

DISCLAIMER: These guidelines were prepared by the Department of Surgical Education, Orlando Regional Medical Center. They are intended to serve as a general statement regarding appropriate patient care practices based upon the available medical literature and clinical expertise at the time of development. They should not be considered to be accepted protocol or policy, nor are intended to replace clinical judgment or dictate care of individual patients.

## USE OF THROMBOLYTICS FOR PULMONARY EMBOLISM

### RECOMMENDATIONS

- **Level 1**
  - **Initial therapeutic anticoagulation with heparin should be given to patients with objectively confirmed pulmonary embolism (PE) and no contraindication to anticoagulation.**
    - **Subcutaneous (SQ) low molecular weight heparin (LMWH), intravenous (IV) or SQ unfractionated heparin (UFH), or SQ Fondaparinux may be used**
    - **Therapeutic anticoagulation can be given during the diagnostic workup of PE to patients with intermediate or high clinical probability and no contraindications to anticoagulation**
  - **Thrombolytic therapy should be reserved for patients who meet the following criteria:**
    - **Massive or sub-massive PE AND**
    - **Evidence of cardiac dysfunction AND**
    - **Low bleeding risk**
- **Level 2**
  - **Thrombolytic therapy is not recommended for patients with low-risk or sub-massive acute PE with minor RV dysfunction, minor myocardial necrosis, and no clinical worsening.**
  - **Consider consultation with interventional radiology for mechanical intervention and/or possible thrombolysis.**
- **Level 3**
  - **Rescue embolectomy should be considered for failed thrombolysis and evidence of continued cardiac dysfunction.**
  - **Fibrinogen levels may be used to monitor thrombolytic therapy.**

### INTRODUCTION

The management and outcomes of patients with acute PE differ based on patient characteristics and the severity level of the PE. Numerous previous studies demonstrated that hypotension and circulatory arrest lead to an increased short-term mortality in acute PE. In the International Cooperative Pulmonary Embolism Registry (ICOPER), the 90-day mortality rate for patients with acute PE and systolic blood pressure <90 mmHg at presentation (108 patients) was 52.4% (95% confidence interval [CI] 43.3% to 62.1%) vs. 14.7% (95% CI 13.3% to 16.2%) in the remainder of the cohort (1). Additionally, The Management Strategy and Prognosis of Pulmonary Embolism Registry (MAPPET) demonstrated that there was an increased in hospital mortality for patients who presented with cardiogenic shock (25%) compared to hemodynamically stable patients (8.1%) (2). Clinical scores such as the Geneva and Pulmonary Embolism Severity Index (PESI) have been proposed to determine the severity of PE

### EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

### LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

diagnosis. A clinical statement has been published by the American Heart Association with the aim of applying the definitions of massive PE, sub-massive PE, and low risk PE, based on specific clinical parameters (2):

- Massive PE: an acute PE with sustained hypotension (SBP < 90mmHg for at least 15 min or requiring inotropic support, not due to a cause other than PE, such as arrhythmia, hypovolemia, sepsis, or LV dysfunction), pulselessness, or persistent profound bradycardia.
- Sub-massive PE: an acute PE without systemic hypotension (SBP>90mmHg) but with either RV dysfunction or myocardial necrosis.
- Low-risk PE: an acute PE with the absence of the clinical markers of adverse prognosis that define massive or sub-massive PE.

## LITERATURE REVIEW

Four registries have documented the outcomes of patients with PE (MAPPET, ICOPER, RIETE, and EMPEROR) and the collective data suggests that there is a trend toward a decrease in all-cause mortality from PE, especially in massive PE, in patients treated with fibrinolysis (2). Patients with low risk PE have an unfavorable risk-benefit ratio with fibrinolysis. Therefore, it is the patients with sub-massive PE that require the clinician to use clinical judgement to determine if thrombolytic therapy should be used. Evidence suggesting development of circulatory or respiratory insufficiency or evidence of moderate to severe RV injury can assist the clinician to determine if the patient would benefit from fibrinolytic therapy. A suggested treatment algorithm for use of fibrinolytic therapy for acute PE management was created in order to appropriately select patients that would have the greatest benefit from thrombolytic therapy, while minimizing the therapy's adverse side effects (2) (Class II).

