate–high risk pulmonary embolism.

Clinical trials have demonstrated more rapid haemodynamic improvement and

Table 2. Pulmonary embolism severity index and simplified pulmonary embolism severity index

Parameter	Original version*	Simplified version†
Age	Age in years	1 point (if age >80 years)
Male sex	+10 points	–
Cancer	+30 points	1 point
Chronic heart failure	+10 points	1 point
Chronic pulmonary disease	+10 points	
Pulse rate ≥110 beats per minute	+20 points	1 point
Systolic blood pressure <100 mmHg	+30 points	1 point
Respiratory rate >30 breaths per minute	+20 points	–
Temperature <36˚C	+20 points	–
Altered mental state	+60 points	–
Arterial oxyhaemoglobin	+20 points	1 point
Risk strata‡	Class I: ≤65 points very low 30-day mortality risk (0–1.6%)	0 points = 30-day mortality risk 1.0% (95% confidence interval 0.0–2.1%)
	Class II: 66–85 points low mortality risk (1.7–3.5%)	≥1 point = 30-day mortality risk 10.9% (95% confidence interval 8.5–13.2%)
	Class III: 86–105 points high mortality risk (3.2–7.1%)	
	Class IV: 106–125 points high mortality risk (4.0–11.4%)	
	Class V: >125 points very high mortality risk (10.0–24.5%)	

* Aujesky et al (2005); † Torbicki et al (2014); ‡ based on the sum of points

clot resolution following thrombolysis but no clear mortality benefits, likely because of the increased risk of bleeding. Although both the MAPPET-3 (Konstantinides et al, 2002) and PEITHO randomized controlled trials of thrombolysis (Meyer et al, 2014) met their primary end points this was driven by a reduced need for subsequent escalation of therapy (largely the need for subsequent thrombolysis) with no overall effect on mortality. In the PEITHO study there was a non-significant trend towards improved outcomes in patients <75 years of age and increased bleeding risk in patients >75 year of age. Meta-analysis suggests that the overall major and intracranial bleeding risk in patients with pulmonary embolism who undergo thrombolysis is 9% and 1.5% respectively (Chatterjee et al, 2014).

Practicalities of thrombolysis

Alteplase is the most commonly used thrombolytic agent for pulmonary embolism with recommended dosing in patients ≥65 kg of a loading bolus of 10 mg over 1–2 minutes followed by 90 mg infused over 2 hours. In patients <65 kg the total dose administered is 1.5 mg/kg. In patients already receiving intravenous heparin the infusion should be stopped before administration of alteplase, the activated partial thromboplastin time checked 2 hours after completion of administration and the heparin infusion restarted when the activated partial thromboplastin time ratio is less than 2 times the upper limit of normal.

Unfractionated heparin is generally converted to low molecular weight heparin 24 hours after thrombolysis. If therapeutic low molecular weight heparin has been given before thrombolysis then the authors would normally commence intravenous heparin as above but delay starting to 18 hours after the last dose of low molecular weight heparin if once-daily dosing and 8–10 hours if twice-daily dosing had been used. Since the whole cardiac output passes through the lungs the use of lower doses of thrombolysis than in other indications (i.e. stroke and myocardial infarction) has been considered. The MOPPET study by Sharifi et al (2013) randomized patients to 50 mg alteplase (10 mg bolus followed by 40 mg over 2 hours) or placebo and reported no significant bleeding complications. Half-dose thrombolysis may therefore be an option especially where the risk *vs* benefit of thrombolysis is not clear, but this approach is not based on a large amount of data.

Alternatives to thrombolysis

In the presence of strong contraindications to systemic thrombolysis then a surgical or catheter-based approach to reperfusion should be considered in high-risk pulmonary embolism. As reported by Todoran and Sobieszczyk (2010) catheter-directed therapies include mechanical disruption of thrombi by catheter, ultrasound or pressurized saline injection. Data suggest that the combination of mechanical disruption and low-dose local administration of thrombolysis can be an effective and safe therapy for high and intermediate risk pulmonary embolism but the role of this approach in the routine care of pulmonary embolism is not clear.

