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Management dilemmas in acute pulmonary embolism

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ABSTRACT

Background Physicians treating acute pulmonary embolism (PE) are faced with difficult management decisions while specific guidance from recent guidelines may be absent.

Methods Fourteen clinical dilemmas were identified by physicians and haematologists with specific interests in acute and chronic PE. Current evidence was reviewed and a practical approach suggested.

Results Management dilemmas discussed include: submassive PE, PE following recent stroke or surgery, thrombolysis dosing and use in cardiac arrest, surgical or catheter-based therapy, failure to respond to initial thrombolysis, PE in pregnancy, right atrial thrombus, role of caval filter insertion, incidental and sub-segmental PE, differentiating acute from chronic PE, early discharge and novel oral anticoagulants.

Conclusion The suggested approaches are based on a review of the available evidence and guidelines and on our clinical experience. Management in an individual patient requires clinical assessment of risks and benefits and also depends on local availability of therapeutic interventions.

INTRODUCTION

Several guidelines on acute pulmonary embolism (PE) have been published.[1–3] Guidance for various scenarios which challenge physicians in the management of acute PE are often not easily accessible in guidelines. Our institution runs an integrated PE service between respiratory and haematology physicians and a large tertiary pulmonary hypertension service. We are not infrequently referred complex acute PE cases from other centres. In this review we discuss the most clinically challenging scenarios.

METHODS

Eight physicians with an interest in the management of acute and chronic pulmonary embolic disease compiled a list of 14 challenging clinical issues faced in their day-to-day practice. A PubMed search for each dilemma was performed, an initial review and suggested approach drafted followed by round-table discussion to achieve consensus regarding management. In many dilemmas, conclusions based on the available literature, were hampered by patient numbers and reporting bias. Suggested approaches were provided based on consensus.

DEFINITION OF PE SEVERITY

In the current paper we have adopted the American Heart Association (AHA) classification.[3] Massive PE is defined as sustained hypotension (systolic blood pressure <90 mm Hg) for >15 min secondary to acute PE or a requirement of inotropes or signs of shock. Submassive PE is defined by evidence of right ventricular (RV) dysfunction and/or evidence of myocardial necrosis. Patients with none of these features are defined as low-risk.

CLINICAL DILEMMAS

Which patients with submassive PE should I thrombolyse?

The pro–con debate published in this issue of *Thorax* highlights the controversy regarding systemic thrombolytics in normotensive patients with PE.[4 5] Clinical trials have demonstrated more rapid, immediate haemodynamic improvement and clot resolution following thrombolysis, but not clear mortality benefits.[6 7] Recent data from a large unselected national registry demonstrated that thrombolysis in normotensive patients with acute PE was associated with increased mortality.[8] Consideration for thrombolysis therefore requires risk stratification. Validated severity scoring systems, such as the PE Severity Index (PESI, table 1), can identify clinical features at the time of presentation associated with poorer outcome.[9] European Society of Cardiology (ESC) guidelines suggest assessing for RV dysfunction (using echocardiography, CT or B-type natriuretic peptide) or ischaemia (troponin) to aid risk stratification.[1] The presence of lower limb deep venous thrombosis (DVT) has also been associated with poorer survival.[10] By combining these factors it is possible to identify a higher risk population with 30-day mortality ≥20% (table 2).[11] A meta-analysis of randomised controlled trials (RCTs) of thrombolysis in massive and submassive PE published prior to 2004 reported a risk of major

Table 1 PE severity index (adapted from Aujesky *et al*[9])

Predictor	Points
Demographic	
Age, per year	Age, in years
Men	+10
Comorbidities	
Cancer	+30
Heart failure	+10
Chronic lung disease	+10
Clinical findings	
Pulse ≥110	+20
Systolic blood pressure <100 mm Hg	+30
Respiratory rate ≥30	+20
Temperature <36	+20
Altered mental status	+60
Saturations <90%	+20

Total points: ≤65 class I (very low risk), 66–85 class II (low risk), 86–105 class III (intermediate risk), 106–125 class IV (high risk), ≥126 class V (very high risk).

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Table 2 Clinical, laboratory and echo parameters predicting 30-day PE-related mortality in normotensive patients (adapted from Jimenez *et al*[11])

	PPV (%)
Trop	10.5
RVD	11.7
DVT	9.6
Trop and RVD	15.2
Trop and DVT	17.1
RVD and DVT	19.6
Trop, RVD and DVT	20.8
High-risk PESI, Trop and RVD	20.7
High-risk PESI, Trop and DVT	24.4
High-risk PESI, RVD and DVT	25.0

DVT, deep venous thrombosis on compression ultrasound; PESI, PE severity index; PPV, positive predictive value; RVD, right ventricular dysfunction on echocardiography; Trop, elevated troponin I.

bleeding of 9.1% and intracranial haemorrhage (ICH) of 0.5% while a recent large RCT of tenecteplase in submassive PE (PEITHO) observed rates of major bleeding of 6.3% and ICH of 2% (compared with 1.5% and 0.2% respectively for heparin alone).[12] Interestingly, bleeding risk was lower and mortality benefit higher in patients <75 years.

Suggested approach: In submassive PE we would not routinely administer thrombolysis. PESI score and the presence or absence of single or multiple poor prognostic factors should be balanced against factors associated with increased risk of bleeding (including age) in identifying suitable candidates for thrombolysis.

What is the risk of thrombolysis in a patient with recent surgery, previous stroke or intracranial space-occupying lesion?

