Current Concepts in the Diagnosis and Management of Pulmonary Embolism

Sridhar Kasturi

Sunshine Heart Institute, Secunderabad, Telangana, Hyderabad, India
Email: sridharkasturi@yahoo.com

Abstract

Acute pulmonary embolism (PE) is one of the most common causes of cardiovascular death. Most often acute PE is associated with under diagnosis, misdiagnosis and delay in diagnosis and management leading to high morbidity and mortality. PE outcomes will improve with proper evaluation of clinical symptoms and signs, relevant diagnostic tests, identifying high-risk patients suitable for early re-perfusion with I.V. or catheter-directed thrombolytic therapy or surgical embolectomy and in some cases additional use of mechanical circulatory support. During clinical evaluation modified Geneva score, Well's score, and Simplified pulmonary embolism severity index (sPE-SI) scores are useful in assessing PE and its adverse outcomes. Hestia criteria are useful in identifying suitable for outpatient management of PE. Long-term management of PE involves identifying patients prone for recurrence and CTPE with appropriate long-term prophylaxis using oral anticoagulants.

Keywords

Pulmonary Embolism, Management of PE

1. Introduction

Acute pulmonary embolism (PE) is due to Deep Vein Thrombosis (DVT) embolism, *i.e.* blood clot or part of it breaks off from the vein. DVT is a formation of thrombosis in the deep vein of the lower extremity or pelvis either partially or blocking blood flow [1]. Acute PE ranges from asymptomatic, incidentally discovered sub-segmental thrombi to massive PE complicated by cardiogenic shock and multi-organ dysfunction. The most common PE source is lower extremity sites and unusual sites are the right heart, upper extremity, renal veins, iliac veins and hepatic veins.

Sudden occlusion of the pulmonary artery and its branches results in abrupt

increase of pulmonary vascular resistance to a level of afterload that cannot be matched by the RV causing RV dysfunction, failure, and sometimes sudden death due to Electro-mechanical dissociation. Clinical symptoms and signs of PE depend on the extent and duration of the pulmonary artery obstruction and pre-existing cardiopulmonary status.

Epidemiology

PE is the 3rd most common cause of cardiovascular death [2]. It constitutes approximately 100,000 to 180,000 deaths/annum in USA. Vein thrombus-embolism (VTE) mortality was observed in more than 370,000 people of 6 European countries annually, which is more than the reported combined mortality from AIDS, breast cancer, prostate cancer and traffic accidents. Clinical spectrum of PE varies from asymptomatic to complete cardiovascular collapse. Autopsy based study of 1000 patients observed 15.9% was the reported incidence of PE in India. PE is underestimated, underdiagnosed and undertreated in most patients, and it was estimated that only 8% of patients were exactly diagnosed as a case of PE before death. Untreated DVT/PE has serious long term consequences like recurrent VTE, post-thrombotic syndrome, venous ulceration and chronic thromboembolic pulmonary hypertension (Figure 1). Every effort should be made to clear the clot as early as possible to improve acute hemodynamic status by reversing acute and sub-acute RV dysfunction, chronic thrombotic pulmonary embolism (CTPE), and lowering the mortality rate. CT-PE is a serious complication of PE occurs in 4% of patients and if untreated, associated with a 90% mortality rate.