Outpatient management

Patients at low risk of early mortality may be considered for outpatient management. Studies of early discharge by Aujesky et al (2005, 2011) have used a variety of definitions of low risk (e.g. pulmonary embolism severity index I or II, simplified pulmonary embolism severity index of 0 or low NT-proBNP levels) and have demonstrated that these low-risk patients may be safely discharged. It is unclear which approach is best and whether additional assessment of right ventricular dysfunction and ischaemia are required to allow safe discharge. Outpatient management of pulmonary embolism has previously required low molecular weight heparin administration during warfarin initiation but the availability of direct oral anticoagulants provides the possibility of a more convenient ambulatory treatment. It is important that a proper system is in place for ambulatory management of acute pulmonary embolism including support and follow up (*Figure 2*). Admission may still be required as a result of ongoing pain or social situation. Guidelines for the ambulatory management of acute pulmonary embolism are currently under development by the British Thoracic Society.

Direct oral anticoagulants

Three direct oral anticoagulants have been approved in Europe for the management of pulmonary embolism and deep vein thrombosis. Rivaroxaban and apixaban are direct Xa inhibitors while dabigatran is a direct thrombin inhibitor. All are non-inferior to vitamin K antagonists with

Figure 2. Example of a protocol for the ambulatory management of acute pulmonary embolism.

Emergency Department / Respiratory Medicine
Patient with Pulmonary Embolism suitable for ambulatory care

Name:
DoB:
(Affix Patient Label Here)
Hosp No.:
NHS No.:
Consultant:

To be completed by:
1. ED doctor who diagnosed PE and then re-assessed by ED middle grade or consultant *OR*
2. Respiratory middle grade/consultant in charge of patient's care

Date_____ Time_____

PE diagnosed on (circle)
CTPA
DVT on leg ultrasound and clinical PE
Other (e.g. V/Q)……

Results
D-dimer: …….micrograms/L Date:……
Troponin (HSTNT) …….nanograms/L Date:……
Creatinine …….micromol/L Date:……

Renal function: calculated creatinine clearance

$$\text{CrCl} = \frac{(140 - \text{age}\ldots\ldots) \times \text{weight (kg)}\ldots\ldots}{\text{Serum Creatinine (micromol/L)}\ldots\ldots} \quad \begin{matrix}\textbf{X 1.04 (female)}\\ \textbf{X 1.23 (male)}\end{matrix} = \ldots\ldots\ (\text{mL/min})$$

PESI SCORE:

Criteria All observation values should be first measured in department pre-treatment	**Score**	
Age	1 point per year	
Male gender	10	
Active cancer within 6 months	30	
History of heart failure	10	
History of chronic lung disease	10	
Pulse ≥110 bpm	20	
Systolic BP <100 mmHg	30	
Respiratory rate ≥30 bpm	20	
Temperature <36°C	20	
Altered mental status (disorientation, lethargy, stupor, or coma)	60	
Arterial oxygen saturation < 90%	20	
	Total score:	

Assessment of suitability for ambulatory care:	**Yes***	**No**
PESI score >85		
Troponin (HSTNT) ≥18		
Right ventricle dilated on CTPA		
Calculated creatinine clearance <30ml/min		
Pain inadequately controlled		
Inadequate social support		
Any other reason for admission		
Discharge from hospital/department between 8pm and 8am		

*** If "yes" to any question, then patient is not suitable for ambulatory care**

Ambulatory care patients must have been given the following (*tick when completed*):
- Supply of therapeutic dose dalteparin (until seen in clinic) ☐ ***or*** rivaroxaban (21 day pack) ☐
- Patient counselling and written information ☐
- Appointment to attend STH Thrombosis Service (via Anticoagulation Clinic) within 72 hours ☐

DVT CDU nurse Signature:_____ Name:_____ Date:_____
ED or Respiratory middle grade/consultant
Signature::_____ Name:_____ Date:_____

ED: Refer patient to Thrombosis Nurse (via Anticoagulation Clinic) using diary booking system.
All other areas: fax this form and Anticoagulation Referral Form A to ext 68690.

Key: < = less than; ≤ = less than or equal to; > = more than; ≥ = more than or equal to

respect to venous thromboembolism recurrence while gastrointestinal bleeding risk (apixaban) and intracerebral bleeding risk (rivaroxaban) is lower than with warfarin. Monitoring of anticoagulation levels is not routinely required. Dabigatran is highly renally excreted which can create important practical issues. Importantly both the EINSTEIN-PE (Buller et al, 2012) and AMPLIFY (Agnelli et al, 2013) trials with rivaroxaban and apixaban did not require pre-treatment with low molecular weight heparin which may make them attractive options for early discharge. There are no data to support their use in malignancy or in patients with antiphospholipid syndrome, and they are contraindicated in patients with mechanical heart valves and in pregnant patients (*Table 3*). The authors suggest that they should not be routinely used in patients initially with intermediate–high risk pulmonary embolism who may subsequently require reperfusion.

