

## PRACTICE RECOMMENDATIONS

# Management of Acute Pulmonary Embolism: Consensus Statement for Indian Patients

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## Abstract

Pulmonary embolism (PE) is an important cause of morbidity and mortality among hospitalized patients. Although the exact epidemiology of PE is not known in India, some of the studies show that more frequently it is missed and not managed appropriately leading to significant cardiovascular morbidity and mortality.

**Justification and purpose:** Indian guidelines for the diagnosis and treatment of acute PE are not yet formulated. The objective of this consensus statement is to propose a diagnostic and management approach for acute PE in India.

**Process:** A working group of 15 experts in the management of acute PE (cardiologists, pulmonologist, haematologist, emergency specialist and intensivists). This consensus statement makes recommendations for diagnosis and management for PE based on literature review, including Indian data.

**Recommendations:** Patients with acute PE should be immediately stratified according to early mortality risk. For risk stratification, clinical parameters, markers of RV dysfunction and myocardial injury should be used. The clinical prediction criteria (Simplified Geneva score and PE rule out criteria) should be routinely used in emergency department. ECG, Chest X-Ray, routine labs, D-Dimer, nt Pro-BNP/BNP, Troponin I or T, hFABP, echocardiography, lower limb compression ultrasonography (CUS), CT-pulmonary angiography, ventilation-perfusion scintigraphy (V/Q scan), and pulmonary angiography should be selected in suspected cases of PE as per risk stratification. Anticoagulation should be immediately started in high or intermediate clinical probability of PE during ongoing diagnostic workup. In high risk PE, anticoagulation with UFH should be started without delay. Initial treatment with unfractionated heparin, LMWH or fondaparinux should be continued for at least 5 days and may be replaced by vitamin K antagonists only when target INR levels for  $\geq 2$  consecutive days is achieved. Thrombolytic therapy is recommended in all patients with high risk PE, unless contraindicated. Routine use of thrombolytics in non-high risk PE is not recommended but may be considered in selected cases with intermediate-risk PE. Thrombolytic therapy is not recommended in patients with low risk PE. Anticoagulation should be given for at least 3 months. Need for longer duration should be reevaluated after risk-to-benefit evaluation at that time. Recurrence is common; hence long-term anti-coagulation may be required in selected cases. Pulmonary embolism response team (PERT) composed of specialists in various fields has been suggested.

## Introduction

Pulmonary embolism (PE) is an important cause of morbidity and mortality among hospitalized patients.<sup>1</sup> Worldwide the incidence of acute venous thromboembolism ranges between 23-69/100,000 population/year. Close to 10% of all patients with acute PE die during first 3 months after diagnosis.<sup>2</sup> Though the exact epidemiology of PE in India is largely unknown, an autopsy study showed the

overall incidence of PE in patients admitted in the medical wards of a tertiary care centre in North India to be 15.9%, mainly affecting younger population below 50 years

of age. The incidence of significant PE contributing to the death of the patients was 12.6%.<sup>1</sup>

Indian guidelines for the diagnosis and treatment of

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**Table 1: Risk stratification of PE according to PE-related early mortality rate<sup>5</sup>**

PE related early mortality risk	Risk markers		
	Clinical (shock or hypotension)	RV dysfunction (Echo, MDCT, natriuretic peptides)	Myocardial injury (cardiac troponins, h-FABP)
High >15%	+	(+)*	(+)*
Non High Intermediate 3-15%	-	+	+
		+	-
		-	+
Low <1%	-	-	-

h-FABP denotes heart-type fatty acid-binding protein; LMWH, low-molecular-weight heparin or fondaparinux; MDCT, multidetector computed tomography (pulmonary angiography); PE, pulmonary embolism; RV, right ventricle; UFH, unfractionated heparin

\*In the presence of shock or hypotension, it is not necessary to confirm RV dysfunction/myocardial injury to classify high risk of PE related early mortality risk.

acute PE are not yet formulated. The objective of this consensus statement is to propose a diagnostic and management approach for acute PE in India.

## Method

A working group of 15 experts in the management of acute PE (cardiologists, pulmonologist, haematologist, emergency specialist and intensivists) was formed. This consensus statement makes recommendations for diagnosis and management for PE based on literature review, including Indian data. We recommend that the best suitable medical decision should take into consideration the age, comorbidities, and cost of treatment. The clinician should make use of evidence based recommendations while treating an individual patient.

## Classification of PE

The American Heart Association classifies PE into three categories<sup>3</sup>:

**Massive PE:** Acute PE with sustained hypotension (systolic blood pressure <90 mm Hg for at least 15 minutes or requiring inotropic support, not due to a cause other than PE such as arrhythmia, hypovolemia, sepsis or left ventricular dysfunction), pulselessness or persistent profound bradycardia (heart rate <40 bpm) with signs or symptoms of shock.