2. Classification, Assessment of Clinical (Pre-Test) Probability and Risk stratification

PE patients can be categorized as low-risk PE, sub-massive PE, and massive PE. Low-risk PE constitutes 55% of PE patients carries a good prognosis with a
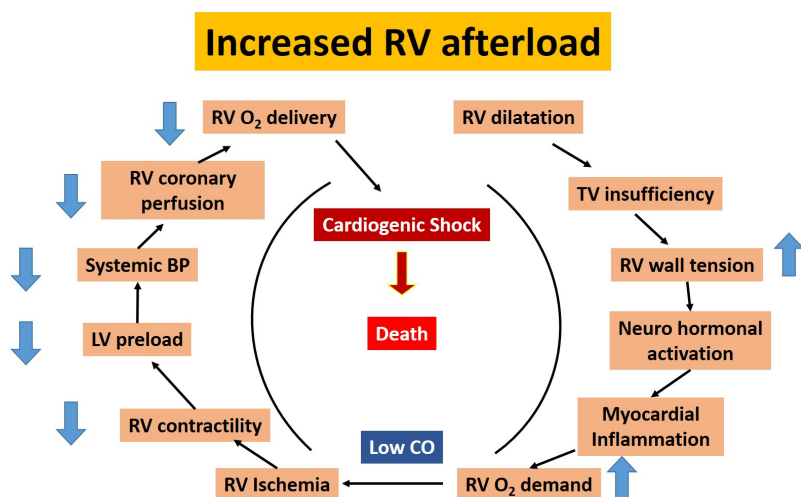

Figure 1. Key factors contributing to hemodynamic collapse and death in acute pulmonary embolism.

mortality of 1%, sub-massive PE was observed in 40% of patients with a mortality of 21% at three months. In contrast, massive PE was observed on average of 5% of PE patients with 58% mortality at three months [3].

Pulmonary embolism can be predicted clinically using wells score and revised Geneva score in a clinically suspected PE case to plan appropriate strategies for treating PE (Table 1).

The spiral of hemodynamic collapse in acute PE (Figure 1): ESC 2019 PE guidelines.

Risk assessment of PE:

PE patients can be classified (Table 2) as a high-risk, intermediate-risk and low-risk group. High-risk group patients are with hemodynamic instability in contrast to the other two groups. Low-risk patients are without elevated Troponin-I, RV dysfunction, and PESI III to IV or SPESI ≥ 1. Intermediate risk group patients have increased troponin I or RV dysfunction with PESI III to IV or SPESI ≥ 1.

Table 3: Simplified pulmonary embolism severity index (PESI) [4].

Patients with none of the clinical variable (*i.e.*, the total score of 0) are considered as low risk and have mortality and pulmonary embolism-related complication rates significantly lower as those with a score of ≥1.

Table 1. Pulmonary embolism can be predicted clinically using wells score and revised Geneva score.

Revised Geneva Score		Wells Score	
Variable	Points	Variable	Points
Predisposing factors		**Predisposing factors**	
Age > 65 years	+1		
Previous DVT or PE	+3	Previous DVT or PE	+1.5
Surgery or fracture within one month	+2	Recent surgery or immobilization	+1.5
Active malignancy	+2	Cancer	+1
Symptoms		Symptoms	
Unilateral lower limb pain	+3		
Hemoptysis	+2	Hemoptysis	+1
Clinical Signs		Clinical Signs	
Heart rate		Heart rate	
75 - 94 beats/min		>100 beats/min	
	+3		+1.5
±95 beats/min	+5		
Pain on lower limb deep vein at palpitation and unilateral edema	+4	Clinical signs of DVT	+3
		Clinical Judgement	
		Alternative diagnosis less likely than PE	+3
Clinical Probability	**Total**	**Clinical Probability (3 levels)**	**Total**
Low	0 - 3	Low	0 - 1
Intermediate	4 - 10	Intermediate	2 - 6
High	±11	High	± 7
		Clinical Probability (2 levels)	**Total**
		PE unlikely	0 - 4
		PE likely	> 4

Table 2. Classification of PE by American heart association (2011) and European society of cardiology (2019).

