

REVIEW

Acute pulmonary embolism: a concise review of diagnosis and management

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pulmonary embolism, diagnosis, prognosis, early discharge.

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Abstract

An acute pulmonary embolism (aPE) is characterised by occlusion of one or more pulmonary arteries. Physiological disturbance may be minimal, but often cardiac output decreases as the right ventricle attempts to overcome increased afterload. Additionally, ventilation-perfusion mismatches can develop in affected vascular beds, reducing systemic oxygenation. Incidence is reported at 50–75 per 100 000 in Australia and New Zealand, with 30-day mortality rates ranging from 0.5% to over 20%. Incidence is likely to increase with the ageing population, increased survival of patients with comorbidities that are considered risk factors and improving sensitivity of imaging techniques. Use of clinical prediction scores, such as the Wells score, has assisted in clinical decision-making and decreased unnecessary radiological investigations. However, imaging (i.e. computed tomography pulmonary angiography or ventilation-perfusion scans) is still necessary for objective diagnosis. Anti-coagulation remains the foundation of PE management. Haemodynamically unstable patients require thrombolysis unless absolutely contraindicated, while stable patients with right ventricular dysfunction or ischaemia should be aggressively anti-coagulated. Stable patients with no right ventricular dysfunction can be discharged home early with anti-coagulation and review. However, treatment should be case dependent with full consideration of the patient's clinical state. Direct oral anti-coagulants have become an alternative to vitamin K antagonists and are facilitating shorter hospital admissions. Additionally, duration of anti-coagulation must be decided by considering any provoking factors, bleeding risk and comorbid state. Patients with truly unprovoked or idiopathic PE often require indefinite treatment, while in provoked cases it is typically 3 months with some patients requiring longer periods of 6–12 months.

Introduction

Pulmonary embolism (PE), which along with deep vein thrombosis (DVT) are collectively termed venous thromboembolism (VTE), has a reported incidence of 50–75 per 100 000 across Australia and New Zealand, with a mortality rate of 1.73 per 100 000 population per year.^{1–4} Furthermore, incidence rates rise exponentially with age and PE will become an increasing burden in Australia as our population ages.^{1,5} In acute pulmonary embolism (aPE) 30-day mortality rates can range from 0.5% to over 20% depending on symptoms at presentation.¹ Diagnosis

is complicated by a wide range of presenting symptoms and has historically lacked a standardised approach, often relying on radiological imaging for diagnosis.⁵ To address this, clinical prediction scores (CPS) were developed to standardise clinical decision-making for both diagnosis (i.e. Wells Criteria,⁶ Revised Geneva Score,⁷ Pulmonary Embolism Rule-out Criteria (PERC)⁸) and prognosis (i.e. the simplified Pulmonary Embolism Severity Index (sPESI)⁹). Nonetheless, aPE admissions have risen from 23 per 100 000 in 1993 to 65 per 100 000 in 2012,¹⁰ while patients meeting 'massive PE' criteria (i.e. haemodynamically unstable and/or requiring mechanical ventilation) have decreased. This overall increase is thought to be due to increased computed tomography pulmonary angiogram (CTPA) availability

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and an increase in sub-segmental PE diagnoses.^{11,12} However, controversy remains over estimation of prognostic risk, with both the sPESI and markers of right heart dysfunction likely to provide a solution. Furthermore, as the direct oral anti-coagulants (DOAC) are becoming the preferred medications in aPE management,^{13–15} increased research into early discharge and home treatment of patients continues to change the way we manage this patient group.^{5,16–18}

To formulate an evidence-based review of aPE, Ovid (Medline) and PubMed were searched for articles published since 1990. Additional citations were obtained from PE guidelines of the European Society of Cardiology (ESC),⁵ American Heart Association (AHA),¹⁶ American College of Physicians (ACP)¹⁷ and American College of Chest Physicians (ACCP).¹⁸

Pathophysiology and presentation

Presentation is highly variable and results from complete or partial obstruction of the pulmonary vasculature causing increased pulmonary pressures and ventilation-perfusion (V/Q) mismatches. It is important to note that the degree of obstruction can range from minimal disturbance to completely obstructed arteries. As such, patients may be asymptomatic in some instances and severely compromised in others. As vascular obstruction increases, supply to downstream lung parenchyma decreases, leading to poor perfusion of alveoli capillary beds. This can result in a mismatch between ventilation and perfusion, causing type 1 respiratory failure. Occlusion greater than 30–50% cross-sectional area of an arterial bed slowly increases pulmonary artery pressure by release of thromboxane and other vasoactive metabolites in response to endothelial cell stress.¹⁹ However, in the acute setting there may not be a rise in pulmonary artery pressure. Instead, RV function may be impaired due to increased afterload and myocardial ischaemia as the coronary perfusion gradient declines from low systemic blood pressure and increased chronotropic activity.⁵ Unsustainable ventricular stress can cause prolonged contractions, ischaemia and desynchronisation between the ventricles.²⁰ If pulmonary pressures remain elevated, often from incomplete emboli breakdown, pulmonary hypertension may develop and persist long after the initial event. Though variable in presentation, studies have shown a predominance of certain signs and symptoms, with dyspnoea at rest, pleuritic chest pain and cough the most common symptoms. Of the three, pleuritic chest pain was considered the most specific. Common clinical