Thrombolysis after recent surgery

We identified 25 reports, including 64 patients, thrombolysed (the majority for PE) following major recent surgery[13–37] (see online supplementary table S3). Major bleeding occurred 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 (ACCP) guidelines suggest that recent surgery (excluding recent brain or spinal surgery or trauma) is a relative contraindication and that the bleeding risk reduces significantly 2 weeks after surgery.

Thrombolysis in the presence of intracranial space-occupying lesions

A review of 12 patients with intracranial neoplasms thrombolysed for various indications identified ICH in a single patient (8.3%).[38] Guillan *et al*[39] identified five cases (five meningiomas, one cholesteatoma and one paranasal tumour) receiving systemic thrombolysis for stroke without complications. The risk of ICH is dependent on tumour type and localisation. A clinicopathological study showed the risk of microscopic and macroscopic spontaneous bleeding to be 50% in metastatic melanoma and ranging from 29.2% in oligodendroglioma to 2.8% in meningioma.[40]

Thrombolysis after recent ischaemic stroke

Previous ischaemic stroke within 3 or 6 months is a contraindication to thrombolysis in ACCP and ESC guidelines.[1 2] A study involving 145 patients with a stroke within 3 months who received thrombolysis for a further stroke did not show an increase in ICH rate.[41]

Suggested approach: In patients with a massive PE within 1 week of surgery we would favour mechanical treatment if available. Within 1–2 weeks following surgery, thrombolysis may be an acceptable risk depending on the nature of the surgery. In our opinion previous ischaemic stroke is not an absolute contraindication to thrombolysis but there are no data to guide an acceptable timescale since the stroke. Selected intracranial space-occupying lesions, for example meningiomas, would not influence our decision to thrombolyse.

A patient with an acute cerebral infarct is found to have an acute PE: what should I do regards anticoagulation?

Patients rarely present with a stroke and PE simultaneously due to paradoxical embolisation across a patent foramen ovale (PFO).[42 43] More frequently (1–10% of cases) patients may develop an acute PE following a stroke.[44] PE is the most common cause of death 2–4 weeks post stroke.[44] In the absence of anticoagulation, the majority of haemorrhagic transformation involves petechial bleeds with low risk of mass effect.[45–47] However, low and intermediate dose heparin early after stroke presentation is associated with an increased rate of haemorrhagic transformation.[48–50] Stroke guidelines advise delaying anticoagulation for 2 weeks post ischaemic stroke in patients with atrial fibrillation but give discordant advice regarding anticoagulation for coexisting PE. UK stroke guidance suggests anticoagulation for proximal DVT or PE while AHA guidelines do not recommend initial anticoagulation in patients with moderate to severe stroke.[51 52]

Suggested approach: The risk–benefit ratio for individual patients should be assessed; however, our general approach is to anticoagulate all patients with a cerebral infarct and PE. In patients with PE with a primary haemorrhagic stroke or recent significant haemorrhagic transformation we would consider inferior vena cava (IVC) filter insertion and delayed anticoagulation.

What is the optimal type and dose of thrombolytic agent and what should I do if a patient is already on low molecular weight heparin?

Thrombolytic agents for PE should be administered peripherally.[2] Several thrombolytic agents have been studied: urokinase, streptokinase and recombinant tissue plasminogen activators (alteplase, reteplase, desmoteplase and tenecteplase).[2 3] Alteplase is the most widely used thrombolytic agent for PE; recommended dosing in patients ≥65 kg is a loading bolus of 10 mg over 1–2 min followed by 90 mg infused over 2 h.[53] In patients <65 kg the total dose administered is 1.5 mg/kg; for example a patient weighing 60 kg should receive a 10 mg loading bolus followed by 80 mg over 2 h. In patients already receiving intravenous heparin we stop the infusion prior to administration of alteplase, check activated partial thromboplastin time (APTT) 2 h following completion of administration and restart heparin when the APTT ratio is <2× the upper limit of normal. If there is good clinical response to thrombolysis we would convert to low molecular weight heparin (LMWH) 24 h following thrombolysis. If therapeutic LMWH had been administered prior to thrombolysis we would usually start heparin infusion as above but delay commencement to 18 h following the last dose of LMWH if once-daily dosing and 8–10 h if twice-daily dosing had been used. Two RCTs have investigated the efficacy and side effects of half-dose alteplase in predominantly submassive PE.[54 55] Superior efficacy with no increase in bleeding risk was observed when compared with anticoagulation alone,[54] and equal efficacy with less haemorrhage was seen when compared with standard-dose anticoagulation.[55]

Suggested approach: If thrombolysis is indicated for PE we would administer a 10 mg bolus of alteplase followed by a further 90 mg over 2 h (up to a maximum of 1.5 mg/kg). If thrombolysis is indicated but there is a high risk of haemorrhage we would consider using a half-dose regimen.

Which patients in an arrest or peri-arrest situation should I consider thrombolysing in the absence of definitive radiological evidence of PE?

If PE is suspected clinically in an acutely deteriorating patient who is too unwell for CT pulmonary angiogram (CTPA) then echocardiography may identify signs of acute right heart strain suggestive of acute PE.[56 57] Thrombolysis can increase the return of spontaneous circulation and survival to discharge in patients with known or suspected PE who have cardiac arrest.[58–60] British Thoracic Society guidelines suggest a bolus dose of 50 mg alteplase in the peri-arrest or arrest situation.[61] Patients who have arrested and then regained circulation may also be suitable for emergency pulmonary embolectomy.[62] Patients in whom the cause of arrest is unclear should not receive thrombolysis during cardiopulmonary resuscitation.[2] A recent large RCT demonstrated that thrombolysis in out-of-hospital cardiac arrest when the cause of arrest is undifferentiated is not associated with significant mortality benefit.[63]

Suggested approach: Thrombolysis should be administered in the peri-arrest or arrest situation when PE is either known or suspected.