The safety and efficacy of intravenous versus intrapulmonary rt-PA were evaluated in a multicenter European study of patients with massive bilateral PE (3). After diagnosis was confirmed by pulmonary angiography, intravenous (n=15) or intrapulmonary (n=19) rt-PA was given as a 10 mg bolus followed by 20 mg/hour over the first 2 hours. All patients received an intravenous bolus of 5000 IU heparin followed by a continuous infusion of 1000 IU/hour. Follow-up pulmonary angiography was performed at the end of the 2-hour infusion period. If massive PE was present, a second infusion of 50 mg rt-PA was given over 5 hours by the same route. Following rt-PA infusion, both groups had significant improvements in mean pulmonary arterial pressure and pulmonary angiographic severity score. Intrapulmonary infusion did not offer a significant benefit over the intravenous route of administration. Forty-seven percent (16/34) developed some degree of bleeding, primarily at puncture and/or surgical sites. (Class I)

Meneveau et al. compared rescue surgical embolectomy and repeat thrombolysis in patients who did not respond to thrombolysis (4). A prospective single-center registry revealed 40 patients who did not respond to thrombolysis within the first 36 hours. Fourteen were treated by rescue surgical embolectomy and 26 by repeat thrombolysis. There was a trend toward higher mortality in the medical group (10/26) vs. the surgical group (1/14). There were significantly more recurrent PEs in the repeat thrombolysis group (35% vs. 0%, respectively). While there was no significant difference in the number of bleeding complications between the two groups (four each), all four bleeding episodes in the repeat fibrinolysis group were fatal. Rescue embolectomy was recommended for patients with persistent RV dysfunction following initial thrombolysis.

The effects of heparin plus Alteplase vs. heparin plus placebo for the treatment of acute sub-massive PE were evaluated in a prospective, randomized trial (5). Two hundred fifty-six patients with right ventricular dysfunction or pulmonary hypertension, without hemodynamic instability, were included. Alteplase was administered as a 10 mg bolus, followed by 90 mg intravenously over 2 hours. The incidence of the combined primary endpoint (in-hospital mortality plus clinical deterioration requiring escalation of treatment) was significantly higher in the heparin/placebo group (24.6% vs. 11%; p=0.006). However, when assessed individually, there was no significant difference in in-hospital mortality between groups. No significant difference in the secondary endpoints of recurrent PE, major bleeding, or ischemic stroke were found. Of note, the trial has been critiqued due to the low incidence of major bleeding in the Heparin/Alteplase group (0.8%) (Class I).

Recent diagnostic advancements have helped reveal a subset of patients that may benefit from thrombolysis in the setting of sub-massive PE. A recent review by Konstantinides suggests the need for risk stratification of normotensive patients with PE, to identify a subset of patients that may carry an intermediate mortality risk, often associated with development of right ventricular (RV) failure (6). Increasing experience with echocardiography, and helical CT has improved the ability to detect RV dysfunction by non-invasive means. Echo findings of RV enlargement, hypokinesis of the free wall, leftward septal shift, and evidence of pulmonary hypertension are suggestive of RV dysfunction, and may carry a 2-3 fold increased risk of death (7,8) (Class III).

CT findings of RV enlargement defined by a right/left ventricular dimension ratio  $>0.9$  were found to independently predict 30-day PE related mortality (7). This trend was equivalent to echocardiographic findings in a recent registry evaluation by Fremont et al. 950 patients with acute PE underwent echocardiographic assessment upon hospital admission, including measurement of RV/LV ratios (8). While sensitivity (72%) and specificity (58%) values were less than overwhelming, for predicting in-hospital mortality, RV/LV ratio  $\geq 0.9$  was found to be an independent predictive factor (OR, 2.66;  $p=0.01$ ) (7). RV hypokinesis was also found to be an independent predictor of early death among normotensive (SBP  $>90$ ) patients with PE. Evaluation of ICOPER (International Cooperative Pulmonary Embolism Registry) data revealed a 17% 30-day mortality associated with RV hypokinesis despite preserved SBP (1).

Cardiac biomarkers such as Troponin I, brain natriuretic peptide and Heart-type FABP (H-FABP) may identify those patients with early or developing myocardial cell damage possibly related to PE. Kline et al evaluated 8 biomarkers and found BNP and Troponin to demonstrate modest, but significant prognostic accuracy for prognostic significance in detecting RV hypokinesis in the setting of sub-massive PE (9). While these biomarkers have low specificity and positive predictive value for PE-related mortality, when considered in conjunction with the aforementioned imaging findings they may prove useful in identifying candidates for thrombolytic therapy prior to the development of hemodynamic instability. (Class III)

Low dose thrombolytic therapy (tPA) in moderate PE was evaluated in a prospective randomized study (10). Over 22 months, 121 patients with symptomatic moderate PE (defined by combination of physical exam, echo, CT, and or ventilation perfusion scan) were randomized to either low dose tPA and anticoagulation or anticoagulation alone. Primary end points evaluated at 28 months were development of pulmonary hypertension and recurrent PE. In the treatment group, pulmonary hypertension was seen in 16% vs. 57% in the control group ( $p<0.001$ ). No difference in recurrent PE was observed. A secondary endpoint with significance was hospital length of stay; treatment group was  $2.2\pm 0.5$  days vs.  $4.9\pm 0.8$  days in control group ( $p<0.001$ ). No difference was seen comparing mortality, or significant bleeding events. (Class I)