Rivaroxaban is initially prescribed orally at a dose of 15 mg twice daily for 3 weeks followed by 20 mg once daily. Apixaban is initially prescribed orally at a dose of 10 mg twice daily for 5 days followed by 5 mg twice daily. Since food intake has an impact on the absorption and bioavailability, rivaroxaban should be taken with food. Dosing may require adjustment in the presence of mild to moderate renal dysfunction and the summary of product characteristics should be consulted.

Role of thrombolysis in specific situations

Patients with relative contraindications to thrombolysis

Recent surgery

Major bleeding occurs in >50% of patients receiving thrombolysis within 1 week of surgery and in 20% of patients thrombolysed 1–2 weeks postoperatively. American College of Chest Physicians guidelines by Kearon et al (2012) suggest that recent surgery is a relative contraindication to thrombolysis with the bleeding risk falling significantly 2 weeks following surgery. Recent brain or spinal surgery or major trauma are stronger contraindications to thrombolysis.

Intracranial space-occupying lesions

The risk of intracerebral haemorrhage is dependent on tumour type and localization. The risk of spontaneous bleeding is around 50% in metastatic melanoma, 29% in oligodendroglioma and 3% in meningioma.

Recent stroke

Thrombolysis is contraindicated in American College of Chest Physicians and European Society of Cardiology guidelines for 3 or 6 months following ischaemic stroke. A study involving 145 patients with a history of an ischaemic stroke within the previous 3 months who then received thrombolysis for a further stroke did not show an increased risk of intracerebral bleeding. There are no good data to guide the risk of thrombolysis in patients with previous intracerebral haemorrhage.

Table 3. Approach to choice of anticoagulation class

Drug	Advantages in patients with
Vitamin K antagonist	Good international normalized ratio control
	Antiphospholipid syndrome
	Mechanical heart valves
	Extremes of weight
	Renal impairment (creatinine clearance <30 ml/min)
Direct oral anticoagulants	Poor international normalized ratio control
	Patient convenience
	Ambulatory pulmonary embolism treatment
	Warfarin intolerance
Low molecular weight heparin	Malignancy
	Pregnancy
	Severe hepatic impairment

Anticoagulation in acute pulmonary embolism with acute cerebral infarcts

Patients occasionally present with a stroke and pulmonary embolism simultaneously as a result of paradoxical embolization across a patent foramen ovale. More commonly patients may develop an acute pulmonary embolism after a stroke as a result of reduced mobility. Low–intermediate dose heparin early after ischaemic stroke is associated with an increased rate of haemorrhagic transformation. Stroke guidelines therefore advise delaying anticoagulation in patients with atrial fibrillation for 2 weeks following ischaemic stroke. Advice regarding anticoagulation for coexisting venous thromboembolism in acute stroke is less clear, with UK stroke guidelines (International Stroke Trial Collaborative Group, 1997; Bath et al, 2002; Camerlingo et al, 2005) suggesting anticoagulation for proximal deep vein thrombosis or pulmonary embolism, and American Heart Association guidelines by Jaff et al (2011) recommend initial anticoagulation being withheld in patients with moderate to severe ischaemic stroke.

Pulmonary embolism in pregnancy

As reported by Shaul and Hall (1997) warfarin is teratogenic in the first trimester and is associated with neural abnormalities throughout pregnancy. However, low molecular weight heparin does not cross the placenta and so is the anticoagulation method of choice in pregnancy. A retrievable inferior vena caval filter may be considered in a patient with an acute pulmonary embolism within 1 month of the expected delivery date to allow temporary cessation of anticoagulation around delivery. Thrombolysis is relatively safe in pregnancy and in general should be administered if indicated for high-risk pulmonary embolism. If a high-risk pulmonary embolism develops in the peripartum period then the risk of significant haemorrhage is higher and mechanical methods of reperfusion should be used where available.