signs included unilateral swelling of the calf and sinus tachycardia.^{5,21,22}

Diagnosis of suspected PE

Pre-test probability and CPS

The three-tier Wells Criteria (Table 1) standardises clinical judgement for diagnosing aPE before investigations are performed^{6,7,23} and is the favoured CPS by international guidelines on PE diagnosis and management.^{5,17,18} The Wells Criteria separates patients into low-, intermediate- and high-risk groups for aPE, directing whether to 'rule in' or 'rule out' the diagnosis. A 2010 meta-analysis²⁴ found a pre-test probability for aPE of 5.7% for low risk, 23.2% for intermediate risk and 49.3% for high risk. However, a definitive diagnosis still requires imaging (CTPA or V/Q scan) and most patients will require a D-dimer or the PERC^{8,25} to 'rule-out' a PE,

Table 1 The simplified pulmonary embolism severity index, Wells Criteria and pulmonary embolism rule-out criteria components with allocated weighting and scoring^{6,8,9}

Simplified Pulmonary Embolism Severity Index	Scoring: 0 = low risk; ≥1 = high risk
Each worth one point out of six	Age >80 History of cardiopulmonary disease History of active cancer Heart rate ≥110 Systolic blood pressure <100 Arterial oxygen saturation <90%
Wells Criteria	Scoring: <2 = low risk; 2–6 = intermediate risk; >6 = high risk
3 points	Clinical symptoms of DVT
3 points	PE the most likely diagnosis
1.5 points	Heart rate > 100/min
1.5 points	Immobilisation or surgery within 4 weeks
1.5 points	Previous DVT or PE
1 point	Haemoptysis
1 point	Malignancy
Pulmonary embolism rule-out criteria	Scoring: 0 = PE ruled out, >1 = PE unable to be ruled out
1 point	Age ≥ 50
1 point	Heart rate >100/min
1 point	Arterial oxygen saturation <95% on room air
1 point	Unilateral leg swelling
1 point	Haemoptysis
1 point	Recent surgery or trauma (within 4 weeks) requiring general anaesthesia
1 point	Prior PE of DVT
1 point	Hormone use (i.e. OCP, HRT)

DVT, deep vein thrombosis; HRT, hormone replacement therapy; OCP, oral contraceptive pill; PE, pulmonary embolism.