**Sub-massive PE:** Acute PE

without systemic hypotension (systolic blood pressure  $\geq$ 90 mm Hg) but with either right ventricular (RV) dysfunction or myocardial necrosis.

RV dysfunction means the presence of at least one of the following:

- RV dilation (apical 4-chamber RV diameter divided by LV diameter >0.9) or RV systolic dysfunction on echocardiography or CT
- Elevation of BNP (>90 pg/ml) or
- Elevation of N-terminal pro-BNP (>500 pg/mL) or
- ECG changes (new right bundle-branch block, antero-septal ST elevation or depression, or T-wave inversion)

Myocardial necrosis is defined as either of the following:

- Elevation of troponin I (>0.4 ng/mL) or troponin T (>0.1 ng/mL)

**Low risk PE:** Acute PE and the absence of clinical markers of adverse prognosis that define massive or submassive PE.

In another classification based on the clinical parameters, markers of RV dysfunction and myocardial injury, acute PE is classified into "high risk" and "non-high risk" categories. The latter can further be sub-divided into "intermediate risk" and "low risk" cases.<sup>4,5</sup> The terminologies "high risk" for acute massive PE and "intermediate risk" for sub-massive PE are now being

**Table 2: Revised Geneva Score<sup>10</sup>**

Item	Original	Simplified
Previous DVT or PE	3	1
Heart rate 75-94/min	3	1
Heart rate >95/min	5	2
Surgery or fracture <1 month	2	1
Hemoptysis	2	1
Active malignancy	2	1
Unilateral lower limb pain	3	1
Pain on lower limb deep vein palpation and unilateral edema	4	1
Age >65 y	1	1
Clinical probability		
PE unlikely	<5	<2
PE likely	>5	>2

suggested and commonly used.<sup>6</sup> It will be appropriate to use this classification in India to simplify risk stratification (Table 1).

## Diagnosis of PE

The working group felt that the most important barrier in management of PE is early recognition and diagnosis. PE remains unconfirmed in large number of patients with clinical suspicion. In fact, in an autopsy study, PE was suspected antemortem in only 9.4% cases.<sup>1,7,8</sup>

Signs and symptoms, though not sensitive and specific, can help in suspecting the diagnosis. The symptoms of PE include dyspnoea, chest pain, cough, haemoptysis and syncope while the common signs include tachycardia or bradycardia, tachypnoea, cyanosis, hypotension, and signs of deep vein thrombosis (DVT).<sup>9</sup>

The patients with suspected PE need to be stratified into specific risk category to provide appropriate investigation and treatment plan, as diagnostic work-up and management differs depending on the risk categories. Different clinical prediction systems are available for stratifying the risk according to signs and symptoms. These include Wells rule, Geneva score and PE rule out criteria (Tables 2, 3 and 4). We recommend routine use of

**Table 3: Wells rule<sup>10</sup>**

Item	Original	Simplified
Previous PE or DVT	1.5	1
Heart rate >100/min	1.5	1
Surgery or immobilization <4 wk	1.5	1
Hemoptysis	1	1
Active malignancy	1	1
Clinical signs of DVT	3	1
Alternative diagnosis less likely than PE	3	1
Clinical probability		
PE unlikely	<4	<1
PE likely	>4	>1

these clinical prediction systems in emergency departments.

### Investigations<sup>3,4,12,13</sup>

The battery of investigations for risk stratification and diagnosis in suspected acute PE include ECG, chest X-ray, routine labs, D-dimer, nt pro-BNP/BNP, troponin I or T, hFABP, echocardiography, lower limb compression ultrasonography (CUS), CT-pulmonary angiography, ventilation-perfusion scintigraphy (V/Q scan), and pulmonary angiography. The positive findings in different investigations include:

**ECG:** New complete or incomplete right bundle branch block (RBBB), anteroseptal ST elevation or depression, anteroseptal T-wave inversion.

**Echo:** Right ventricle (RV) dilation (apical 4-chamber RV diameter divided by LV diameter > 0.9), RV systolic dysfunction (estimated RVSP >40 mm Hg), interventricular septal shift or bowing, McConnell's sign (hypokinesia or akinesia

**Table 4: PERC rule out criteria<sup>11</sup>**

Pulmonary Embolism Rule-Out Criteria (PERC Rule)
Age <50 yr
Pulse oximetry >94% (breathing room air)
Heart rate <100 beats/min
No prior venous thromboembolism
No recent surgery or trauma requiring hospitalization, intubation or epidural anesthesia within prior 4 wks
No hemoptysis
No estrogen use
No unilateral leg swelling

If all criteria are met, probability of developing clinically diagnosed VTE is <2%.

of the mid-RV free wall). New echocardiographic parameters of RV dysfunction: tricuspid annular plane systolic excursion (TAPSE) and right ventricle myocardial performance index (RV-MPI) correlate well with morbidity and mortality in acute PE. The sensitivity of echo in diagnosing acute PE is 31-52% while specificity ranges between 87-96%.