AHA CLASSIFICATION (2011)	ESC CLASSIFICATION (2019)*
MASSIVE PE	**HIGH-RISK PE**
Hypotension, defined as a systolic blood pressure < 90 mm Hg, a drop of >40 mm Hg for at least 15 minutes, or need for vasopressor support	One of the following clinical presentations: cardiac arrest, obstructive shock, persistent hypotension (systolic BP < 90 mmHg or a systolic BP drop > _40 mmHg for >15 min
SUBMASSIVE PE	**INTERMEDIATE RISK PE**
Acute PE without systemic hypotension (systolic blood pressure > 90 mm Hg) but with either RV dysfunction or myocardial necrosis[3]	Acute PE without systemic hypotension (systolic blood pressure > 90 mm Hg) but with either RV dysfunction or elevated cardiac troponin levels[3] Additionally, include PESI/sPESI criteria.
LOW-RISK PE	**LOW-RISK PE**
Acute PE and the absence of the clinical markers of adverse prognosis that define massive or sub-massive PE[3]	No RV dysfunction/no elevated cardiac troponins/normal PESI

Table 3. Simplified pulmonary embolism severity index.

Variable	Points
Age > 80 years	1
History of cancer	1
History of heart failure or chronic lung disease	1
The pulse rate of ≥110 bpm	1
Systolic blood pressure < 100 mmHg	1
Oxygen saturation < 90% on room air	1

3. Diagnosis and Management of PE

Management of PE depends upon early diagnosis and assessing risk status to decide appropriate re-perfusion and anticoagulant therapy on fast track basis to reduce mortality and morbidity associated with misdiagnosis and delay in the treatment of PE (Figure 2).

3.1. Plasma D-Dimer

Plasma D-Dimer is the degradation product of cross-linked fibrin. ELISA derived assays have the highest sensitivity, its measurement recommended in out-patient/emergency department patients with low or intermediate clinical probability, or PE unlikely to reduce the need for unnecessary imaging and irradiation.

3.2. Troponin

Elevated plasma troponin (Trop-T/I) concentrations on admission may be associated with a worse prognosis in the acute phase of PE. Elevated Trop-T/I levels
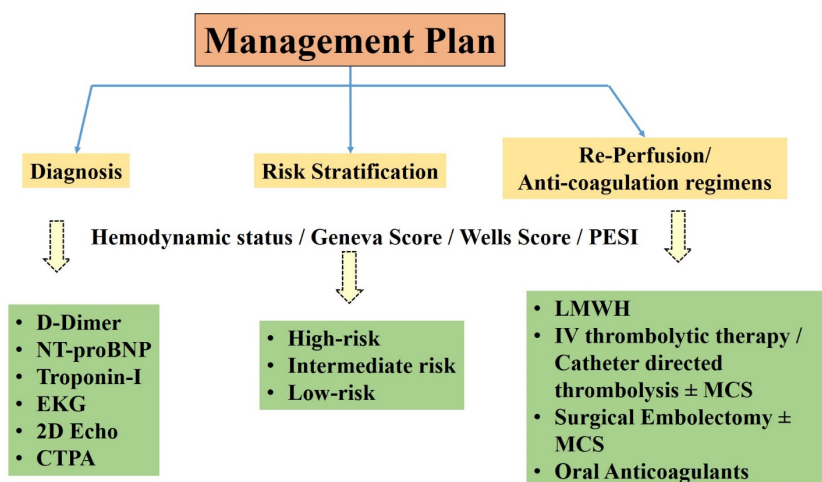
Figure 2. Management of PE.

are observed in approximately 50% of the patients with acute PE, associated with an increased risk of death and significant adverse events in the acute phase. A meta-analysis showed that elevated troponin concentrations were associated with an increased risk of mortality, both in unselected patients (OR 5.2, 95% CI 3.3 - 8.4) and in those who were hemodynamically stable at presentation (OR 5.9, 95% CI 2.7 - 13.0) [5].

3.3. BNP and proBNP

Elevated BNP or NT-proBNP levels associated with low specificity and positive predictive value for increased mortality rate in hemodynamically stable patients with PE, but low levels of BNP or NT-proBNP will exclude an unfavorable early clinical outcome, with high sensitivity and a negative predictive value. A meta-analysis of 13 studies showed 51% of 1132 patients with acute PE with elevated brain natriuretic peptide (BNP) or N-terminal (NT)-proBNP levels contributed to high risk of early death and a complicated in-hospital Course [5].