Fibrinolytic therapy in patients with intermediate risk pulmonary embolisms was evaluated by a randomized, double blinded trial (11). Patients were normotensive with evidence of RV dysfunction on echo or myocardial injury defined by elevated troponin. 1006 patients were randomized to either tPA plus heparin or placebo plus heparin. Main outcomes were death or hemodynamic decompensation at 7 days. Safety outcomes were major extracranial or intracranial bleeding at 7 days. Death or decompensation was seen in 2.6% of the tPA group vs. 5.6% of the placebo group ( $p=0.02$ ). Extracranial bleeding occurred in 6.3% vs. 1.2% ( $p<0.001$ ). Stroke occurred in 2.4% vs. 0.2% ( $p<0.003$ ). At day 30, 2.4% of the tPA group had died compared to 3.2% in the placebo group ( $p=0.42$ )(Class I).

## **SUMMARY**

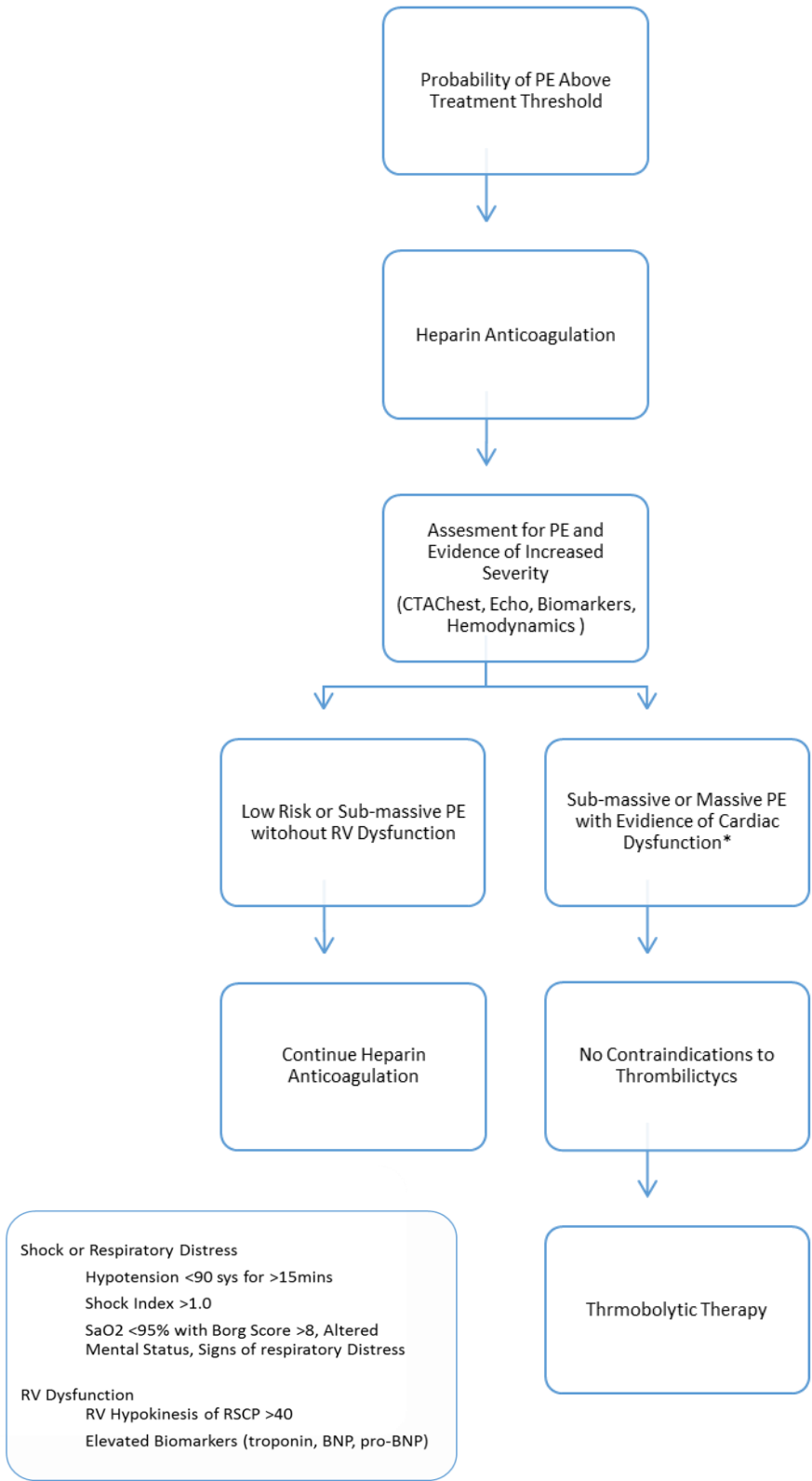
The role of thrombolytic agents in the management of massive pulmonary embolism (PE) has specific advantages and disadvantages based on severity of the pulmonary embolus, and the presence of certain clinical conditions that would place the patient at high risk for adverse side effects. Alteplase (recombinant tissue-plasminogen activator; rt-PA), streptokinase, and Urokinase effectively restore pulmonary blood flow when administered by the intravenous or intrapulmonary route. Data gathered from the MAPPPET, ICOPER, RIETE, and EMPEROR registries suggest that there is a trend toward a decrease in all-cause mortality in patients with massive PE who are treated with fibrinolytic therapy. The data for fibrinolytic