I feel it is too unsafe to perform thrombolysis: what are the surgical and non-surgical alternatives?

If thrombolytic therapy is contraindicated and a patient has significant accessible PE and persisting haemodynamic compromise then embolectomy, performed by an open surgical or catheter-based approach, should be considered.[1] Older case series observed mortality rates for surgical embolectomy of >20%;[3] however an intraoperative mortality of 6% was reported in 47 consecutive patients.[64] Catheter-directed therapies include mechanical disruption of thrombi by catheter, ultrasound or pressurised saline injection.[65] Suction may be used to perform thrombectomy or aspirate fragments of macerated emboli following other techniques. A recent meta-analysis observed 87% clinical success.[66] Local intra-clot thrombolytic was used in 67% of cases and was associated with superior clinical success, postulated due to increased thrombus surface area exposed to thrombolysis after fragmentation. Major complications of catheter-directed therapy including pulmonary artery rupture and massive haemoptysis were seen in 2.4% of cases while haemodynamic deterioration due to fragmented emboli was unpredictable.[66] Although the incidence of major bleeding in the meta-analysis was low (18 non-cerebral haemorrhages requiring transfusion and 1 intra-cerebral haemorrhage reported in 594 patients[66]) the absolute risk of bleeding related to intra-clot thrombolysis in an individual patient with a contraindication to systemic thrombolysis is not clear. There are few data comparing thrombolysis, surgical embolectomy and catheter-based intervention as primary treatment for massive PE. Current guidelines restrict surgical embolectomy to situations when thrombolysis has failed or is contraindicated.[1] Although there is increasing interest in the expansion of surgical embolectomy to the initial management of massive PE, randomised trial data are required.[62 64 67–70]

Suggested approach: No comparative data exist to guide primary management of massive PE in the presence of a strong contraindication to systemic thrombolysis. Management is dependent on local availability of cardiothoracic surgery and catheter-based therapy.

A patient with a recent acute PE fails to respond to initial therapy: what should I do?

If a patient with acute PE fails to respond to initial anticoagulation, with worsening cardiovascular instability and/or respiratory failure, then thrombolysis should be considered. In the MAPPET-3 study of submassive PE, delayed thrombolysis was performed in 23% of patients treated initially with heparin, with no difference in mortality compared with patients receiving up-front thrombolysis.[6] Although reperfusion is greater the earlier thrombolysis is given, benefit may be observed when administered up to 14 days from symptom onset.[71] Failure to improve following thrombolysis may be related to persistent thrombus, complications such as lung infarction or infection or existence of chronic clot. Reassessment with additional imaging may therefore be required. In the presence of persistent clot, repeat thrombolysis or mechanical therapy may be considered. A single centre retrospective study of treatment in failed thrombolysis demonstrated that mortality in patients receiving repeat thrombolysis was 38% compared with 7% in patients undergoing embolectomy, although bias in management approach cannot be excluded.[72] Supportive therapy for lung infarction may include ventilatory support, treatment of superadded infection and inotropic support. If underlying chronic thromboembolic disease is suspected, referral for pulmonary endartectomy and the use of bridging pulmonary vasodilator therapy should be considered. The role of pulmonary vasodilators in purely acute disease has also been assessed.[73] Inhaled nitric oxide may improve gas exchange in acute PE.[74 75] Limited data suggest possible benefit from nebulised iloprost [76 77] while a small RCT failed to demonstrate benefit from intravenous epoprostenol.[78] There are limited reports of benefit from sildenafil in animal models and humans with acute PE.[79]

Suggested approach: Thrombolysis should be considered when a patient initially treated with anticoagulation alone develops worsening cardiovascular instability or respiratory failure. Failure to improve following thrombolysis should trigger reassessment for residual clot or complication of PE. Surgical embolectomy is preferable to re-thrombolysis for persistent obstructing acute PE.

How should I manage a pregnant patient with significant PE?

In non-massive PE, therapeutic LMWH has been shown to be safe and effective at preventing recurrent PE and does not cross the placenta.[80] Warfarin administration is teratogenic in the first trimester but is also associated with neural abnormalities during any trimester and UK obstetric guidelines advise against its use during pregnancy.[81 82] If PE is within a month of the expected date of delivery then a retrievable IVC filter should be inserted. A recent review identified 189 pregnant patients receiving thrombolysis for venous thromboembolism (VTE); major bleeding occurred in 2.6% with no maternal mortality.[83] The peripartum period poses a challenge with greater risk of haemorrhage associated with thrombolysis. The use of mechanical disruption, lower-dose catheter-directed thrombolysis and surgical embolectomy has been described and is dependent on local availability.[30 84 85]

Suggested approach: Therapeutic LMWH is the anticoagulant of choice in pregnancy. Systemic thrombolysis should be administered for massive PE in pregnancy; however if bleeding risk is

high (eg, in the peripartum period) then surgical or mechanical methods are suggested, depending on local availability.

An echo demonstrates thrombus in the right atrium: what is the optimal management?