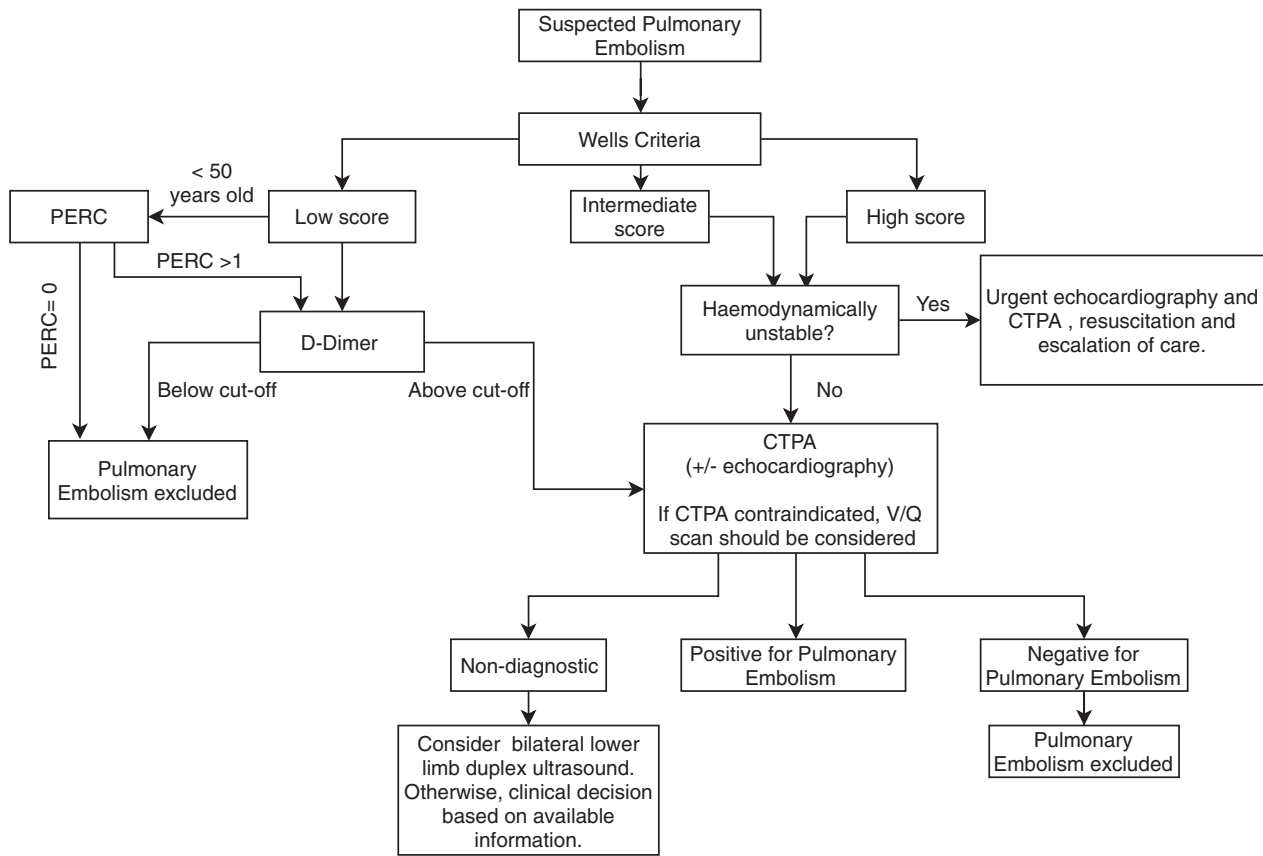


Figure 1 A suggested diagnostic pathway for acute pulmonary embolism based on services available in most Australian hospitals.

given the 5.7% pre-test probability in the low-risk group (Fig. 1).

Haemodynamically unstable patients

Patients with a systolic blood pressure of <90 mmHg, a drop of >40 mmHg for >15 min or cardiogenic shock have between a 38% and 58% case fatality rate.²⁶ Evidence shows 3–5% of patients present in this manner,²⁷ but this is likely an underestimate due to high pre-hospital mortality rates.²⁸ Essential steps in diagnosis are early access to CTPA or transthoracic echocardiography (TTE) (Fig. 1). In these cases, point-of-care TTE is becoming recognised as a first-line method of identifying RV dysfunction that is more specific and at least as sensitive as CTPA.^{5,29,30} Assessment of RV dysfunction by TTE should look for evidence of RV hypokinesis, RV free wall strain, end diastolic area, ejection fraction for both ventricles, RV systolic pressure (measured through a tricuspid regurgitant jet) and flow dynamics with spectral Doppler.^{29–32} In haemodynamically unstable patients with unequivocal signs of RV dysfunction on TTE and

where CTPA is not immediately available, reperfusion therapy should be considered after excluding any contraindications (Fig. 2).^{5,16,18,33} These investigations further aim to rule out differential diagnoses, such as cardiac tamponade, acute coronary syndrome and aortic dissection.

Intermediate and high-risk patients

Intermediate or high probability patients are recommended to undergo a ‘rule in’ approach.⁵ The PIOPED II study reported CTPA sensitivity of 83%, specificity of 96% and a positive predictive value of 96% in aPE detection when a high pre-test probability had been determined by a CPS.³⁴ Conversely, positive predictive value was 58% for a low pre-test probability. The 2014 ESC guidelines consider detection of a PE to the segmental level as diagnostic.⁵ While CTPA is the predominant diagnostic modality, V/Q scans are an alternative when CTPA is contraindicated (i.e. contrast allergy and renal impairment).²³ V/Q scans are categorised by the PIOPED II criteria^{35,36} as PE present, non-diagnostic/uncertain