**Enzymes:** Elevation of D-dimer (>500 µg/L); elevation of N-terminal pro-BNP (>500 pg/mL); BNP (>90 pg/mL); elevation of troponin I (>0.4 ng/mL); elevation of troponin T (>0.1 ng/mL); elevation of H-FABP (>6 ng.mL).

**Compression ultrasonography (CUS):** It can be done at bed-side using simple four point examinations i.e two groin and two popliteal fossae. The sensitivity of CUS for the presence of PE on MSCT was 39% while specificity was 99%.

**Table 5: Differentiating between high risk and non-high risk PE**

Test	Non-high risk PE	High risk PE
Shock index (heart rate/systolic blood pressure)	<1.0	≥1.0
Pulse oximetry reading	>95%	<95%
Echocardiography	Normal RV systolic function Normal RV size No tricuspid regurgitation	RV hypokinesia RV dilation RVSP >40 mm Hg
Troponin I or T level	Normal	Elevated
B-type natriuretic peptide level	<90 picograms/mL	≥90 picograms/mL
N-terminal pro-B-type natriuretic peptide	<900 picograms/mL	≥900 picograms/mL
D-dimer level	<4000 nanograms/mL	>8000 nanograms/mL

(Modified from reference 14)

**Computed tomographic pulmonary angiography (CT-PA):** RV dilation (4-chamber RV diameter divided by LV diameter >0.9); thrombus in pulmonary arteries up to segmental level. The sensitivity and specificity of CT PA are 83% and 96% respectively.

**Pulmonary angiography (PA)** is the gold standard test with 100% sensitivity. The specificity of PA is 90%; however, it is rarely employed.

**Ventilation-perfusion (VQ) scan:** Unavailability of the test and expertise for interpretation during odd hours, and high proportion of inconclusive results limits the use of VQ scan.

In the Indian context, out of many available investigations, based on available resources, CT and echocardiography appear to be most appropriate investigations for definitive diagnosis of PE.

### Risk Stratification

Diagnostic work-up and management of PE is based on the risk category, hence patients with suspected PE need to be stratified into specific risk category. Recent guidelines suggest risk stratification on the basis of PE related early mortality risk, rather than the anatomical position and burden of thrombus which describe massive and sub-massive PE.<sup>4,5</sup> Based on the clinical signs and investigation findings, the patient can be stratified into high, intermediate and low risk pulmonary embolism.<sup>14</sup> (Table 5)

### Summary

- Patients with acute PE should be immediately stratified according to early mortality risk.
- For risk stratification, clinical parameters, markers of RV dysfunction and myocardial injury should be used.
- Terminologies "high risk", "intermediate risk" and "low

