



Role of thrombolytics in the management of sub-massive pulmonary embolism

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Abstract

Introduction

Venous thromboembolism carries a high rate of in-hospital mortality, and pulmonary embolism is the third most common cause of cardiovascular death, with more than 600,000 cases occurring in the United States annually. The indications and use of thrombolytic therapy in the treatment of acute PE is highly controversial, especially regarding its use in the setting of sub-massive pulmonary embolism. This review discusses the risk stratification of patients with pulmonary embolism, outline prognostic factors, and discuss current recommendations and controversies regarding both systemic and catheter-directed thrombolytic use.

Conclusion

The use of thrombolysis, either catheter-directed or systemic, in sub-massive pulmonary embolism, remains controversial at this time.

Introduction

Venous thromboembolism (VTE) is responsible for up to 15 % of all in hospital deaths, and the annual incidence of pulmonary embolism (PE) is between 23 and 69 cases per 100,000¹. Pulmonary embolism is the third most common cause of cardiovascular death, and more than 600,000 cases occur in the United States annually².

The incidence increases exponentially with age, with the mean age at presentation of 62; PE affects men and women equally³. Patient-related risk

factors include age, previous VTE, active malignancy, underlying coagulopathy, smoking, and oral contraceptive usage.

Several circumstances increase the risk of PE including protracted immobility, major fracture, air travel, pregnancy, and chemotherapy⁴.

In patients with a PE, severity of presentation is generally related to the extent of embolism, degree of pulmonary artery obstruction, and the presence and severity of cardiopulmonary impairment⁵, as displayed on the CT images in figure 1 and figure 2. Approximately 5% of patients die of the initial PE or a PE in the subsequent 7 days⁶. The risk of death due to PE is estimated to be 70% if cardiopulmonary arrest occurs, but only 2% in patients who are not hypotensive⁷.

The use of thrombolytic therapy in the treatment of acute PE remains highly controversial and debated amongst clinicians.

Traditional teaching and current guidelines recommend thrombolysis when a pulmonary embolism causes cardiogenic shock or haemodynamic collapse. For an acute PE, studies have demonstrated thrombolytic therapy followed by heparin achieves more rapid resolution of thromboembolism compared with heparin alone⁸.

Thrombolytic agents are responsible for superior resolution of lung scan abnormalities and improvement of pulmonary vascular haemodynamics at 24 hours⁸.

However, there are presentations of acute PE outside of haemodynamic instability or cardiovascular collapse where a clinician might entertain thrombolysis administration, including severe hypoxemia, extensive clot burden, patent foramen ovale,

free floating atrial or ventricular thrombus and right ventricular (RV) dysfunction.

There is limited data regarding the use of thrombolysis in the setting of sub-massive pulmonary embolism. This review will discuss the risk stratification of patients with pulmonary embolism, evaluate prognostic factors, and discuss current data for thrombolytic use.

Discussion

Definition of Sub-massive Pulmonary Embolism

Once the diagnosis of acute PE has been established, the patient's risk of death should be stratified into either a low-risk, intermediate-risk (sub-massive) or high risk group, according to the presence of shock or RV dysfunction. No consensus exists on the exact definition of "intermediate-risk", as named by the European Society of Cardiology or "sub-massive", as named by the American Heart Association, PE to date⁹.

Current classification based on the European Society of Cardiology and American Heart Association define sub-massive or intermediate PE as a systolic blood pressure greater than 90 mm Hg but with echocardiographic evidence of RV dysfunction or pulmonary hypertension, or the presence of myocardial injury¹⁰.

RV dysfunction, as defined by the American Heart Association, can be defined either by evidence of RV dilation seen on echocardiography or CT, elevation of brain natriuretic peptide (BNP) greater than 90 pg/mL, elevation of N-terminal pro-BNP greater than 500 pg/mL, myocardial necrosis with troponin elevation, or specific electrocardiographic changes such as a new incomplete or complete

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right bundle-branch block, anteroseptal ST changes, or anteroseptal T wave inversion⁵. The presence of RV dysfunction is associated with a 2-fold increase in 90-day mortality¹¹.