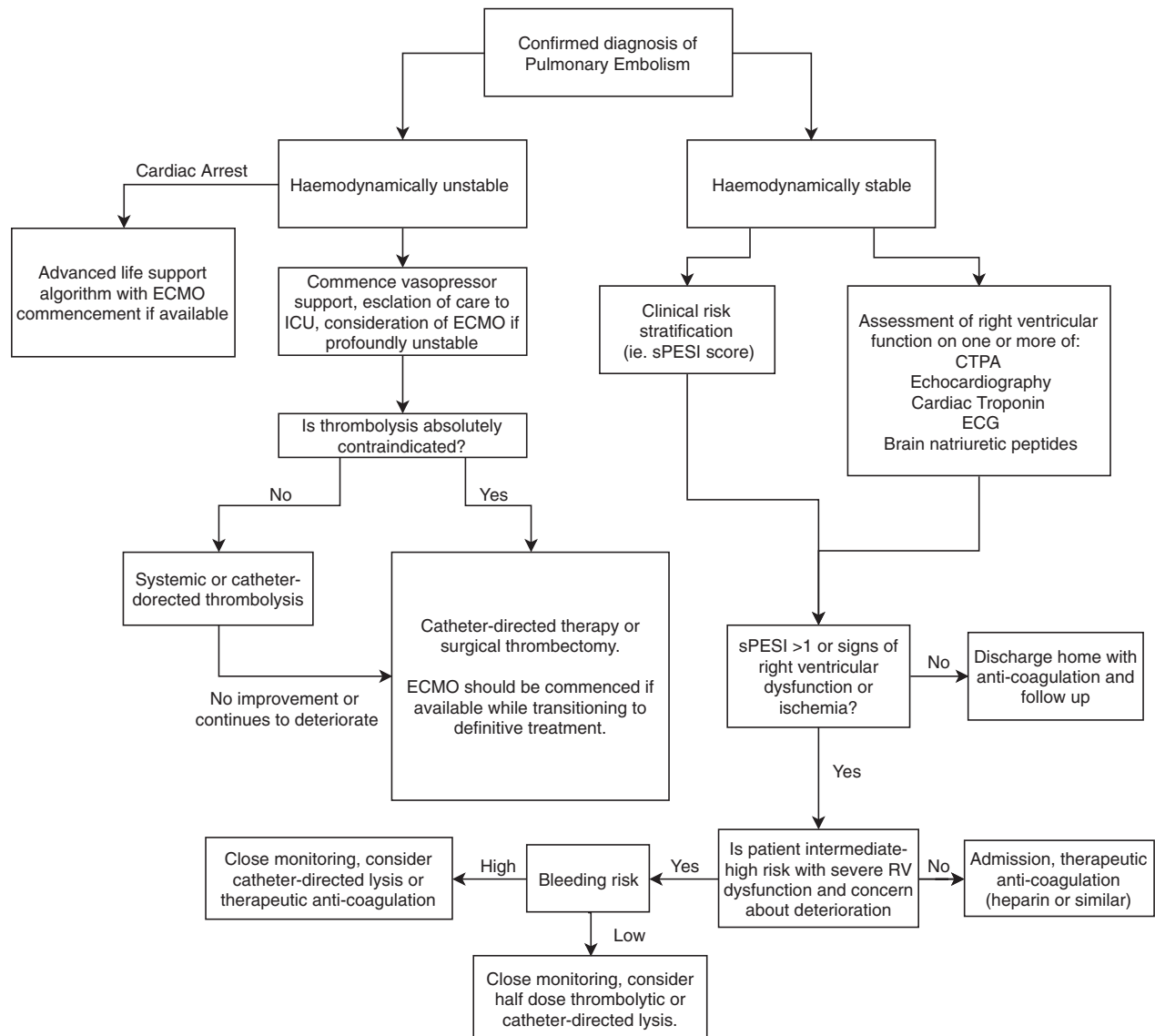


Figure 2 A suggested simplified management pathway for acute pulmonary embolism based on services available in most Australian hospitals.

and PE absent. These studies found the PE present (high probability) and PE absent (low/normal probability) categories to be 97.7% specific and 77.4% sensitive for acute PE. However, the non-diagnostic scans are an area of ongoing criticism. Evidence suggests that single photon emission computed tomography is superior in providing a diagnostic outcome compared with planar V/Q and is usually the preferred option of the two.^{5,18,36}

Low-risk patients

Evidence in low-risk patients supports a ‘rule out’ approach.^{5,23} D-dimer testing is recommended, with a meta-analysis reporting a 0.14% 3 month VTE incidence

in patients with a ‘non-high’ pre-test probability and a negative D-dimer.³⁷ The 2014 ESC guidelines concur that clinicians ‘...can exclude 30% of patients with suspected PE based on a negative (D-dimer) and low clinical probability’.⁵ Extensive studies^{37–42} found that 3 month VTE risk in low probability groups was between 0.0% and 0.4% (95% confidence interval (CI) 0.0–0.5). However, D-dimer, is non-specific with numerous other reasons for elevation such as age, cancer, pregnancy, recent surgery, concurrent infection and active bleeding. A more recent study has suggested use of an age-adjusted D-dimer, which resulted in a 5% absolute reduction in imaging of patients.⁴³ Additionally, in low-risk patients under 50 years of age, the PERC score

(Table 1) can be applied. If the PERC score is 0, the 45-day VTE incidence is reported at <1%.⁸ A 2013 meta-analysis further supported that PERC can confidently rule-out PE in low probability patients.²⁵

Predicting prognosis and stratification for management

The simplified PESI

After a diagnosis is made, high prognostic risk patients are identifiable by signs of shock and respiratory failure, but intermediate and low-risk patients are difficult to differentiate.⁴⁴ The three most sensitive CPS are the PESI, sPESI and ESC guideline risk stratification criteria, with sensitivities of 0.89, 0.92 and 0.88, respectively, with the sPESI (Table 1) as the most validated.^{5,45,46} A sPESI score = 0 ('low risk') has a reported 30-day mortality rate of 1.0–1.5%, while a score ≥ 1 ('high risk') is 10.7–10.9%, but can be over 20% in haemodynamically unstable patients.^{9,47,48} When determining from low- to intermediate-risk patients, the sPESI score alone appears superior to other markers of right heart dysfunction (i.e. cardiac troponin,⁴⁹ CTPA and electrocardiography (ECG)^{5,17,18}). There is good evidence that brain natriuretic peptide (BNP) further aids low risk determination.^{50,51} The utility of the sPESI is in its ability to assist in decisions to admit or discharge patients. A sPESI ≥ 1 indicates a need for admission, while a sPESI = 0 should prompt consideration of early discharge and outpatient management.^{44,52–56} The sPESI is a useful tool in decision-making, but it should not be the only factor considered when making early management choices.