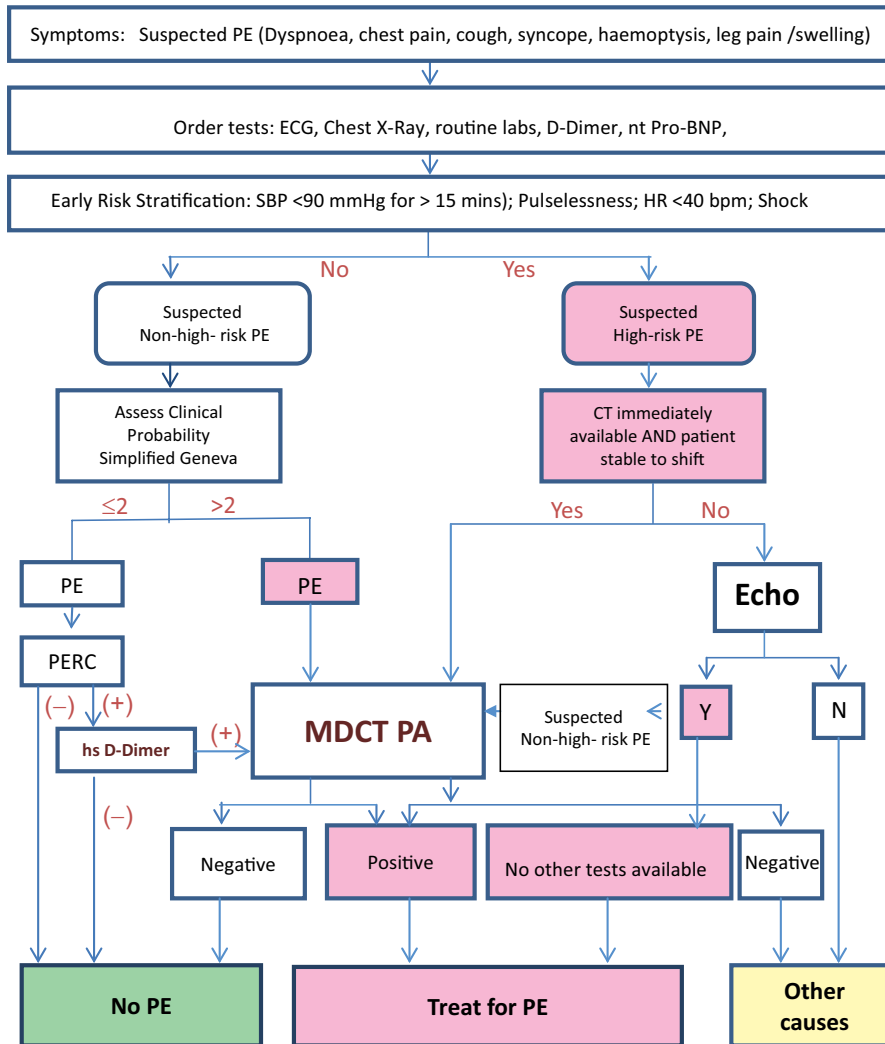


Fig. 1: Consensus algorithm for diagnosis of acute PE

risk" should be used to simplify the risk stratification.

- The clinical predictions criteria (Simplified Geneva score and PE rule out criteria) should be routinely used in emergency departments
- ECG, chest X-ray, routine labs, D-dimer, nt Pro-BNP/BNP, Troponin I or T, hFABP, echocardiography, lower limb compression ultrasonography (CUS), CT-pulmonary angiography, ventilation-perfusion scintigraphy (V/Q scan), and pulmonary angiography should be selected in suspected cases of PE as per risk stratification.

## Management of Acute PE

Consensus group reviewed current evidences available for various therapies and agreed that the goals of PE management include prevention of death from the current embolic event, to reduce the chances of recurrent embolic events and to minimize long term morbidity due to the event. Prompt diagnosis and appropriate treatment is critical to avoid fatal complications of acute PE.

## Anticoagulants and Thrombolytics in the Management of Acute PE

Anticoagulants and thrombolytics are the mainstay of treatment in medical management

of acute PE. Heparin causes reduction of thrombus size while thrombolytics actively break fibrin molecules.<sup>15</sup>

### Initial Anticoagulants

We recommend that during diagnostic workup, anticoagulation should be started at the earliest for patients with intermediate or high clinical probability of PE and having no contraindications to anticoagulation. Immediate full anticoagulation should be given to all patients with suspected PE.

### UFH, Low-molecular-weight Heparin Therapy (LMWH) and Fondaparinux

Current guidelines recommend starting unfractionated heparin (UFH), low-molecular weight heparin (LMWH), or fondaparinux (all Grade 1A) in addition to an oral anticoagulant (warfarin) at the time of diagnosis, and to discontinue UFH, LMWH, or fondaparinux only after the international normalized ratio (INR) is 2.0 for at least 24 hours, but no sooner than 5 days after warfarin therapy has been started (grade 1C recommendation). The recommended duration of UFH, LMWH, and fondaparinux is based on evidence suggesting that the relatively long half-life of factor II, along with the short half-lives of protein C and protein S, may provoke a paradoxical hypercoagulable state if these agents are discontinued prematurely. For patients with acute non massive pulmonary embolism recommend LMWH over UFH (Grade 1A). However, in patients with acute PE and severe renal failure, UFH is preferred over LMWH (Grade 2 C).<sup>16</sup>

LMWHs have many advantages over UFH including greater bioavailability, longer duration of action and possibility of use by subcutaneous route. In addition, a fixed dose of LMWH can be used, and laboratory monitoring of aPTT is not necessary. LMWH is at least as effective and safe as UFH. No significant differences in recurrent thromboembolic events,

**Table 6: Thrombolytic agents in acute PE**

Thrombolytic	Dose
Alteplase <sup>19</sup>	10 mg bolus, 90 mg IV infusion over 2 hrs
Urokinase <sup>20</sup>	4400-IU/Kg bolus, followed by 4400 IU/kg/hr for 12-24 h
Streptokinase <sup>21</sup>	250000 IU IV bolus followed by 100000 IU/h infusion for 12-24 h
Retepase <sup>22</sup>	Double 10 U IV bolus 30 minutes apart
Tenecteplase <sup>23</sup>	Weight-adjusted IV bolus over 5 s (30-50 mg with a 5- mg step every 10 kg from <60 to >90 kg)