Clinical presentation

The clinical presentation for acute pulmonary embolism is widely variable. Patients may present with haemodynamic compromise, severe dyspnoea, hypoxemia, syncope or cardiac arrest. However, some patients may be completely asymptomatic or present with minimal symptoms. In the Prospective Investigation of Pulmonary Embolism Diagnosis II (PIOPED II), the following frequencies of symptoms and signs were noted among patients with PE who did not have pre-existing cardiopulmonary disease: dyspnoea at rest or with exertion (73 %), pleuritic pain (44 %), calf or thigh pain (44 %), calf or thigh swelling (41 %), cough (34 %), >2-pillow orthopnoea (28 %), and wheezing (21%)¹². Physical examination may demonstrate tachypnoea, tachycardia, distended neck veins, right ventricular heave, or an accentuated pulmonic component of heart sounds¹².

Echocardiogram

Echocardiography has been shown to identify patients at increased risk of adverse events from acute PE in many studies. Echocardiography can also be used to further delineate patients without a massive PE into intermediate-risk PE or low-risk PE groups, as shown in figure 3¹³.

Echocardiographic signs of RV dysfunction include RV dilatation (RV end diastolic dimension >30 mm), interventricular septal flattening with paradoxical motion, increased RV/LV ratio greater than 0.9, RV hypokinesis, pulmonary arterial pressures greater than 30mm Hg, and increased tricuspid regurgitation jet velocity greater than 2.6 m/s¹⁴.

Global RV dysfunction occurs in patients with moderate or severe outflow obstruction, defined by perfusion defects of 25 % or more¹⁴.



Figure 1: Axial contrast enhanced computed tomography showing bilateral endoluminal thrombus within the right and left pulmonary arteries and at the bifurcation (Blue arrows). PA = Trunk of Pulmonary Artery.

Laboratory

Biomarkers, including serum troponin I or T and BNP, may be useful in detecting RV dysfunction in patients with acute PE¹⁵. Troponin levels are increased secondary to increased RV wall tension, reduced right coronary artery flow, increased RV myocardial oxygen demand, RV myocardial ischemia and subsequent leakage of these enzymes from the RV myocytes into the bloodstream¹⁶. Elevated natriuretic peptides, including BNP and N-terminal pro-BNP, have been shown to be predictive of adverse short-term outcomes in acute PE⁵.

BNP is released from the RV in response to increased pressure and stretch and has been shown to correlate with the presence of RV dysfunction¹⁷. These biomarkers have high negative predictive values but low positive predictive values, such that low levels predict low risk of adverse outcomes, but elevated levels alone do not dictate the need for aggressive early treatment other than anticoagulation therapy¹⁸.

Prognostic scores

Once a patient is diagnosed with having an acute PE, several prognostic markers can be used to stratify



Figure 2: Coronal contrast enhanced computed tomography showing large occlusive endoluminal thrombus within the right pulmonary artery. Ao = Thoracic Aorta.

Table 1: Components of the Pulmonary Embolism Severity Index (PESI).

Simplified PESI (Pulmonary Embolism Severity Index)	
Age > 80	History of Cancer
History of Chronic Cardiopulmonary Disease	Heart Rate > 110
Systolic Blood Pressure < 100 mm Hg	Oxygen Saturation < 90%

patients into the appropriate risk group. The presence of haemodynamic collapse or shock, RV dysfunction, and

myocardial injury place patients at a higher risk for PE-related mortality. The Pulmonary Embolism Severity Index (PESI) and the simplified PESI (sPESI) can predict 30 day mortality by categorizing patients into 5 classes based on risk factors and presentation¹⁹.