Right heart strain on CT

The consensus of the international guidelines and more recent studies shows that signs of right heart dysfunction on CTPA are a negative prognostic indicator. Markers of increased pulmonary pressure such as RV dilatation, septal bowing or an increased RV/left ventricular (LV) ratio are findings that would warrant admission and commencement of anticoagulation therapy but there are some limitations in RV assessment.^{5,16–18,29,30} The benefit of RV assessment on CTPA is that most patients will undergo this investigation as part of their routine diagnostic work-up and calculation of a RV/LV ratio to >0.9 and >1.0 (respectively) has been shown to predict accurately in-hospital death and clinical deterioration in haemodynamically stable patients.^{50,57} While CTPA has a high negative and positive predictive value in patients with an intermediate or high pre-test probability, it is

limited in its dynamic cardiac assessment unless a gated study is performed.^{23,29,30} Furthermore, there is contradictory evidence that RV dilatation, one of the common parameters, is not significant in prognostic prediction.⁵⁸ As such, most patients will undergo a CTPA scan as part of their work-up and assessment of the RV is an important component of this investigation.

Echocardiography

Echocardiography imaging of the right heart is a quick, portable, safe and cost-effective investigation, but requires a substantial level of skill and training. TTE allows static and dynamic assessment of RV function, such as ventricle wall hypokinesis, which has been shown to be superior in specificity and equal in sensitivity compared with CTPA.^{31–33} Surrogate markers of pulmonary hypertension (i.e. RV free wall stain, end diastolic area and tricuspid regurgitation) on TTE also correlate with increased short- and long-term mortality.^{47,59,60} In haemodynamically stable patients, however, there has been conflicting evidence for its utility but increasing use nonetheless in identifying signs of right heart strain at initial presentation, to assess RV function.^{5,18,59} If present, patients will be classified at least intermediate-low risk with escalation to intermediate-high if myocardial ischaemia is present concurrently.^{5,16,18} The main limitation of TTE is poor inter-patient standardisation and limited utility when specific training is unavailable.^{5,18,59} Presence of right heart dysfunction at the time of diagnosis requires admission for further assessment with a follow-up study organised within 6 months to monitor for development of pulmonary hypertension and RV dysfunction.^{5,18,59,60}

High-sensitivity troponin

Major guidelines recommend high-sensitivity troponin in prognostic risk stratification.^{5,16–18} A meta-analysis reported an odds ratio of 5.24 for early mortality in patients with elevated troponin (both I and T).⁶¹ Furthermore, a sPESI = 0 and below cut-off high-sensitivity troponin T resulted in 0% 30-day mortality.⁶² Yet, there is limited prognostic value in normotensive patients, based on studies which showed no significance for prognostic prediction⁶³ and that the sPESI is superior in determining low-risk patients.⁴⁹ If a cardiac troponin level is available from the diagnostic work-up, it should be used as an adjunct to the sPESI score for prognostic stratification, but an additional test is not recommended.

Electrocardiogram

Findings of sinus tachycardia, S1Q3T3 patterns, right bundle branch blocks and ST segment elevation/depression are considered by the AHA guidelines in both prognosis and diagnosis.¹⁶ The ESC, ACP and ACCP guidelines employ these ECG changes in relation to diagnosis only.^{5,17,18} As such, ECG is recommended more as a diagnostic tool. Any signs of RV strain should prompt further investigation.

BNP and N-terminal prohormone of BNP

BNP and N-terminal prohormone of BNP (NT-proBNP) are recommended in ESC and AHA guidelines for differentiating of low and intermediate risk. ESC guidelines prefer troponin T/I over BNP/NT-proBNP in prognostic assessment due to a larger evidence base.^{5,16} Combining a sPESI score with BNP/NT-proBNP for early discharge decisions is recommended, due to a high sensitivity and negative predictive value.^{50,51} However, a sPESI = 0 appears sufficient if natriuretic peptide studies are unavailable. As such, natriuretic peptide biomarkers are recommended to assist low versus intermediate risk classification and should be used in determining patients suitable for early discharge and home management.

Management of aPE

Management of haemodynamically unstable patients

Haemodynamic instability has been defined as sustained hypotension (systolic blood pressure below 90 mmHg for 15 min) with evidence of shock or haemodynamic compromise.⁵

Thrombolytic management

Early administration of thrombolytic agents should be administered either systemically or by catheter-directed thrombolysis (CDT).^{5,18,64,65} Systemic thrombolysis does have absolute contraindications to consider (Table 2); however, it is currently recommended unless there is active and uncontrolled bleeding as the benefit outweighs the risks of intra- and extra-axial haemorrhage.^{16,18,26,64,66} Alternatively, CDT is also recommended if experienced clinicians are available to perform to procedure and the patient has a high bleeding risk or absolute contraindication to systemic thrombolysis. There is increasing evidence that CDT results in less episodes of major bleeding and haemorrhagic stroke compared with systemic treatment but it is not recommended over systemic thrombolysis.^{5,18,67–70}

Table 2 Absolute and relative contraindications to systemic thrombolysis^{5,16,18,64}

Absolute†	Relative‡
Major facial, brain or head trauma/injury within 3 weeks	Major trauma or surgery (excluding facial, brain, head) within 3 weeks
Previous intra-cranial haemorrhage	Transient ischaemic attack in the preceding 6 months
Ischaemic stroke in last 3 months	Pregnant or within 1 week post-partum
Active bleeding	Uncontrolled blood pressure of >180 mmHg systolic or >100 mmHg diastolic
Structural intra-cranial cerebrovascular disease or neoplasm	Ischaemic stroke greater than 3 months ago
Gastrointestinal bleeding within the last month	Currently anti-coagulated
Recent surgery encroaching on brain or spinal canal	Traumatic cardiopulmonary resuscitation
	Pericarditis or pericardial fluid
	Diabetic retinopathy
	Age >75 years
	Traumatic resuscitation
	Non-compressible puncture site

†Could cause life-threatening event. ‡Caution is advised, but indicated if benefit outweighs the risks.