Right atrial thrombus occurs in 4–8% of patients with acute PE.[86–90] Two main types of thrombus have been described: type A has high early mortality and consists of long, thin, worm-like mobile thrombi associated with clinically severe PE.[91] Low cardiac output, higher pulmonary arterial pressure and more severe tricuspid regurgitation may slow transit of clot from peripheral veins to the pulmonary vasculature.[90] Type B consists of immobile, non-specific thrombi with absence of associated PE in 60% of cases and low early mortality. A small proportion of thrombi are intermediate in character (type C), being mobile but not worm-like in shape, and have the potential to obstruct right atrial or ventricular outflow.[91–93] CTPA is highly effective at identifying type A thrombi with a sensitivity of 100%, although false positives may be observed in patients with non-dilated right ventricles due to incomplete contrast filling.[89] The optimal management of patients with right atrial thrombus is unclear. Two-week mortality in 42 patients treated with heparin, thrombolysis or surgical embolectomy was equally poor (20–25%).[86] A systematic review of 177 cases observed lower mortality in patients receiving thrombolysis (11%) compared with anticoagulation (29%) and surgery (24%).[94] In a series of 16 consecutively thrombolysed patients, right atrial thrombus disappeared in all patients within 24 h with 30-day survival of 100%.[90] In a minority of patients thrombus may straddle a PFO leading to additional risk of systemic embolisation. A literature review of 88 such patients demonstrated similar mortality (14%) but higher incidence of stroke in patients treated with anticoagulation rather than surgical embolectomy.[95] Patients treated with thrombolysis had a much higher mortality (36%), although they had more haemodynamic compromise. AHA guidelines therefore recommend surgical embolectomy as the optimal treatment in this group.

Suggested approach: Thrombolysis is suggested for type A thrombus while type B thrombus may be treated with anticoagulation alone. Surgical embolectomy is suggested for thrombus straddling a PFO; if this is not available then anticoagulation alone is a reasonable approach unless thrombolysis is indicated due to the severity of the underlying PE. Surgical embolectomy is suggested for type C thrombus if the thrombus is extremely large and associated with risk of right atrial or ventricular outflow tract obstruction should it dislodge.

Which patients with acute PE may benefit from an IVC filter?

Retrievable IVC filter insertion in acute PE should be performed if anticoagulation is contraindicated or temporary cessation of anticoagulation within 1 month is envisaged. An RCT of IVC filter insertion involving 400 patients with proximal DVT receiving anticoagulation demonstrated a reduction in subsequent PE, counterbalanced by an increase in recurrent DVT with no effect on mortality.[96 97] ACCP guidelines recommend against IVC filter insertion in patients with PE receiving anticoagulation, although they recognise that there is uncertainty regarding the risk and benefits in patients with hypotension.[2] Retrospective analysis of data collected by the International Cooperative PE Registry found IVC filter insertion to be associated with a reduced 90-day mortality in the setting of massive PE, although only 10% of patients received IVC filters and two-thirds of patients did not receive thrombolysis.[98] A large RCT of retrievable IVC filter insertion in patients with PE and associated DVT (PREPIC-2) has recently been presented in abstract form.[99] No effect on recurrent PE, complications or mortality was observed.

Suggested approach: We generally limit IVC filter use in acute PTE to the small number of patients in whom anticoagulation is contraindicated. Routine placement of IVC filters in submassive PE and proximal DVT is not supported by current evidence. If possible we use retrievable filters, which should ideally be removed within the recommended time scale.

How can I differentiate between acute and chronic PE?

It is not infrequent to see patients with significant proximal chronic thromboembolic disease who have erroneously been thrombolysed. Several factors may suggest chronic rather than acute PE. Long duration of symptoms, a previous VTE, features of pulmonary hypertension on examination in the absence of systemic hypotension and or tachycardia and bilateral bruits due to stenoses (appreciated during breath hold on auscultation) favour a chronic process.[100] Electrocardiographic and echocardiographic changes indicating longstanding increased RV afterload include a dominant R wave in V1 with absence of tachycardia and a systolic pulmonary artery pressure >60 mm Hg on echocardiography (the RV cannot acutely generate a higher pressure).[101] McConnell's sign (RV free wall hypokinesis with preserved RV apical contraction) and the '60/60' sign (pulmonary acceleration time below 60 ms with a tricuspid gradient of 30–60 mm Hg on echocardiography) suggest acute rather than chronic PE.[56 57] An increased RV–LV ratio may be present in acute and chronic thromboembolic disease but the presence of RV hypertrophy and large bronchial arteries are suggestive of chronic disease.[102] Within the pulmonary arteries, mural calcified thrombus forming an obtuse angle with the vessel wall, completely stenosed and narrowed segmental vessels and signs of recanalisation with contrast flowing either side of 'webs' of organised thrombi are suggestive of chronic disease.[103] Within the parenchyma, peripheral wedge-shaped infarcts may be present in acute PE while a mosaic perfusion pattern with reduction in pulmonary arterial size in low attenuation areas of the lung suggests chronic disease.

Suggested approach: A chronic history, markedly elevated systolic pulmonary arterial pressures, RV and bronchial artery hypertrophy, thrombus calcification, webs and a mosaic perfusion pattern should raise suspicion of chronic rather than acute PE.

In which patients should I consider early discharge?