Please refer the current locally approved prescribing information of each product for dosage, indication, contraindications, precautions and other safety information.

major bleeding, or mortality have been reported between them. LMWH can be given safely in an outpatient setting which led to the development of programs where clinically stable patients with PE are treated at home with substantial cost savings. An international, open-label, randomized trial comparing outpatient versus inpatient treatment (both using the LMWH enoxaparin as initial therapy) of low-risk patients with acute PE concluded that outpatient treatment was non inferior to inpatient treatment.<sup>17</sup>

Fondaparinux catalyzes factor Xa inactivation by antithrombin without inhibiting thrombin. Once-daily fondaparinux was found to have similar rates of recurrent pulmonary embolism, bleeding, and death as IV UFH, according to a randomized open-label study involving 2213 patients with symptomatic pulmonary embolism.<sup>18</sup>

Except in patients presenting with massive PE, LMWH or fondaparinux is recommended over IV UFH<sup>16</sup> due to advantages of better predictable bioavailability, fast onset of full anticoagulant effect, and no need for monitoring anticoagulant effect. If needed, factor Xa levels can be monitored, in case of ambiguity regarding dosing accuracy.

**Table 7: Contraindications for thrombolytic treatment<sup>4</sup>****Absolute contraindications**

Haemorrhagic stroke or stroke of unknown origin (any time) or ischemic stroke in last 6 months  
Trauma or tumour of central nervous system  
History of major trauma/surgery or head injury in last 3 weeks  
Gastrointestinal bleeding in last month or known bleeding

**Relative contraindications**

Transient ischemic attack in last 6 months  
Oral anticoagulant therapy  
Pregnancy or within 1 week post-partum  
Non-compressible punctures  
Traumatic resuscitation  
Refractory hypertension  
Active peptic ulcer  
Advanced hepatic disease  
Infective endocarditis

UHF infusion has an advantage of possibility for quick adjustment of anticoagulation; especially when thrombolytic therapy is started.

**Summary<sup>4</sup>**

- Anticoagulation should be immediately started in high or intermediate clinical probability of PE during ongoing diagnostic workup.
- In high risk PE, anticoagulation with UFH should be started without delay.
- LMWH or fondaparinux is recommended as an initial treatment for most patients with non-high risk PE.
- UFH with an aPTT target of 1.5-2.5 times normal should be an initial treatment in patients with high risk of bleeding and severe renal dysfunction.
- Initial treatment with unfractionated heparin, LMWH or fondaparinux should be continued for at least 5 days and may be replaced by vitamin K antagonists only when target INR levels for  $\geq 2$  consecutive days is achieved.

**Thrombolytics**

In acute pulmonary embolism, thrombolytic therapy is

effective in rapidly relieving the thromboembolic obstruction and offers beneficial effects on haemodynamic parameters. Various available thrombolytics with their dosage are mentioned in Table 6. Streptokinase, urokinase and alteplase are approved for use in PE. As reteplase and tenecteplase, though likely to be as effective are not currently approved for acute PE we do not recommend their use as first choice.

Recently published results of MOPETT trial showed that  $\leq 50\%$  of the standard dose of tPA is safe and effective in the treatment of moderate PE. A presentation of 100 cases at the ACC 2014 recommended, that when the clinician is undecided about thrombolysis or complete evaluation cannot be done due to unavailability of tests or cost constraints, half dose tPA (10 mg bolus and 40 mg infusion over two hours) can be administered along with weight-adjusted unfractionated heparin. This reduces the chance of bleeding, but remains effective as pulmonary thrombi respond differently from arterial thrombi. However, this half dose therapy is currently not an approved dose for thrombolysis.<sup>24</sup>

**Evidence for Thrombolytics in Acute PE**

Strong positive evidence is available for use of thrombolytics in the management of acute PE. A meta-analysis of 11 randomized studies in patients with acute PE, thrombolytic therapy was associated with significant reduction in recurrent PE or death in high risk hemodynamically unstable patients.<sup>25</sup> Other studies ICOPER (1999),<sup>26</sup> RIETE (2007),<sup>27</sup> EMPEROR (2008)<sup>28</sup> have also shown benefits with thrombolytics in significantly reducing the mortality rate in acute massive PE.<sup>3</sup> Alteplase should be preferred over streptokinase and urokinase based on the current evidence on efficacy, safety and clinical experience.<sup>3</sup> rt-PA rapidly improves right-ventricular function and pulmonary perfusion among

patients with PE and may lead to lower rate of adverse clinical outcomes.<sup>29</sup>

Contraindications for the use of thrombolytic treatment are given in table below (Table 7).