Interventional and surgical techniques

Other catheter-directed techniques (i.e. fragmentation or rotational fragmentation) or surgical embolectomy are considered when thrombolysis (both systemic and catheter-directed) has failed or is contraindicated. Surgical embolectomy can be performed to the segmental level with a mortality rate of 20–30%.^{5,16,70} Long-term post-operative outcomes (including mortality and quality of life) appear to be favourable with a 96% survival rate at 4 years reported.^{5,16} Though there is some suggestion that inferior vena cava filters can be used acutely where thrombolysis is contraindicated their role is more in prophylaxis against future events.^{18,71,72}

Fluid administration

While convenient to administer as a treatment for hypotension, the administration of intravenous fluids in acute PE should be approached with caution. Rarely are these patients hypovolaemic, and volume expansion may have deleterious effects due to the nature of right ventricular (RV) pathology. Embolus within the pulmonary arteries causes increased RV afterload; this is exacerbated by pulmonary vasoconstriction resulting from hypoxia and hypercarbia, common in significant PE. Judicious intravenous fluid administration may augment RV pre-load, improving cardiac output in the face of this increased

afterload. It is important to remember, however, that the thin walled RV is easily distensible, particularly in the acute setting. In chronic pulmonary hypertensive conditions, remodelling and hypertrophy make the RV somewhat protected against over-distension in the face of volume challenge. Due to ventricular interdependence, a distended RV in acute PE will cause displacement of the interventricular septum towards the LV, particularly since reduced pulmonary blood flow may result in comparatively low filling pressures in the left side of the heart. This septal movement acutely reduces LV diastolic compliance, resulting in reduced LV preload.⁷³

This combination, of RV distension and LV compromise, can quickly precipitate a fatal spiral in acute PE. Increased RV wall tension with increased RV oxygen demand will worsen ventricular ischaemia, further reducing RV contractility, which will further reduce filling to the LV. This leads to overall reduced cardiac output, which in turn further reduces RV coronary perfusion pressure, and so on. Judging the appropriate amount of fluid administration is thus notoriously difficult in RV failure. Central venous pressure will be a poor guide to adequacy, as it will inevitably rise due to back-pressure in the failing right ventricle. It may be more helpful to use serial echocardiography to guide volume expansion, watching carefully for signs of RV distension and septal impingement of the left ventricle.

Vasoactive support

Patients will often require vasopressor support in addition to more definitive measures to restore RV function and maintain coronary perfusion.⁵ Escalation of care to an intensive care unit with close monitoring and multidisciplinary team care is required. Transport to a centre that can provide this level of support should be seriously considered if not available at the treating centre. Norepinephrine (noradrenaline) is often used to support blood pressure, due to its favourable vasoactive profile.⁷⁴ The combination of positive inotropy, systemic vasoconstriction and venoconstriction mildly improving pre-load, without marked pulmonary vasoconstriction, is desirable in the hypotensive patient with aPE. To augment cardiac output, positive inotropes may be required. Dobutamine, an inotrope active at beta receptors, has been shown to reduce pulmonary vascular resistance in patients with heart failure.⁷⁵ Similarly, milrinone (a selective phosphodiesterase inhibitor) is frequently chosen as an inotrope in patients with chronic pulmonary hypertension and/or cardiac failure, due to its combination of positive inotropy and pulmonary vasodilatation.⁷⁶ These properties make it a useful agent in augmenting cardiac output in aPE, but caution should be exercised due to the systemic

vasodilation that can occur (as with dobutamine) at higher doses. Theoretically, milrinone may require less cardiac work than dobutamine due to lesser increase in heart rate, and as such may be favourable in acute PE. There is also emerging interest in the new class of calcium sensitisers, such as levosimendan, that can augment cardiac output without commensurate increase in oxygen demand. Improvements in RV function have been demonstrated in patients with LV failure; however, their role in aPE is undefined.⁷⁷

Pulmonary vasodilators

Inhaled nitric oxide is a highly selective pulmonary dilator, due to its exceptionally short half-life. It effectively reduces RV afterload, mediated through direct pulmonary arterial dilation and also through improvements in gas exchange via pulmonary vasodilation in well ventilated lung units. It is effective in improving pulmonary haemodynamics and RV performance in acute RV failure.⁷⁸ The major advantage of nitric oxide is its absence of systemic haemodynamic effect, and thus can be used even in the profoundly shocked, hypotensive patient with acute PE without fear of precipitating cardiovascular collapse.