Clinical severity scoring systems have more clearly identified patients at low risk of complications from acute PE who may not require hospitalisation. PESI is the most widely validated scoring system and has been utilised in prospective randomised management studies to demonstrate the safety of such an approach, which may be appropriate in up to 40% of patients.[104 105 106] Outpatient management of PE generally requires LMWH administration during oral anticoagulant initiation,[105] although the introduction of oral factor Xa inhibitors provides the possibility of a more convenient ambulatory treatment for patients.[107 108] Safe early discharge of patients is dependent on a robust multidisciplinary approach involving rapid imaging, accurate assessment and adequate support and follow-up mechanisms for the discharged patient. Admission of patients at very low or low risk may still be advisable due to patient concern or ongoing pain. Repeat PESI scoring after 48 h in patients initially assessed as unsuitable for discharge may reclassify them as appropriate for outpatient anticoagulation.[109]

Suggested approach: Patients with a very low or low PESI score may be offered early discharge and outpatient anticoagulation but a robust system of support and follow-up is mandatory.

What is the role of the newer oral agents in the management of acute PE?

At the time of writing, rivaroxaban, a direct Xa inhibitor, is the only new oral anticoagulant (NOAC) licensed and approved for the treatment and secondary prevention of DVT and PE in the UK.[108] Other NOACs (dabigatran: a direct thrombin inhibitor; and apixaban and edoxaban: direct Xa inhibitors), however, have also been shown to be non-inferior to conventional anticoagulant therapy with favourable safety profiles in the treatment of patients with PE. In the dabigatran (RE-COVER)[110] and edoxaban (HOKUSAI)[111] studies, all patients initially received heparin for 10 and 7 days. The rivaroxaban (EINSTEIN-PE) and apixaban (AMPLIFY) studies excluded patients who had had more than 48 h of heparin, thus these therapies introduce the option of managing patients without parenteral anticoagulation.[112 113] Patients with active malignancy were excluded from these studies (LMWH remains the standard of care for these patients), and NOACs should not be used in pregnant or lactating women, or in patients with significant renal impairment. Importantly, no regular monitoring is required.

Suggested approach: Other NOACs may also become licensed in the future but currently rivaroxaban can be considered an option for the acute management of haemodynamically stable patients with PE within its product license.

What should I do about an incidental or isolated subsegmental PE?

Demonstration of unsuspected PE occurs in up to 5% of thoracic CT scans performed for non-PE indications, the majority in the context of malignancy.[114–118] In malignancy, most incidental PEs are lobar or segmental in distribution while VTE recurrence rate, mortality and complications are not significantly different between incidental and symptomatic PE.[119] The ACCP guidelines suggest asymptomatic PE should be treated as symptomatic PE.[2] Isolated subsegmental PEs are demonstrated in 1–5% of CTPAs performed for suspected PE and 10% of CTPAs with demonstrable PE.[114 120–122] Optimal management of these patients is unclear. Pooled data from 105 patients with predominantly isolated subsegmental PE with no evidence of DVT on serial imaging who did not receive anticoagulation found no patients with recurrent PE after 3 months.[120] The authors therefore suggested that the risk of haemorrhage may outweigh the benefit of anticoagulation in isolated PE, assuming negative serial compression ultrasound of lower limb veins.[120] This approach has been challenged by a large prospective study which found similar risk factors and recurrence rates in patients with symptomatic subsegmental versus more proximal PE, although it is unclear how many patients had a single subsegmental PE.[123]

Suggested approach: Incidental and isolated subsegmental PE should generally be managed in the same manner as symptomatic and non-subsegmental PE.

CONCLUSION

The suggested approaches are based on a review of the available evidence and guidelines and on our clinical experience. For many of the dilemmas the evidence base is not substantial and is potentially hampered by reporting bias. Management in an individual patient will require clinical assessment of risks and benefits and will also depend on local availability of therapeutic interventions.

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Thrombolysis for acute submassive pulmonary embolism: CON viewpoint

A John Simpson

The normotensive patient with confirmed pulmonary embolism (PE) and right ventricular (RV) dilatation presents a significant dilemma to clinicians. On one hand, a string of publications have demonstrated that RV dysfunction is associated with adverse outcomes in patients with PE;[1–5] on the other, thrombolysis carries a significant risk of bleeding.[6 7] However, evidence emerging in recent years has provided a strong case against using thrombolysis in this setting, greatly aiding clinical decision-making in submassive PE (taken here to mean confirmed PE in a normotensive patient with evidence of RV dilatation and/or RV dysfunction and/or pulmonary hypertension). The aim of this article is to review some of the most important data surrounding this debate.

The decision to administer systemic thrombolysis would be easier if submassive PE had a high mortality rate that was significantly reduced by treatment. However, this is not the case. In larger studies, inhospital or 30-day mortality for submassive PE treated without thrombolysis is typically between 1% and 5%,[3 8–11] though lower and higher rates have been described.[12–14] In the excellent, landmark randomised controlled trial (RCT) of thrombolysis versus heparin alone for submassive PE, mortality was 3.4% in the thrombolysed group and 2.2% in the 'heparin-alone' group.[8] The argument is commonly made that trials exclude elderly patients or patients with comorbidities, artificially reducing mortality rates. However, the large RIETE registry also suggests a 90-day mortality of around 3% in patients with submassive PE.[15] The problem for advocates of thrombolysis in PE is that it may be technically impossible to demonstrate beneficial effects on mortality. This is because an RCT comparing thrombolysis and standard treatment would require prohibitively large numbers of patients to generate sufficient statistical power to detect a clinically meaningful difference in mortality.