The original PESI obtained a total point score by adding the patient's age to the points assigned to each of ten variables: male sex (+10 points), history of cancer (+30 points), heart failure (+10 points), chronic lung disease (+10 points), pulse ≥ 110 bpm (+20 points), systolic blood pressure < 100 mmHg (+30 points), respiratory rate ≥ 30 breaths per minute (+20 points), temperature < 36 degrees C (+20 points), altered mental status (+60 points), and arterial oxygen saturation < 90 percent (+20 points).²⁰ The total point score categorizes the patient according to his or her risk for mortality. The sPESI and components are shown in table 1 and table 2.

Systemic Thrombolysis

For small to sub-massive embolic events with relative haemodynamic stability, the treatment of choice is standard anticoagulation, including low-molecular-weight heparin, unfractionated heparin, factor Xa inhibitors, and direct thrombin antagonists. These agents are passive in that they allow for the natural degradation of the thrombus and prevent recurrent thromboembolic events.

Fibrinolytic medications, such as tissue plasminogen activator (tPA), urokinase, streptokinase, and tenecteplase, lead to thrombus degradation through enzymatic conversion of plasminogen into plasmin, leading to the cleavage of fibrin and thrombus dissociation. These agents may speed the resolution of right ventricular outflow compromise and accelerate restoration of haemodynamic stability compared with the use of standard anticoagulation alone. For patients with PE-related haemodynamic instability and no contraindications,

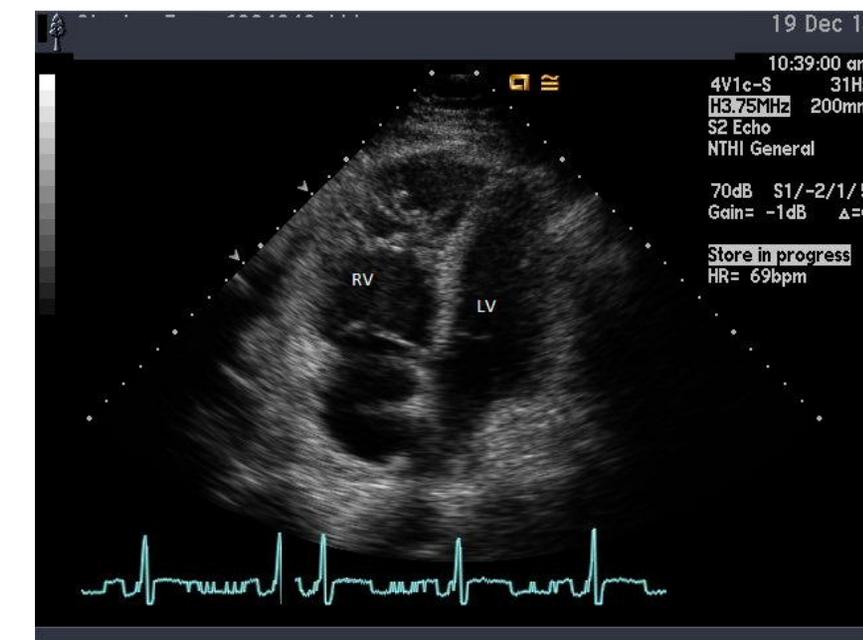


Figure 3: Apical four chamber view of a patient with acute sub-massive pulmonary embolism with right ventricular enlargement greater than left ventricular size. RV = Right ventricle. LV = left ventricle.

Table 2: A simplified Pulmonary Embolism Severity Index was created due to complexity and difficulty assessing the clinical situation. This score assigns one point for each of the following variables: age > 80 years, a history of cancer, chronic cardiopulmonary disease, a heart rate ≥ 110 beats per minute, a systolic blood pressure < 100 mmHg, and an SpO₂ saturation < 90 percent.

Risk Class	PESI Score (sum of points)	30 Day Mortality Rate
I	< 65	0-1.6%
II	66-85	1.7%-3.5%
III	86-105	3.2%-7.1%
IV	106-125	4.0%-11.4%
V	> 125	10.0%-24.5%

Table 3: This is a description of relative and absolute contraindications to the use of systemic thrombolytic medications.