### **Intermediate Risk PE: Evidence to thromolyse or not to thromolyse**

It is known that isolated RV dysfunction is a marker for poor outcome in patients with PE especially those with hemodynamic instability. RV dysfunction in hemodynamically stable patients is also a predictor of worse outcome and appears to be related to the presence of recurrent PEs. Ten percent of hemodynamically stable patients with RV dysfunction will deteriorate into shock with 50% mortality rate attributed to those with recurrent PEs.<sup>19</sup>

The evidence for use of thrombolytics in intermediate risk PE is summarised below.

A randomized study involving 256 patients compared heparin plus alteplase with heparin alone in sub massive PE showed significantly higher incidence of in-hospital death or clinical deterioration requiring an escalation of treatment in heparin/placebo group compared to heparin/ alteplase group. Probability of 30- day event-free survival was higher in the heparin-plus-alteplase group. Fatal or cerebral bleeding was not observed in patients receiving heparin plus alteplase. Alteplase can improve the clinical course of stable patients with submassive PE.<sup>19</sup>

In another study, comparing alteplase plus heparin versus anticoagulants alone, total median hospital stay was significantly shorter in the alteplase group, with no difference in the ICU stay. Age more than 65 years and comorbidity were independent predictors for a prolonged hospital stay, whereas thrombolysis independently predicted a shorter

total stay in multivariate analysis. Thrombolysis may lead to reduction of hospital stay for patients with intermediate-risk PE, possibly indicating that it is more effective than anticoagulant therapy alone in this group of patients.<sup>30</sup>

Tenecteplase, a mutant form of rt-PA differs biologically from alteplase and is not yet approved for acute management of PE. In Pulmonary embolism thrombolysis (PEITHO), a double blind, randomized, comparative trial, tenecteplase prevented hemodynamic decompensation, however major bleeding was seen in higher number of patients receiving tenecteplase compared to placebo.<sup>31</sup>

TOPCOAT, a randomized trial in intermediate-risk PE patients, comparing tenecteplase with low-molecular- weight heparin versus low-molecular-weight heparin alone was terminated early. The results showed a greater survival rate in the first 5 days, shorter hospital stay, and greater quality of life at 90 days compared to low-molecular-weight heparin alone.<sup>32</sup>

Various options to reduce bleeding while maintaining efficacy are being evaluated. In patients with intermediate risk PE, ultrasound-assisted catheter-directed thrombolysis (USAT) is superior to anticoagulation with only heparin in reversing right ventricular dilatation at 24 hours, without increased bleeding risk.<sup>33</sup> The results of ULTIMA trial shows that in patients with pulmonary embolism at intermediate risk of death, low-dose, catheter-directed ultrasound-accelerated thrombolysis with small doses of tPA is better than heparin alone in reversing RV dilatation and dysfunction at 24 hours. There is no risk of additional bleeding complications.<sup>33</sup> The results of SEATTLE II study, will provide additional information about the safety of USAT.<sup>34</sup>

The results justify the concept of risk stratification of normotensive

patients with acute PE. Early "advanced recanalization" treatment prevents clinical deterioration in patients with evidence of right ventricular dysfunction with cardiac necrosis. The patient's age should be taken into account when weighing the expected benefits versus risks of systemic thrombolysis in clinical practice.

#### **Summary**

- Thrombolytic therapy is recommended in all patients with high risk PE, unless contraindicated
- Routine use of thrombolytics in non-high risk PE is not recommended but may be considered in selected cases with intermediate-risk PE. Both half dose thrombolysis and ultrasound catheter-based low dose thrombolysis have been found to be effective with significantly less bleeding. This would allow more patients to benefit from therapy taking into account the long term benefit on development of pulmonary hypertension
- Thrombolytic therapy is not recommended in patients with low risk PE

### **Catheter-Based Therapy or Surgical Treatment**

The goals of catheter based therapy include rapid reduction in pulmonary artery pressure, RV strain, pulmonary vascular resistance, increase in systemic perfusion. Three types of percutaneous intervention include aspiration thrombectomy, thrombus fragmentation and rheolytic thrombectomy.<sup>3</sup> All these have now been replaced by ultrasound assisted low dose tPA catheter based therapy. This therapy is expensive and requires expertise which may not always be available. Surgical therapy is considered in high risk patients when thrombolysis is contraindicated.