Faced with this problem, those who champion thrombolysis might argue first that RV dilatation (and particularly persistent RV dilatation)[16] is associated with a poor prognosis in PE,[1–5] and second that thrombolysis improves RV dynamics acutely.[17–20] Consequently, they may suggest we should thrombolyse patients who have sufficient thrombus load to generate RV dilatation. Again, however, there is very little evidence in submassive PE to support this contention. A crucial point is that RV dilatation is a dynamic process. A large study indicated that 93% of patients with submassive PE, treated without thrombolysis, had normal RV systolic pressure (assessed by echocardiography) 6 months after diagnosis.[10] The same study reported two inpatient deaths among 200 patients with submassive PE.[10]

The emerging picture is that, at the point of presentation, patients with submassive PE are highly likely to survive if treated with heparin alone and that the associated RV dilatation is likely to resolve spontaneously in the significant majority. The nagging doubt, of course, surrounds the small proportion of patients who will have persistent RV dysfunction, particularly as this group seems vulnerable to recurrent venous thromboembolism (VTE).[16] The decision to give thrombolysis would again be easier if, at the point of presentation, we had tools accurately identifying those patients in whom RV function will fail to improve. However, two problems arise. First, while biomarkers such as brain natriuretic peptide afford some additional information,[21–24] they do not yet provide anywhere near the level of prognostic accuracy on which to base the decision to thrombolyse.[25] Second, even if they did, we have no evidence to suggest that early thrombolysis could outperform existing treatment options for these patients. Extending this argument, the two major concerns in patients with persistent RV dysfunction are the higher rate of recurrent VTE in patients with residual thrombus load[16 26] and the development of chronic thromboembolic pulmonary hypertension (CTEPH).[27 28] However attractive it may be theoretically, we have no strong evidence to inform whether early thrombolysis can reduce VTE recurrence—we know that longer-term anticoagulation does.[29] Similarly, we have no evidence that early thrombolysis reduces the risk of CTEPH, yet modern treatments significantly improve outcomes for this important complication.[30 31] So, instead of early thrombolysis, why not repeat echocardiography at 3 months, prolong anticoagulation in those with persistent RV impairment and assess carefully for evidence of CTEPH in the ensuing period?

The theoretical argument against this approach might be the hypothesis that thrombolysis improves haemodynamics acutely and that a normally functioning RV might lead to fewer complications downstream. However, careful studies have shown that while thrombolysis improves RV dilatation more than heparin alone in the first 12 h, the benefits are lost by 48 h.[20] There is no evidence in submassive PE to suggest that the early haemodynamic improvements translate into benefits in terms of survival, VTE recurrence or development of CTEPH.[8] Where early thrombolysis does seem to benefit patients with submassive PE is in reducing the amount of supportive care (eg, blood pressure support) required in the early stages of admission to hospital.[8] However, again, at the point of presentation, we have no accurate way to predict which patients will require extra haemodynamic support, and the extra supportive care we can give obviates any excess mortality in patients who do not receive thrombolysis.

The arguments against thrombolysis above would matter less if the risks of bleeding associated with thrombolysis were acceptable. Registry data and data from existing RCTs suggest that in the specific setting of PE, thrombolysis is associated with major bleeding rates of

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10%–20%.[6 7 32 33] The great anxiety with thrombolysis clearly relates to major intracranial haemorrhage (ICH). The large ICOPER registry reported that 3% of patients receiving thrombolysis for PE developed ICH;[6] other studies report rates approximating to this value.[34] We must keep in mind that 30-day mortality in submassive PE (with or without thrombolysis) is around 3%. Data suggest that the risk of haemorrhage after thrombolysis for PE is greater in older patients and patients with cancer,[7] precisely the groups known to be at the highest risk of death from PE.[15] Other interesting evidence suggests that women may be at higher risk for thrombolysis-induced haemorrhage than men, while simultaneously having lesser haemodynamic benefits,[33] but this requires confirmation.

The arguments presented above are firmly against routine use of thrombolysis in submassive PE. They are in keeping with the conclusions of recent comprehensive international guidelines and meta-analyses which found no evidence to support thrombolysis in this setting.[35–37] However, in many ways the real question should be whether, as a profession, we improve outcomes for patients when we give thrombolysis in the 'real world'. Perhaps clinical experience and assessment at the bedside drive a beneficial use of thrombolysis that could be undetectable in trials or in strict study protocols? Two recent studies throw light on this issue. Data from the large RIETE registry suggest that we do use thrombolysis to advantage in hypotensive patients with PE.[38] However, interestingly, thrombolysis was associated with significantly increased mortality (odds ratio 2.32) among normotensive patients with symptomatic acute PE.[38] A further study from Pennsylvania provided additional interesting insights—not only did surprisingly few patients with PE receive thrombolysis, but mortality from thrombolysis was significantly increased among patients in whom indications for the treatment were the lowest.[39] While recognising inherent limitations in retrospective studies, and the fact that the latter study did not specifically analyse submassive PE, the inference seems to be that doctors appear reluctant (perhaps nervous) to give thrombolysis for PE and that inappropriate thrombolysis has important detrimental consequences.