Mechanical support

In patients with profound haemodynamic instability or cardiac arrest (discussed below) venoarterial-extracorporeal membrane oxygenation (VA-ECMO) may be a temporary or bridging measure to restore tissue perfusion. VA-ECMO is also indicated for patients who fail to reperfuse after thrombolysis, have contraindications to immediate treatment or where diagnosis is uncertain.^{79,80} ECMO is only available in certain centres, and due to a significant risk profile (including infection, vascular complications and haemorrhage), it should be reserved for life-threatening cases of aPE as a rescue therapy.

Cardiac arrest in aPE

In an undifferentiated cardiac arrest, it is not recommended to give thrombolytic agents.¹⁶ All cardiac arrests should follow advanced life support algorithms with time to cardiac compressions minimised and timely investigations to rule in or out causes. Cardiac arrest in aPE may have a mortality rate as high as 95% with 90% of arrests occurring within 2 h of initial symptoms.⁸¹ In patients who fail to respond to early resuscitation interventions, ECMO can be initiated during cardiopulmonary resuscitation (CPR), but mortality rates remain high.^{5,80} Evidence of RV overload on TTE during CPR would be considered enough evidence to assume PE if other major

causes of arrest are adequately excluded.^{18,81} Evidence is poor in the management of this event but thrombolysis with prolonged CPR improves 24-h survival rate, survival to discharge and long-term neurological function but also a notable increase in risk of severe intra- and extra-axial bleeding.⁸²

Management of stable patients with evidence of right heart dysfunction

In haemodynamically stable patients with evidence of right heart dysfunction on imaging and/or myocardial ischaemia (intermediate-low risk if one factor present, intermediate-high risk if both present) thrombolysis is not generally recommended.^{5,16–18} The Pulmonary Embolism Thrombolysis (PEITHO) trial⁸³ found that thrombolysis significantly decreased all-cause death or haemodynamic collapse within 7 days (2.6% vs 5.6% in placebo group) but increased both intra-cranial and extra-cranial haemorrhage (by 2% and 5.1% respectively). Subsequent meta-analyses found that thrombolysis prevents clinical deterioration and may decrease all-cause mortality or recurrent PE.^{84–86} Furthermore, two of the analyses report no statistically significant increase in major bleeding,^{85,86} while one found a significant increase in major bleeding in patients over 65 years of age.⁸⁴ Current guideline recommendations are that the intermediate-risk group should receive aggressive anti-coagulation and not thrombolysis^{5,16,18} (Fig. 2). However, in patients at high risk of deterioration, severe RV dysfunction or worsening oxygenation there is evidence to support the use of early CDT,^{65,68,87} especially systems that are ultrasound-assisted.^{67,69} Another option in this group is half-dose tissue plasminogen activator, which decreased development of pulmonary hypertension with no significant complications.⁸⁸ Systemic thrombolysis is not recommended in this patient group by major guidelines^{5,16,18} (Fig. 2).

Anti-coagulation guidelines

Traditionally, PE has required admission to facilitate bridging from unfractionated heparin or low-molecular-weight heparin (LMWH) to a vitamin K antagonist (VKA). A minimum of 5 days bridging is required with daily monitoring of the international normalised ratio. The international normalised ratio must be between 2.0 and 3.0 for two consecutive days before concurrent heparin therapy can be ceased.^{5,18,89} However, the trials showing non-inferiority of DOAC to VKA^{13–15} have altered management guidelines in Australia, where rivaroxaban and apixaban are now listed on the Pharmaceutical Benefits Scheme. Rivaroxaban and apixaban

have a significantly lower bleeding risk when compared to VKA but currently have no direct reversal agent.^{5,18,90,91}

Current recommendations for anti-coagulation duration are separated by cause of VTE, such as (i) provoked by a transient risk factor (i.e. long haul flight or oral contraceptive pill); (ii) provoked by surgery; (iii) permanent risk factor (i.e. cancer); and (iv) unprovoked.^{5,16,18} Patients with surgery associated PE have a lower risk of recurrence than those provoked by non-operative and permanent risk factors.⁹² Furthermore, thrombophilia testing is not recommended when VTE is precipitated by a major transient risk factor.⁹³ Durations of treatment are summarised in Table 3.^{13–15,90,91,94–99} Indefinite, not necessarily meaning life-long, anticoagulation with rivaroxaban or apixaban significantly lowers recurrence rate with no increase in bleeding risk when compared to aspirin and placebo respectively. Though DOAC are superior to aspirin in recurrence prevention, indefinite aspirin is recommended in cases where DOAC are unsuitable.^{93,94,97} All patients must also have follow up organised, often including V/Q scan or echocardiography, to reassess clot burden and monitor for development of chronic thromboembolic pulmonary hypertension that may occur if thrombus resolution is not achieved.^{5,16,18}