Absolute Contraindications to Thrombolysis	Relative Contraindications to Thrombolysis
Suspected Abdominal Aortic Aneurysm	Age Greater than 75
History of Intracranial Hemorrhage	Current use of Anticoagulation Therapy
Known Structural Intracranial Disease	Non-compressible Vascular Puncture Site
Known Malignant Intracranial Neoplasm	Pregnancy
Cerebrovascular Accident within 3 Months	Cardiopulmonary Resuscitation Greater than 10 Minutes
Duration Active Hemorrhage Recent Internal Hemorrhage	Recent Surgery on the Brain or Spinal Canal
History of Severe or Uncontrolled Hypertension	Recent Closed Head Trauma
Dementia	Recent Facial Trauma with Fracture
Cerebrovascular Accident Beyond 3 months	Recent Cerebral Injury

thrombolytics have been shown to improve outcomes²¹. The use of systemic thrombolytic therapy in sub-massive pulmonary embolism is controversial. Thrombolytics should be given within the first 48 hours of presentation; however, there may be some benefit of use within a time span of two weeks^{22,23}. There are significant risks pertaining to the use of thrombolytics, thus requiring the clinician to be cognizant of the

absolute and relative contraindications of systemic thrombolytic therapy, which are displayed in table 3²⁴. Recent surgical procedures, depending on the site, and recent minor injuries are not necessarily barriers to administering thrombolytics.

Clinical Studies

In their randomized, multicentre, controlled trial, Wang et al., evaluated the efficacy and safety of low dose tPA

(50mg delivered over two hours) regimen against a standard regimen of 100mg delivered over two hours²⁵.

They enrolled 118 patients with acute pulmonary embolism with either haemodynamic instability or massive thrombus burden. Study endpoints included echocardiographic evidence of improvement of right ventricular dysfunction, improvement of lung perfusion defects on perfusion lung scans, and improvement in overall thrombus burden on CT angiogram. No significant difference was identified in overall efficacy or recurrent embolic event between the 50mg versus the 100mg dose regimens of tPA. There were 3 patient deaths (6%) in the high dose group and one (2%) in the low dose group.

Total haemorrhage prevalence and frequency of major haemorrhagic events was elevated in the 100mg group (32% and 10%) in comparison to the 50mg group (17% and 10%) but was statistically insignificant. When adjusted for a BMI less than 24 kg/m², there was a significantly lower total number of haemorrhagic episodes in the low dose group. A major limitation of this study is the small sample size, limiting the powering of the study for efficacy and safety.

Zhang et al. performed a systematic review and meta-analysis assessing the efficacy and safety of low dose recombinant tissue-type plasminogen activator (rt-PA) in the treatment of acute pulmonary embolism²⁶. Five studies were included in their analysis for a total of 440 patients. Three studies compared low dose rt-PA (0.6mg/kg, maximum 50mg or 50mg infusion over two hours) with standard dose (100mg infusion over two hours). Two studies compared low dose (0.6mg/kg, maximum 50mg over a 2 minute bolus or 10mg bolus with 40mg provided over 2 hours) with heparin. In comparison to heparin therapy, low dose rt-PA appeared to promote faster thrombus resolution without concomitant rise in major haemorrhagic events.

In comparison to standard rt-PA regimen, the reduced dose therapies did not demonstrate inferiority in efficacy in attaining improved haemodynamics, and had a more favourable haemorrhagic event profile than standard dose therapy. These results suggest a reduced rt-PA dosage may provide a feasible alternative for patients with acute pulmonary embolism.

Another study retrospectively evaluated 46 well matched patients with the diagnosis of massive or submassive venous thromboembolism who received thrombolytic therapy²⁷. Twenty-three patients were treated with 50mg of recombinant tissue plasminogen activator (rt-PA) per hour and 23 patients received 100mg rt-PA every two hours. Prior to and within the 24 hours following therapy, both groups were evaluated with echocardiogram. They determined findings of recovery from embolic event, as inferred from vital symptoms, right ventricular size, and systolic pulmonary artery pressure to be statistically insignificant between the two groups.