We are left in a difficult and sobering position when faced with a patient with submassive PE. The evidence would suggest that your patient has around a 2%–3% chance of dying in hospital and you are highly unlikely to save his/her life in the acute phase by using thrombolysis. The RV dilatation is highly likely to resolve spontaneously. There is a chance of up to one in five that you will induce significant bleeding with thrombolysis, and a one in 30 chance that you will cause ICH. Results from the important, large and beautifully designed PEITHO trial of thrombolysis for normotensive patients with RV dysfunction have been eagerly awaited in the expectation that they will provide increased clarity in this debate.[40]

The literature currently cannot help with your anxieties that a very small proportion of patients with submassive PE will progress to recurrent VTE or CTEPH, and that at the point of presentation you cannot accurately predict who they will be. However, you at least know that you can monitor patients with submassive PE and that you have effective, proven therapeutic options for preventing recurrent PE and treating CTEPH.

The real problem of course (and part of the reason for having this important debate) is that we have no reliable and accurate tools to pinpoint the important minority of patients with submassive PE who genuinely might benefit from thrombolysis or perhaps from surgical embolectomy. Biomarkers and risk profiling are slowly leading us in the direction of this kind of stratified medicine, and this is a key area for future research. A further, very exciting prospect (as highlighted in the accompanying article (http://dx.doi.org/10.1136/thoraxjnl-2013-203413)) is whether low dose thrombolysis can impact on clinically important endpoints in submassive PE without the unacceptable risks of haemorrhage. The recent MOPETT trial offers some real hope in this regard, but will face the exceptionally difficult trial design issues inherent to demonstrating benefits in meaningful clinical endpoints.[41] In the meantime, the real risks of causing unintentional harm to our patients cast a forbidding shadow over the theoretical benefits of thrombolysis in submassive PE.

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Thrombolytic therapy for submassive pulmonary embolus? PRO viewpoint

Luke S Howard

If we had robust evidence one way or the other to inform us on the use of thrombolytics in submassive pulmonary embolus (PE), we would not need this debate. But, we do not and, so, we do. The stakes are considered high both in favour and against thromobolysing submassive PE, so we cannot brush the debate under the carpet while we await the evidence. It is accepted that high-risk/massive PE, defined as haemodynamic instability, merits aggressive treatment due to unacceptable mortality, which outweighs the risk of haemorrhage. At the other end of the spectrum, patients with low-risk PE do not, such that they may even be treated as outpatients.

This leaves a grey area in between. When faced with a patient with a large thrombus load with a right ventricle (RV) that is dilated and pressure-loaded, but who is normotensive, as the attending clinician, we know they are at increased risk of death and long-term complications, such as chronic thromboembolic pulmonary hypertension (CTEPH).[1 2] We may fall back on the Hippocratic Oath to '*first, do no harm*', but the fuller translation reads '*I will use treatments for the benefit of the ill in accordance with my ability and my judgment, but from what is to their harm and injustice I will keep them*'. Thus, rather than hide behind a lack of evidence, we must review what we have and come to a balanced decision, and justify it.

In proposing the argument that submassive PE should be treated with thrombolysis, we must first accept that direct mortality due to the PE itself, not confounding conditions, remains unacceptably high with anticoagulation alone. A more aggressive strategy is required. As long as the benefits of thrombolysis outweigh the risks, then thrombolysis offers the best currently available approach. When this is coupled with the further benefits of likely reduction in CTEPH, the case becomes even stronger.

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The American Heart Association (AHA)[3] has proposed a definition of submassive PE as either:

- RV dysfunction, defined as RV dilation on echocardiography or CT, systolic dysfunction on echocardiography, elevation of brain natiuretic peptide (BNP)/N-terminal pro BNP (NT-proBNP) or evidence of new RV strain on ECG; or
- myocardial necrosis, defined as elevation of troponin I or T.

These measures either alone or in combination have been shown in many studies to be associated with worse survival, but this definition itself has not been prospectively studied. Jimenez *et al*[4] collected data from 591 normotensive PE patients (those who had received thrombolysis at the physician's discretion were not included) and showed that there was a 10% overall mortality. Pulmonary embolism may often occur on the background of other serious medical conditions, which may themselves lead to death. In these cases, it is hard to see how thrombolysis could improve the outcome, but Jimenez *et al* demonstrated that the rate of PE death, as opposed to all cause death, was 6.7%. When some of the criteria for submassive PE were applied, the rate of PE-related mortality increased to 11% with a positive troponin, 12% with echocardiographic evidence of RV dysfunction and 10% with complete compression ultrasound evidence of deep vein thrombosis (DVT).

Presented with data such as these, we may ask why studies of thrombolysis have not shown improvement in mortality. The reasons may be twofold. The first is that patients recruited into studies may have less severe disease, either due to a looser definition of submassive PE or due to those with more severe signs of right heart dysfunction not being recruited at the physician's discretion in order they be thrombolysed outside the protocol. Looking at the largest trial to date of thrombolysis in submassive PE,[5] only 31% of patients in the standard treatment arm had RV dysfunction on echocardiography and the mortality rate in that same arm was just over 2%. Contrast this with >10% mortality in the study by Jimenez *et al*[4] if patients had one or more of RV dysfunction, positive troponin or DVT. The AHA document[3] pools all the randomised thrombolysis studies in PE up to 2011, and only one has more than 100 patients in each arm[5] and it is therefore also not surprising to appreciate that these studies will be underpowered to detect a significant reduction in mortality. The studies were performed in different categories of patients and over 40 years, making pooling difficult, although it is worth noting there was a 30% non-significant reduction in mortality in the patients receiving thrombolysis. We can perhaps therefore conclude that trials may be under-representative of the true mortality of submassive PE. Of interest, however, a study not included, due to later publication,[6] randomised only patients with documented RV dysfunction on echocardiography, thus enriching the population, and in this study there was a significant reduction in PE-related mortality with 6/35 patients dying in the heparin group and 0/37 dying in the thrombolysis group.