therapy use in patients with sub-massive PE is not as well defined and require the clinician to use clinical judgment to determine if fibrinolytic therapy is appropriate. Patients with sub-massive PE who fail to respond to initial anticoagulation therapy, and who demonstrate worsening in their clinical condition seen as new hemodynamic instability, worsening respiratory insufficiency, severe RV dysfunction, or myocardial necrosis may benefit from thrombolytic therapy. Thrombolytic therapy should be reserved for patients who have a low risk of bleeding. Intrapulmonary administration has not been consistently shown to be superior to intravenous dosing. Administration of thrombolytics in the intensive care unit setting should be reserved for patients who are not stable for transport to the interventional radiology suite. Given the allergic reactions associated with streptokinase and long infusion duration of both streptokinase and urokinase, rt-PA is a reasonable first-line thrombolytic.

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**Table I: PE Fibrinolytic Treatment Algorithm**



**Table II: Dosing Information**

Thrombolytic Regimens for the Treatment of Pulmonary Embolism		
Thrombolytic	IV	Intrapulmonary (Not FDA-approved)
Alteplase (Recombinant tissue-plasminogen activator; rt-PA;Activase <sup>®</sup> )	100mg over 2 hours	10mg bolus over 10 minutes and re-evaluate need for continuation; may proceed with 20 mg/hr for 2 hours if necessary (2,8)
Streptokinase <sup>®</sup> (Streptase <sup>®</sup> )	250,000 units over 30 minutes, followed by 100,000 units/hour for 24 hours	100,000 units/hr (9-11)
Urokinase <sup>®</sup> (Abbokinase <sup>®</sup> )	4,400 units/kg over 10 minutes, followed by 4,400 units/kg/hour for 12 hours	Variable

**Table III: Absolute Contraindications to rt-PA**

- Active internal bleeding
- Prior intracranial hemorrhage
- Known cerebrovascular disease or AVM
- Ischemic stroke within the last 3 months
- Suspected aortic dissection
- Intracranial or intraspinal surgery or trauma ( $\leq$  2 months)
- Intracranial neoplasm
- Arteriovenous malformation or aneurysm
- Bleeding diathesis
- Severe uncontrolled hypertension

**Table IV: Relative Contraindications to rt-PA**

The following conditions may increase the risk of bleeding and must be weighed against the anticipated benefits:

- Recent ( $\leq$ 10 days) major surgery
- Cerebrovascular disease
- Recent ( $\leq$ 10 days) GI or GU bleeding
- Recent ( $\leq$ 10 days) trauma
- Hypertension:  $>180$  mmHg systolic or  $\geq 110$  mmHg diastolic
- Likelihood of left heart thrombus (e.g., mitral stenosis with atrial fibrillation)
- Acute pericarditis
- Subacute bacterial endocarditis
- Hemostatic defects secondary to severe hepatic or renal disease
- Significant liver dysfunction
- Pregnancy
- Diabetic hemorrhagic retinopathy or other ophthalmic hemorrhaging
- Septic thrombophlebitis or occluded AV cannula at seriously infected site
- Advanced age (e.g.,  $>75$  years old)
- Traumatic or prolonged cardiopulmonary resuscitation ( $>10$  min)
- Patients currently receiving oral anticoagulants
- Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.

**Table V: Contraindications/Precautions to Heparin Therapy**

- Hypersensitivity to heparin
- Active bleeding
- Severe thrombocytopenia
- Increased risk of hemorrhage, such as:
  - Selected traumatic injuries (i.e., severe liver laceration, intracranial hemorrhage, spinal cord injury)
  - Dissecting aneurysm
  - Treatment with drotrecogin alfa (activated) (Xigris™)
  - Hemophilia or other blood disorders
  - Epidural catheter
  - Subacute bacterial endocarditis
  - Uncontrolled hypertension

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