**Table 8: Recommendations for IVC filters in settings of acute PE<sup>3</sup>**

Category of patient	Recommendation
Adult patients with any confirmed acute PE with contraindications to anticoagulation or with active bleeding complication	An IVC filter is recommended
Recurrent acute PE despite therapeutic anticoagulation	Reasonable to place an IVC filter
Acute PE with very poor cardiopulmonary reserve, including those with high risk PE	Placement of an IVC filter may be considered
Patients requiring permanent IVC filtration (e.g. long-term contraindication to anticoagulation)	Reasonable to select a permanent IVC filter device
Patients with a time-limited indication for an IVC filter (eg, those with a short-term contraindication to anticoagulation therapy).	Reasonable to select a retrievable IVC filter device

## IVC Filters

An IVC filter should not be used routinely as an adjuvant to anticoagulation and thrombolysis in acute PE treatment. Anticoagulation should be restarted in patients with an IVC filter, after contraindications to anticoagulation or active bleeding complications have resolved. Patients should receive retrievable IVC filters and should be regularly evaluated for filter retrieval within the specific filter's retrieval window.

## Warfarin and New Oral Anticoagulants

### Warfarin therapy

Warfarin causes anticoagulant via inhibition of vitamin K-dependent factors. In venous thromboembolism, an INR should be maintained in the therapeutic range of 2-3.<sup>35</sup> The limitations of warfarin use include difficulty in dose titration and its peak effect is not seen till 36-72 hours after dose administration.<sup>36</sup>

### New oral anticoagulants

New oral anticoagulants have multiple advantages including fast onset of action, predictable anticoagulation, targeting specific enzyme, and low interaction potential. In addition, they can be given in fixed doses, and do not need regular coagulation monitoring.<sup>37-40</sup> Some of the newer oral anticoagulants have been tested in clinical studies.

In EINSTEIN-PE study,<sup>41</sup> rivaroxaban 15 mg bid for the first

3 weeks, followed by 20 mg once daily thereafter was compared with standard therapy (enoxaparin plus vitamin K antagonist). Rivaroxaban was found to be non-inferior to standard therapy for primary efficacy outcome of symptomatic recurrent venous thromboembolism. First major or clinically relevant non-major bleeding episode occurred in 10.3% of rivaroxaban patients compared with 11.4% standard therapy patients, while major bleeding was observed in only 1.1% of patients taking rivaroxaban compared to 2.2% in patients on standard therapy. The results support use of rivaroxaban as monotherapy in the management of acute PE.

In RE-COVER trial dabigatran 150 mg bid was non-inferior to warfarin for the prevention of recurrent venous thrombo-embolism in patients presenting with acute venous thromboembolism.<sup>42</sup>

AMPLIFY trial<sup>43</sup> compared apixaban (10 mg bid for 7 days, followed by 5 mg bid for 6 months) versus standard therapy (Enoxaparin plus Warfarin). Apixaban was non-inferior to standard therapy in acute venous thromboembolism. Major or clinically relevant non-major bleeding occurred in 4.3% patients on apixaban compared to 9.7% on standard therapy. The results support use of apixaban monotherapy in the management of acute PE.

### Summary

The trials have shown beneficial effects with newer anticoagulants.