The second reason that trials so far may not have shown a reduction in mortality is that they allow for thrombolysis in the event of haemodynamic collapse. To capture this effect, studies often combine mortality with haemodynamic collapse to detect a treatment response.[5 7]

The authors of the AHA document suggest that since the mortality seen in trials for submassive PE is less than 3%, even with highly effective therapy reducing mortality by 30%, trials will be unsuccessful in proving a mortality benefit, and thus surrogate endpoints should be used.[3] Since we know that PE-related mortality is linked to RV dysfunction which in turn is largely caused by clot burden[2] (likely to be a combination of burden in the lung and leg veins, since DVT increases the risk of death[4]), two good possible surrogates for mortality are haemodynamics and clot resolution.

A recent randomised study of thrombolysis in 'moderate' pulmonary embolism measured systolic pulmonary artery pressure (sPAP) as estimated on echocardiography as its primary endpoint. Thrombolysis versus anticoagulation resulted in a significantly lower sPAP at 48 h. Showing this fall in sPAP at such an early time point is critical to its credibility as a surrogate for PE-related mortality. This has also been documented in several other studies.[3] If only patients with RV dysfunction are considered, thrombolysis improves early RV function and BNP compared with placebo.[6]

The rate of clot resolution over the first 24 h has been shown to change very little with heparin, whereas with thrombolysis,

there is a 30%–35% reduction in perfusion defect.[3] For patients with RV dysfunction, it is this early resolution of clot with thrombolysis which will prove to be beneficial in reducing early complications. One may also postulate that earlier resolution of DVT with thrombolysis may also improve outcomes, since further embolisation may be fatal. Of note, the study by Fasullo *et al*[6] showed a trend towards better DVT resolution in patients receiving thrombolysis, only just missing statistical significance. It will take a large and well-constructed trial with mortality comparable with real-life data in the placebo arm to show mortality benefit with thrombolysis; until that time, surrogate data strongly suggest thrombolysis directly reduces the risk factors for death.

In addition to early PE-related mortality, there are important long-term outcomes from PE, in particular CTEPH. While it may not be common in all comers with PE, 2%–4% of cases,[1] it is likely to be much more common in those patients who have had submassive PE. No study has been performed rigorously using right heart catheterisation to study the incidence of CTEPH postsubmassive PE, especially given the variation in definition. Nonetheless, despite its likely low incidence, in itself it carries a significant risk of death.[1] Even if amenable to surgical endarterectomy, this is a very major surgical operation with its own mortality (<5%) and morbidity.[8] The argument may be less persuasive than early mortality since the associations are less direct, but adds to the weight of the argument in favour of thrombolysis.

Many studies referenced in the AHA statement,[3] in particular those by Kline *et al*[9] and Fasullo *et al*,[6] show lower long-term pulmonary arterial pressures and better RV function in those who were treated upfront with thrombolysis. How much of the improvement in RV function relates to more rapid relief of RV afterload cannot be certain, but the lower pulmonary pressures would suggest better clot resolution, which in itself is associated with lower 6-month mortality.[10] Why anticoagulation fails to catch up with thrombolysis is not fully understood, but studies of plasmin-mediated cleavage of fibrin have demonstrated resistance to fibrinolysis in patients with CTEPH compared with those with acute PE.[11] Allowing endogenous clot lysis to take place 'passively' using heparin alone may not be sufficient therefore to prevent progression to CTEPH in some patients. Identifying these patients upfront is not currently possible, but those with acute pulmonary hypertension are at the greatest risk of CTEPH.[1] That many patients presenting with CTEPH have in the past received thrombolysis[12] is not relevant, since many of these patients will have suffered previously unresolved PE.

While there can be little doubt that thrombolysis leads to faster and possibly more complete clot resolution, it is the risk of serious bleeding, in particular intracranial haemorrhage, which causes reticence when considering thrombolysis. This is a real concern and should not be taken lightly, but what we must consider is the balance of benefit against risk. A recent very large registry study of nearly 16 000 patients with PE showed a non-significant trend towards increased bleeding-related mortality at 90 days in those who received thrombolytics.[13] While the mortality was nearly double in the thrombolysis group (1.16% vs 0.61%, p=0.16), in absolute terms the rate was very low. Given that the entire cardiac output transits through the lung, it has been argued that lower doses of thrombolytics could be used with equal efficacy. Two recent studies have done just this,[14 15] showing equivalent clot resolution and lower rates of bleeding, although the numbers remain small in comparison with large registry studies.

It is the intention of the PEITHO investigators that this debate is settled once and for all,[7] but for the reasons explained above, namely, lower overall than expected mortality and the use of rescue thrombolysis, the PE-related mortality signal may be watered down. Until the data provide a clear answer, we must use our judgement.

In summary, outcomes in patients with true submassive PE remain unacceptably high and thrombolysis has been shown to improve surrogate outcomes for mortality as well as long-term complications. The risks from thrombolysis are low, and when reduced doses are used, evidence so far suggests no decrease in benefit, but a further reduction in bleeding. The next patient you see with submassive PE will want you to act on your best judgement rather than hide behind a 'lack of evidence'.

Disclaimer The views expressed in this article do not necessarily represent the personal views or practice of the author, but have been written to stimulate debate.

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Thrombolysis for acute submassive pulmonary embolism: CON viewpoint

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Management dilemmas in acute pulmonary embolism

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