3.4. EKG

EKG findings vary from patient to patient. Characteristic findings are—sinus tachycardia, T-wave changes, ST-segment changes, right axis deviation, S1-Q3-T3, RBBB and P-pulmonale.

3.5. Chest X-Ray (Figure 3)

Primarily to exclude other diagnoses like pneumonia, pneumothorax, CHF, tumour, and rib fracture, which are also helpful in interpreting the V/Q scan. PE can present with radio-graphical signs on chest X-ray like (https://radiopaedia.org/articles/pulmonary-embolism)—Fleischner sign: Enlarged pulmonary artery, Hampton's Hump: peripheral wedge of airspace opacity and implies lung infarction, Westermark sign: regional oligemia and highest positive predictive value, Knuckle sign: abrupt tapering or cutoff of a pulmonary
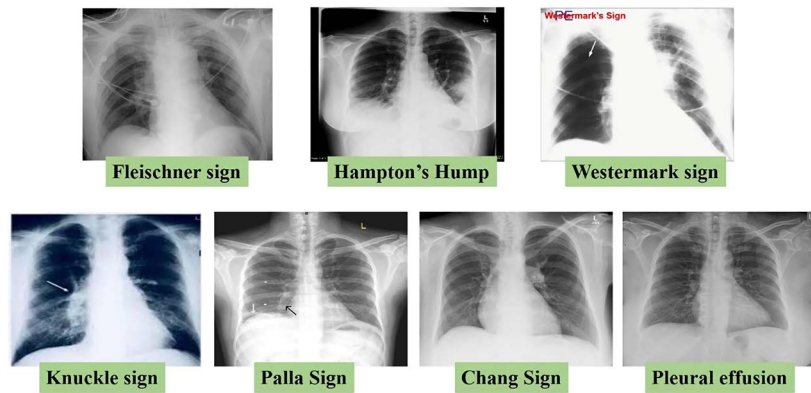
Figure 3. Different radio-graphical signs on chest X-ray of PE (https://radiopaedia.org/articles/pulmonary-embolism).

artery secondary to an embolus, Palla Sign: enlarged right descending pulmonary artery, Chang Sign: dilated right descending pulmonary artery with sudden cut-off, and in some cases Pleural effusion evident (35%).

3.6. Echocardiogram

Transesophageal Echocardiography (TEE) more sensitive than Transthoracic Echocardiography (TTE). It may demonstrate intra-cardiac, main pulmonary artery, and its main branches clots, RV enlargement and signs of right ventricular dysfunction. TTE should be performed to all patients with PE, and feasible in patients with stable hemodynamic status (**Figure 4(a)** & **Figure 4(b)**).

Echocardiographic RV/LV ratio ≥ 0.9 shown to be an independent predictor of hospital mortality. Registry of 1416 patients showed mortality rate is 1.9% if the RV/LV ratio is of <0.9, and 6.6% if the RV/LV ratio is of ≥0.9. Retrospective analysis of 120 patients with hemodynamically stable PE based on chest CT showed mortality at 3 months: 17% if RV/LV ≥ 1.5, 8% if 1 ≤ RV/LV < 1.5 and 0% if RV/LV 1.0 [6].