Sharifi et al. evaluated "safe-dose" thrombolysis with concurrent use of Rivaroxaban for treatment of moderate to severe pulmonary embolism²⁸. This study included 98 patients with symptomatic pulmonary embolism, receiving unfractionated heparin for 24 hours. "Safe-dose" thrombolysis was administered as 50mg total of tPA, 10mg bolus over one minute, followed by an infusion of the remaining 40mg over two hours. Heparin was given during the tPA infusion and for a 3 hour post infusion period, and then was discontinued and the patients were given rivaroxaban at a dose based on creatinine clearance.

Patients were evaluated for improvement in pulmonary artery systolic pressure before and after thrombolysis. In patients receiving rivaroxaban therapy, there was no in-hospital mortality, major or minor haemorrhagic events, or recurrent VTE, and there was a statistically

significant improvement in the mean pulmonary artery systolic pressure (mPASP).

The TOPCOAT trial evaluated whether the use of tenecteplase improved patient outcomes in the treatment of submassive pulmonary embolism²⁹.

The TOPCOAT study enrolled 87 normotensive patients from 8 medical facilities. The patients enrolled had evidence of RV strain and were randomized to receive either tenecteplase or placebo. Every patient received low molecular-weight heparin with subsequent double-blind randomization into an arm that received either placebo or a single weight based bolus of tenecteplase. The trial endpoints were death, circulatory shock requiring vasopressor support, and functional capacity after 90 days using the health quality outcomes metric SF-36. They found patients randomized to the placebo arm had a greater likelihood of reporting a more negative composite health outcome than patients randomized to tenecteplase. Patients treated with tenecteplase required less time in an intensive care unit, overall hospital time, and had no increase in adverse events. There was no difference in frequency of right ventricular dilation or hypokinesia between placebo or treatment arms at 90 day follow up. Three patients in the placebo arm had an adverse outcome within 5 days including 1 death directly attributed to pulmonary embolism related cardiac arrest. One patient treated with tenecteplase died from intracranial haemorrhage.

The Moderate Pulmonary Embolism Treated with Thrombolysis (MOPETT) trial, a prospective randomized study designed to evaluate the role of "safe-dose" thrombolysis in the reduction of pulmonary artery pressure following a moderate PE, was recently published. In this study, a moderate PE was defined as the presence of signs and symptoms of PE plus computed tomographic pulmonary angiography demonstrating >70% involvement with thrombus in ≥ 2 lobar or left or right main pulmonary arteries or by a high

probability ventilation/perfusion scan showing ventilation/perfusion mismatch in ≥ 2 lobes³⁰. Sixty-one of the 121 patients who initially presented were randomized to receive a “safe-dose” of tPA, which was approximately half the standard thrombolytic dose. They also received concomitant anticoagulation with reduced doses of enoxaparin or heparin. The control group received anticoagulation alone. The primary end points consisted of pulmonary hypertension and the composite end point of pulmonary hypertension and recurrent PE at 28 months. Secondary endpoints of the study were total mortality, the duration of hospital stay, bleeding at the index hospitalization, recurrent PE, and the combination of mortality and recurrent PE³⁰.

Pulmonary hypertension at 28 months occurred in 16% of the patients in the thrombolysis group versus 57% in the control group. There was also a lower pulmonary artery systolic pressure at 28 months along with faster resolution of pulmonary hypertension. Overall, there were no episodes of major bleeding in either group.

In his critique of the MOPETT Trial, Dr. Sehgal identified that the MOPETT investigators reported an increased incidence of pulmonary hypertension of 57% in their control group at 28 month follow up³¹. Their contention is that the increased incidence of pulmonary hypertension is potentially due to inadequate anticoagulation during and following hospitalization, as well as effect of underlying cardiopulmonary disease.