Early discharge and outpatient management

Increasing admission rates for aPE, with estimates as high as a 237% since 1993¹⁰ and 80% between 1998 and 2006,¹² has put substantial strain on healthcare systems. However, development of early discharge guidelines in the last decade appears to provide a cost-effective and safe alternative. Two systematic reviews^{99,100} reported early discharge should be considered in patients with a sPESI = 0 and no sign of right heart strain. Subsequent studies found no significant difference between in-patient and out-patient mortality or recurrent VTE when appropriately selected as 'low risk'.^{53,54,56,101} The largest issue remains a lack of standardised criteria for determining low risk patients. A sPESI ≥1 and/or markers of right heart dysfunction should indicate at least intermediate-low risk and encourage admission.^{43,55,56} However, as discussed above, a sPESI = 0 is more accurate than cardiac troponin,⁴⁹ ECG and CTPA^{5,17,18} in determining low risk patients who would qualify for early discharge. In these cases, criteria to discharge early are (i) clinically stable with good cardiopulmonary function, (ii) no contraindications to anti-coagulation, (iii) competent and adherent to medication and (iv) early follow up organised.^{5,16,18,53–56} Safe outpatient management

Table 3 The recommended duration of anti-coagulation for pulmonary embolism based on risk factor contributing to venous thromboembolism (VTE) event

Risk factor classification	Example precipitant	Recommended duration	Recommended anti-coagulant	References
Provoked reversible (major, transient)	Orthopaedic surgery, trauma, intravascular catheter	3 months	Rivaroxaban, apixaban or warfarin	ESC guidelines, 2014 ⁵ ; AHA guidelines, 2011 ¹⁶ ; CHEST guidelines, 2016 ¹⁸ ;
Provoked reversible (non-major, transient)	Oral contraceptive pill, long haul flight, immobilisation, hormone replacement therapy, pregnancy	3 months minimum, but careful evaluation of the bleeding versus recurrence risk. Consider extension to 6 or 12 months (recurrence risk estimated at 5% at 12 months, 15% at 5 years)	Rivaroxaban, apixaban or warfarin	Choosing Wisely guidelines ⁷¹ ; Agnelli <i>et al.</i> , 2013 ⁹⁰ ; Couturaud <i>et al.</i> , 2015 ⁹⁵ ; Enea <i>et al.</i> , 2017 ⁹¹
Provoked irreversible	Cancer	Indefinite	Rivaroxaban, apixaban or warfarin (consider Aspirin after 3 months if anti-coagulation not appropriate)	ESC guidelines, 2014 ⁵ ; AHA guidelines, 2011 ¹⁶ ; CHEST guidelines, 2016 ¹⁸ ; Agnelli <i>et al.</i> , 2013 ⁹⁰ ; Becattini <i>et al.</i> , 2012 ⁹³ ;
Unprovoked	Unknown at time of diagnosis	Indefinite	Rivaroxaban, apixaban or warfarin (consider aspirin after 3 months if anti-coagulation not appropriate)	Brighton <i>et al.</i> , 2012 ⁹⁴ ; Couturaud <i>et al.</i> , 2015 ⁹⁵ ; Enea <i>et al.</i> , 2017 ⁹¹ ; Marik <i>et al.</i> , 2015 ⁹⁷ ; Weitz <i>et al.</i> , 2017 ⁹⁸
Recurrent or second VTE	Any precipitant previously listed	Indefinite	Rivaroxaban, apixaban or warfarin (consider aspirin after 3 months if anti-coagulation not appropriate)	

AHA, American Heart Association; DOAC, direct oral anti-coagulant; ESC, European Society of Cardiology.

requires that patients must be able to see or contact a clinician with knowledge of the condition and anti-coagulation regimen as apixaban and rivaroxaban change dosage during the initial treatment period (for apixaban this is 10 mg twice daily for 7 days and then 5 mg twice daily; for rivaroxaban this is 15 mg twice daily for 21 days and then 20 mg once daily).^{13–15}

Sub-segmental pulmonary emboli

Increasing sensitivity of CTPA is leading to more sub-segmental PE detection both incidentally and in diagnostic work-up. Current evidence suggests these patients should have bilateral lower-limb ultrasounds to identify any DVT and, if present, should be commenced on anti-coagulation. Furthermore, patients with risk factors for recurrent or progressive VTE (Table 3) or cardiorespiratory symptoms that cannot be otherwise explained by another condition should start anti-coagulation.^{5,11,18} In patients with none of the above, it is largely down to patient preference with no strong evidence either way. Regardless, these patients should be followed closely to monitor for any new

symptoms. Sub-segmental PEs are an area of uncertainty and further research into short- and long-term outcomes is needed before a clear recommendation can be made.^{18,102}

Conclusion

Presentation of an aPE is shown to have a substantial morbidity and mortality rate in both the short and long term. The development of CPS to assist diagnostic decision-making and prognostic stratification is facilitating safer admission and discharge decisions, but ultimately this decision still relies on radiology and other biochemical markers. Furthermore, with the advent of DOAC, a paradigm shift in management has occurred to facilitate early discharge and home management of patients at low risk of early mortality. While the last decade has provided great advances in diagnosis and management of PE, research into early discharge, markers and imaging of right heart strain and length of anti-coagulation leave the field ever evolving.

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