3.7. Computed Tomography Pulmonary Angiography (CTPA)

It has an excellent accuracy in diagnosing PE and may provide alternative diagnoses if PE is excluded with short acquisition time. Main disadvantages of CTPA are exposure to radiation and contrast related problems. CT identifies proximal PE, which is more often associated with the hemodynamic imbalance and not very accurate in diagnosing peripheral PE. CT can show enlarged right ventricle and estimation of the right ventricle and left ventricle ratio (**Figure 5**).
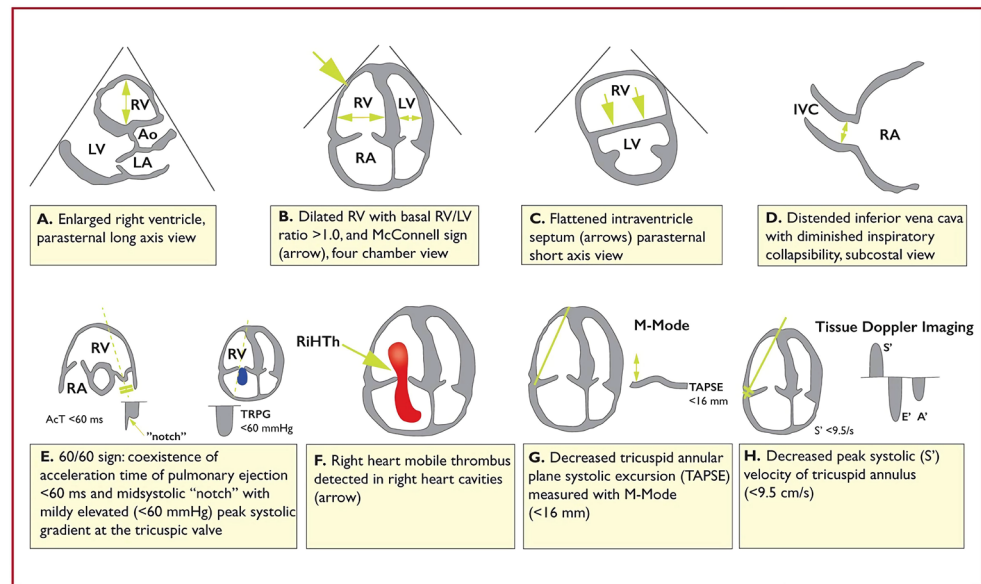
CT scan showing right pulmonary thrombus with RV enlargement (RV/LV ratio > 1) suggestive of massive pulmonary embolism (PE)

3.8. Planar V/Q Scan

Is useful in diagnosing PE but available in limited centres, relatively expensive, no contraindications, inconclusive in 50% cases, and cannot provide the alternative diagnosis.
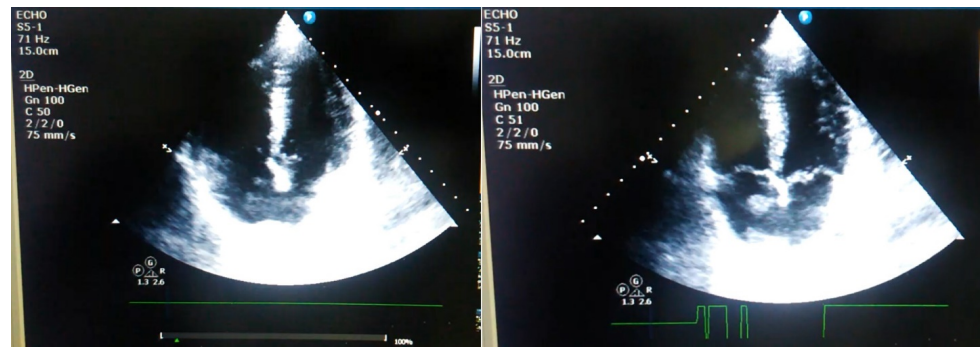
(a)

(b)