Co-morbid cardiopulmonary disease was reportedly similar in the two trial arms; however, the degree and type of disease, as well as overall severity were not reported. Of note, the MOPETT investigators did not identify the prevalence of coexisting left ventricular diastolic dysfunction, which also may have played a role in the development of pulmonary hypertension.

The MOPETT investigators, through a response rendered by Dr. Sharifi, countered by stating the calculation used to determine pulmonary artery systolic pressure (PASP) had a higher pressure value assignment for the right atrial pressure, thus elevating the PASP. The authors indicated that the PASP values as identified by the study were clustered around the 40mmHg cut off point for determination of pulmonary hypertension; if a higher value would have been chosen, the number of individuals with pulmonary hypertension would have been reduced. Dr. Sharifi also contends that the patients in both arms were adequately anticoagulated during the study term. The end result is the reduction in PASP by midterm follow up is greater in patients receiving thrombolysis.

The PEITHO Trial embarked upon a randomized, prospective, multicentre, double-blinded study of 1006 patients receiving thrombolysis with tenecteplase. The patients were haemodynamically stable with confirmed pulmonary embolism, abnormal appearing right ventricle on echocardiography or computed tomography, and a positive troponin result³².

Patients assigned to the treatment arm received a single weight based intravenous bolus of tenecteplase, given over 5 to 10 seconds, with dose ranging between 30-50mg based on weight. All-cause mortality within seven days of randomization and haemodynamic collapse were improved in the treatment arm (n=13, 2.6% and n=8, 1.6%) versus placebo (n=28, 5.6% and n=25, 5.0%). Non-intracranial haemorrhagic events were found to be significantly greater in the treatment arm (n=32, 6.3% and n=6, 1.5%), and the number of patients with cerebrovascular accidents was significantly greater in the tenecteplase arm than placebo (n=12, 2.4% and n=1, 0.2%). Interestingly, all-cause mortality at 30 days for tenecteplase (n=12, 2.4%) and placebo (n=16, 3.2%) respectively

was statistically insignificant. The PEITHO Trial was not appropriately powered to detect appreciable differences in mortality; however, death occurred relatively infrequently in the two groups.

As reported by the statistics, the primary outcome of early death or haemodynamic decompensation was reduced following therapy with tenecteplase; however, a significant increase in risk of intracranial (2.0%) and other major haemorrhagic events necessitates caution when considering thrombolytic therapy in haemodynamically stable patients with pulmonary embolism.

Catheter-Directed Thrombolysis

Another consideration in the management of sub-massive pulmonary embolism is catheter-directed thrombolysis (CDT), including local application of thrombolytic agents. CDT involves the administration of fibrinolytic agents directly to a pulmonary embolism via a centrally placed catheter. This technique may also include mechanical thrombolysis and aspiration, and is typically most successful when applied to central thrombi within five days of symptom onset³³.

One feature of CDT that may render it superior to systemic thrombolysis is a reduced risk of haemorrhagic complication. As compared to systemic thrombolysis which has an associated major haemorrhage risk of 20%³⁴, CDT techniques are associated with major complications in 2.4% of cases in patients with massive pulmonary embolism³⁵.

The lower risk of haemorrhagic complication is secondary to the lower dose of thrombolytics required for catheter-directed interventions compared with systemic use³⁶.

The majority of studies regarding CDT for pulmonary embolism involve patients with life-threatening haemodynamic instability or shock due to thromboembolism, and limited data on the use of CDT in patients with sub-massive pulmonary embolism.

One particular study evaluated the efficacy of manual aspiration of pulmonary emboli using a guide catheter with subsequent placement of a thrombolysis catheter and a directed bolus of urokinase followed by a continuous infusion of urokinase for at least 24 hours³⁷. This study evaluated 63 patients with pulmonary emboli, 46 of which had sub-massive embolism. Of this cohort, 5 patients died, and nine patients had major bleeding. 49 of the 63 patients had repeat catheterization, which showed a decreased in pulmonary artery pressure and right ventricular pressures compared to presentation.