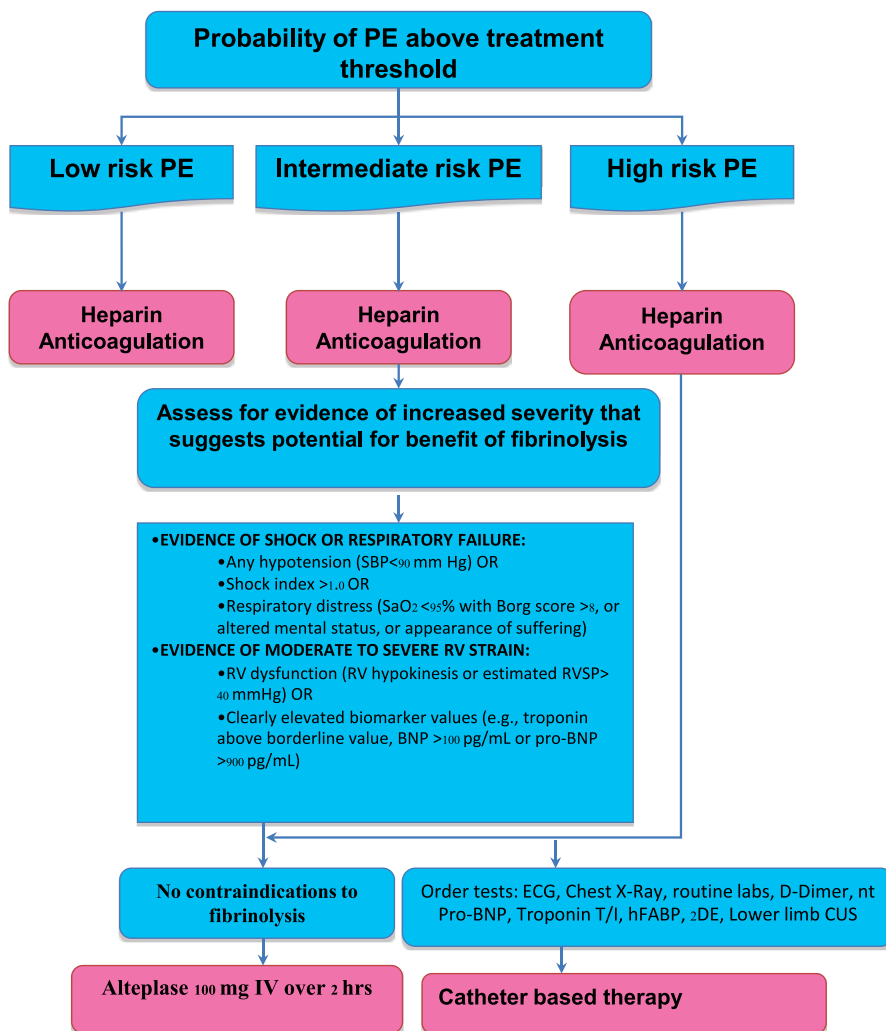
Rivaroxaban has already been approved,<sup>44</sup> while dabigatran has also very recently been approved by FDA for treatment of DVT/PE. Apixaban has been accepted for the treatment of DVT/PE post total hip replacement (THR)/total knee replacement (TKR) surgery.<sup>44</sup>

## Risk of Recurrence and Optimal Duration of Anticoagulation

One of the important decisions in PE management is to decide optimal duration of anticoagulation treatment because of the higher recurrence rates of venous thromboembolism after discontinuing anticoagulation treatment. In 1626 patients with proximal DVT or PE, the cumulative incidence of recurrence increased from 11% after 1 year to 40% after 10 years.<sup>45</sup> Another study confirms, that regardless of treatment duration, there is higher risk of recurrence after discontinuation of oral anticoagulation in patients with PE.<sup>46</sup>

The risk factors for recurrence include idiopathic PE, male gender, location of thrombotic event, raised D-dimer, high body weight and persistent RV dysfunction at the time of discharge from hospital.<sup>47-49</sup> Immobilization, cancer, chronic obstructive pulmonary disease, low HDL and family history are also associated with recurrence.<sup>50</sup>

There is no difference in recurrence rate with 3 versus 6 months of anticoagulant use in idiopathic or unprovoked first events,<sup>51,52</sup> hence, anticoagulation should be given for at least 3 months and need for further treatment should be reevaluated after risk-to-benefit evaluation. (Grade 1A).<sup>16</sup> Similarly, patients with PE and preexisting irreversible risk factors like antithrombin III deficiency, protein S and C, factor V Leiden mutation, or presence of antiphospholipid antibodies



**Fig. 2: Algorithm for use of thrombolytics to treat acute PE**

should also receive long term anticoagulation treatment.<sup>36</sup>

However, individualized assessment is needed for deciding optimal duration for patients in a 'grey zone'.<sup>50</sup>

#### Summary

- Anticoagulation should be given for at least 3 months. Need for longer duration should be reevaluated after risk-to-benefit evaluation at that time.

Recurrence is common; hence long-term anti-coagulation may be required in selected cases.

#### Role of Aspirin in Preventing Recurrence

In a recent, double-blind, placebo controlled study, involving patients

who completed 6-18 months of oral anticoagulation after a first episode of unprovoked venous thrombo-embolism, aspirin 100 mg/day for 2 years reduced risk of recurrence without increase in risk of major bleeding.<sup>53</sup> The risk of protection is inferior compared to vitamin K antagonists and new oral anticoagulants; however, low dose aspirin (75-100mg) might find a place for long-term secondary prophylaxis in selected patients with high bleeding risk.

#### Future Directions: use of Multi-disciplinary Approach

Recently, an innovative concept of a pulmonary embolism response team (PERT) composed of

specialists in various fields has been suggested. PERT team consisting specialists from cardiology, emergency medicine, vascular medicine, cardiac surgery, and pulmonary/critical care can help to streamline management of severe PE. An on-call PERT colleague, upon activation immediately calls an online meeting of specialists which enables to provide rapid consultation with multidisciplinary approach. Kabrhel C et al<sup>54</sup> published their experience of 30 such PERT activations in 12 weeks. Based on this experience, wherever possible, PERT can be formed in India for improving PE diagnosis and outcomes.

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