Right atrial thrombus

Torbicki et al (2003) reported that right atrial thrombus is present in 4–8% of patients with acute pulmonary embolism. Kronik (1989) reported that the main type

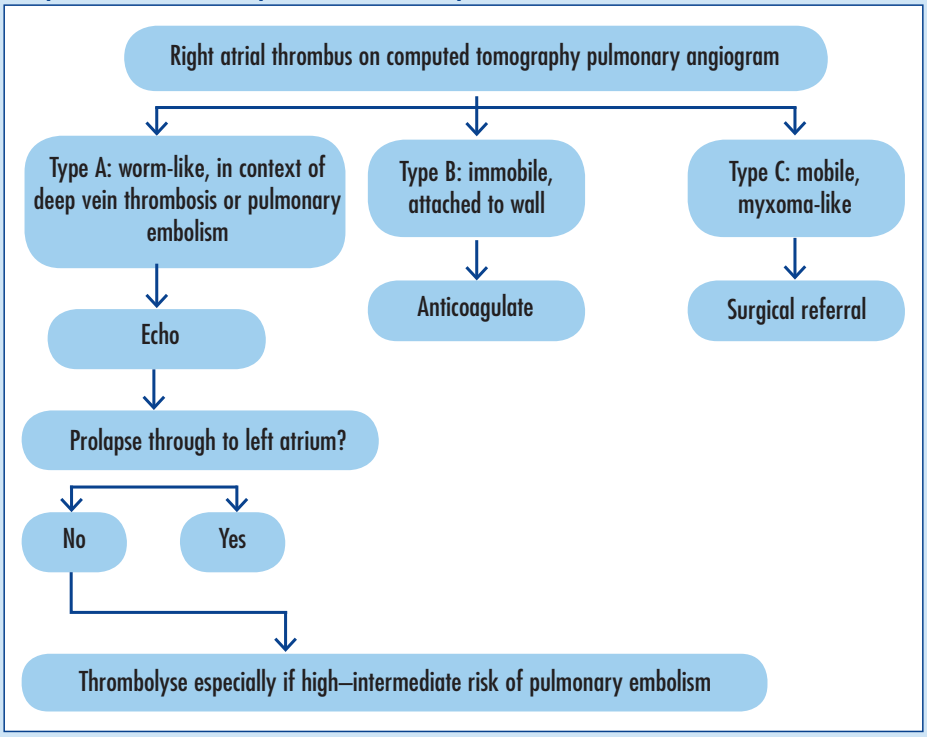
of thrombus is long, thin and 'worm-like' (type A) and represents clot originating in the leg veins held in transit by tricuspid regurgitation resulting from acute pulmonary hypertension and right ventricular dysfunction. Right atrial thrombus is therefore always associated with clinically severe pulmonary embolism and is associated with high early mortality. Occasionally type A thrombus prolapses through a patent foramen ovale into the left atrium, resulting in a risk of systemic embolization. Type B thrombus consists of immobile thrombi, often associated with previous surgery, and often is not associated with coexisting acute pulmonary embolism. A small proportion of thrombi are intermediate in character (type C), being mobile and 'walnut-like', and have the potential to obstruct the right ventricular outflow tract.

Computed tomography pulmonary angiogram is highly effective at identifying type A thrombi with a sensitivity of nearly 100%. Currently available registry data suggest that outcomes in patients with type A thrombus are superior if thrombolysis is administered compared with anticoagulation alone or surgery unless the clot is prolapsing through a patent foramen ovale. In this circumstance surgery appears to be the optimal approach while thrombolysis is associated with worse outcomes, likely related to systemic embolization. Type B thrombus requires anticoagulation alone while in type C thrombus surgery should be considered and thrombolysis should be avoided because of the real risk of precipitating right ventricular outflow obstruction. If a patient with type A thrombus prolapsing through a patent foramen ovale or type C thrombus has circulatory shock (i.e. high-risk or peri-arrest pulmonary embolism) and surgery is not immediately available then systemic thrombolysis would be indicated. *Figure 3* gives a suggested approach to management of right atrial thrombus.

Role of inferior vena caval filter

Retrievable inferior vena caval filter insertion should be considered when anticoagulation is contraindicated or temporary cessation of anticoagulation within 1 month is required (e.g. delivery or surgery). The PREPIC-1 study (PREPIC Study Group, 2005) demonstrated that inferior vena caval filter insertion in patients with proximal deep vein thrombosis receiving anticoagulation reduced the risk of subsequent pulmonary embolism, but increased deep vein thrombosis recurrence with no effect on mortality. The PREPIC-2 study found no reduction in mortality in patients with both acute deep vein thrombosis and pulmonary embolism who received an inferior vena caval filter (Mismetti et al, 2015).