Another study evaluated use of the AngioJet catheter to remove the thrombus by Bernoulli effect followed by regional thrombolysis using tPA 0.6 mg/kg over 15 minutes in 51 patients with acute pulmonary embolism. 29 patients had sub-massive pulmonary embolism and 22 patients had massive pulmonary embolism³⁸. Technical success was achieved in 92.2% of cases, with significant improvement in obstruction and perfusion index in all patients, including those with sub-massive embolisms. Major bleeding occurred in 7.8% of patients, with an in-hospital mortality of 15.7%.

The ULTIMA Trial, a multicentre randomized controlled trial, assessed whether ultrasound-assisted catheter-directed thrombolysis (USAT) is superior to anticoagulation in the reversal of right ventricular dilation in intermediate-risk patients with known PE³⁹. USAT is a therapeutic modality that combines conventional CDT with high frequency (2.2 MHz), low power (0.5 W per element) ultrasound. The ultrasound is incapable of thrombus dissolution alone; however, it induces reversible disaggregation and separation of un-cross-linked fibrin fibres, thereby increasing thrombus permeability for thrombolytic medications. Fifty-nine patients were enrolled with acute main or lower lobe pulmonary embolism with echocardiographic determination of a right to left

ventricular dimension (RV/LV) ratio of greater than 1. They were randomized to receive unfractionated heparin and an USAT regimen of 10 to 20mg rt-PA over fifteen hours (n = 30) or unfractionated heparin alone (n = 29). The primary outcome evaluated was the difference in the (RV/LV) ratio from baseline to 24 hours.

In the USAT group, there was a significant improvement in the (RV/LV) ratio at 24 hours. Reductions in the pulmonary artery systolic pressure, pulmonary artery mean pressure, cardiac index, mean right atrial pressure, and pulmonary artery diastolic pressures were found to be statistically significant. No significant differences were identified in length of hospital stay, and at 90 days there were no episodes of haemodynamic compromise, recurrent venous thromboembolism, or major haemorrhagic events. The authors acknowledge that as a study, the limited subject enrolment in the ULTIMA Trial does not provide enough information to formulate conclusions about the safety and efficacy of USAT in comparison to anticoagulation alone.

The most recent guidelines from the American College of Chest Physicians suggest that catheter-directed thrombolysis be pursued in patients with acute pulmonary embolism and hypotension when “there is a contraindication to thrombolysis, failed thrombolysis or the patient has shock that is likely to result in death before systemic thrombolysis can take effect.”⁴⁰ No mention is made in the guidelines regarding its utility in sub-massive pulmonary embolism. Inferring from data regarding massive pulmonary embolisms, CDT can be considered as safe if not safer than systemic thrombolytics, but whether it improves outcomes over systemic anticoagulation alone remains unclear.

Conclusion

The use of thrombolytic therapy in the setting of sub-massive PE remains

subject to a substantial amount of debate and clinical judgment, which varies from clinician to clinician. The ability to risk-stratify patients based on their risk of in-hospital death aids in determining which therapies are appropriate for the treatment of PE, but the setting of sub-massive pulmonary embolism presents particular challenges due to the paucity of data on the subject. Current data suggests that reduced or “safe-dose” thrombolysis is equivalent to standard dosing.

Any dose of thrombolysis will increase the risk of major haemorrhage over anticoagulation alone, and may not guarantee an appreciable mortality benefit.

The decision of whether to utilize systemic versus catheter-directed thrombolysis further complicates the issue, as there is limited data to guide the clinician. Based on data obtained in the setting of massive pulmonary embolism, it would appear that the use of catheter-directed thrombolytics is at least as effective and likely safer than the use of systemic therapy. However, further specific research is necessary in the area to guide clinicians in the future.

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