Figure 3. Suggested approach to management of right atrial thrombus. Thrombolysis should be considered in any form of thrombus in a peri-arrest or shocked patient.



Screening for malignancy

Approximately 10% of patients presenting with unprovoked pulmonary embolism will develop cancer within the next 5–10 years, with the majority of cases appearing in the first 1–2 years after diagnosis of pulmonary embolism. National Institute for Health and Care Excellence (2012) guidelines suggest that abdominal and pelvic computed tomography should be considered following an unprovoked pulmonary embolism based on the SOMIT study (Piccioli et al, 2004) which randomized 99 patients to extensive and 102 patients to limited screening. In the SOMIT study less advanced malignancy was identified in the group undergoing extensive as compared to limited investigation although there was no difference in mortality between the two groups.

The TROUSSEAU study (van Doormaal et al, 2011) subsequently compared 342 patients extensively investigated with 288 patients receiving limited screening and found no difference in numbers of malignancies identified or in survival. Based on these data the more recent European Society of Cardiology guidelines by Torbicki et al (2014) recommend that the search for occult malignancy should be limited to history, examination, basic laboratory tests including calcium and liver function testing and urinalysis and chest X-ray (where a previous computed tomography had not been performed).

Conclusions

Risk stratification, comprising the presence or absence of shock, a validated risk score and markers of right ventricular dysfunction and ischaemia, is central to the optimal management of patients with acute pulmonary embolism. The role of reperfusion strategies in non-high risk patients with acute pulmonary embolism is not clear. Close monitoring of patients at intermediate–high risk of complications is vital. Patients at very low risk of complications may be suitable for early discharge but a robust system for selection and follow up must be in place. A number of

clinical presentations of acute pulmonary embolism may be particularly challenging; suggested approaches based on the available literature and clinical experience are discussed. BJHM

Tables 1 *and* 2 *are reproduced from Torbicki et al (2014) by kind permission of Oxford University Press.*
Conflict of interest: Dr R Quadery: none; Dr CA Elliot has received payment for lecturing from Bayer; Dr J Hurdman has received payment for lecturing for Bayer; Professor DG Kiely has received payment for lecturing and advisory boards from Bayer; Dr RM Maclean has received payment for lecturing and advisory boards from Bayer; Professor I Sabroe receives an annual unrestricted educational grant from GSK to run the Sheffield Difficult Lung Disease clinical teaching meeting, and in 2013 received an unrestricted educational grant from Triniti Chiesi to support medical humanities research and projects. He attends an annual respiratory research meeting supported by Boehringer Ingelheim, covering travel, accommodation and subsistence at the meeting; Dr JJ van Veen has received payment for lecturing and advisory boards from Bayer, BMS-Pfizer and Boehringer Ingelheim; Dr R Condliffe has received payment for advisory boards from Daiichi Sankyo and for lecturing and advisory boards from Bayer.

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KEY POINTS

- All patients diagnosed as having acute pulmonary embolism should undergo risk stratification.
- Thrombolysis should not be routinely given in patients at non-high risk of pulmonary embolism.
- Surgical embolectomy or catheter-directed therapies should be considered where reperfusion is indicated but there are clear contraindications to systemic thrombolysis.
- Selected patients at low risk of early mortality may be considered for early discharge and outpatient anticoagulation but a robust system of assessment, support and follow up is mandatory.
- Anticoagulation during pregnancy should be via therapeutic low molecular weight heparin. Thrombolysis should be given for high risk pulmonary embolism in pregnancy except in the peripartum period.
- Retrievable inferior caval filter insertion in acute pulmonary embolism should be limited to patients in whom anticoagulation is contraindicated and should be removed as soon as possible once the indication for their use has resolved.
- Initial screening for malignancy after an unprovoked pulmonary embolism should include careful history, physical examination, basic laboratory tests and a chest X-ray with subsequent investigations including computed tomography of abdomen and pelvis, dependent on the results of the initial screening.
- Although direct oral anticoagulants are increasingly used in the management of acute pulmonary embolism, patients must be individually assessed to ensure that the optimal method of anticoagulation is chosen.