Figure 4. (a) Trans-esophageal Echocardiography (TEE), Trans-thoracic Echocardiography (TTE); (b) Graphic representation of transthoracic echocardiographic parameters in the assessment of right ventricular pressure overload (ESC-2019). A' = peak late diastolic (during atrial contraction) velocity of tricuspid annulus by tissue Doppler imaging; AcT = right ventricular outflow Doppler acceleration time; Ao = aorta; E' = peak early diastolic velocity of tricuspid annulus by tissue Doppler imaging; IVC = inferior vena cava; LA = left atrium; LV = left ventricle; RA = right atrium; RiHTh = right heart thrombus (or thrombi); RV = right ventricle/ventricular; S' = peak systolic velocity of tricuspid annulus by tissue Doppler imaging; TAPSE = tricuspid annular plane systolic excursion; TRPG = tricuspid valve peak systolic gradient.
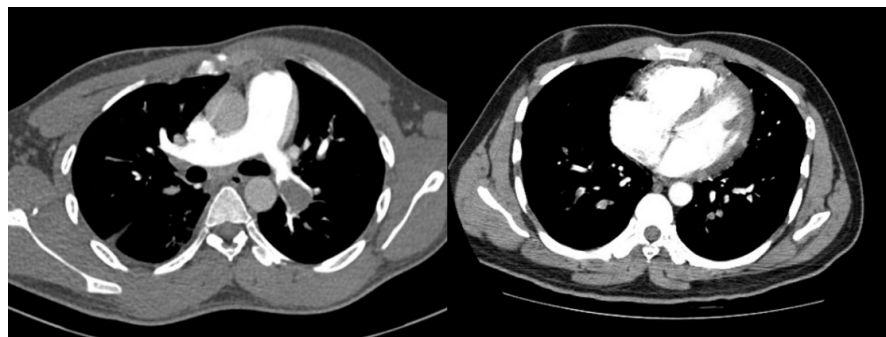

Figure 5. Computed tomography pulmonary angiography for PE.

3.9. Compression Ultrasonography Lower Limb (CUS)

If CUS shows proximal DVT in a patient with clinical suspicion of PE, PE diagnosis is acceptable, and if it shows only a distal DVT, further testing should be considered to confirm PE.

3.10. Pulmonary Angiogram (PA)

Most specific test, can detect even small emboli, presents like intraluminal filling defects, and vascular cutoffs. It is associated with a 0.5% mortality rate.

Bedside echo or emergency CTPA helps categorize and assess risk based on evidence of RV enlargement/RV dysfunction and make the alternative diagnosis. It would be preferable to start low molecular weight heparin (LMWH) in patients with suspected high-risk PE to avoid delay in starting therapy while carrying routine investigations. LMWH or Fondaparinux (Table 4) is recommended (preferred over unfractionated heparin (UFH)) for most patients as the anticoagulation is mandatory to all. Patients When oral anticoagulation is started, in a patient with PE who is eligible for a NOAC (Apixaban, Dabigatran, Edoxaban, or Rivaroxaban), a NOAC is recommended in preference to a Vitamin K Antagonist (VKA).

Table 4 of LMWH and oral anticoagulation.

VKA anticoagulation initiation should be overlapped with parenteral anticoagulation until an INR of 2.5 (range 2.0 - 3.0) is reached. NOACs should be avoided in patients with severe renal impairment, during pregnancy or lactation, and in patients with antiphospholipid antibody syndrome.

4. Management of PE

High-risk or massive PE seen in 5% of patients presenting with acute PE is

Table 4. Recommended LMWH and oral anti-coagulant doses based European society of cardiology 2019 guidelines.

	Dosage	Interval
	1.0 mg/kg	Every 12 h
Enoxaparin	Or	
	1.5 mg/kg	Once daily
Tonzaparin	175 IU/kg	Once daily
	100 IU/kg	Every 12 h
Dalteparin	Or	
	200 IU/kg	Once daily
	86 IU/kg	Every 12 h
Nadroparin	Or	
	171 IU/kg	Once daily
	5 mg (body weight < 50 kg);	
Fondaparinux	7.5 mg (body weight 50 - 100 kg);	Once daily
	100 mg (body weight > 100 kg);	

associated with at least 15% risk of in-hospital death, particularly during the first hours after admission (Figure 6). The crucial determining factor in PE management is the presence and severity of RV systolic dysfunction resulting from acute pressure load. These patients should be treated with reperfusion treatment and hemodynamic support. Thrombolytic therapy of PE is well tolerated with
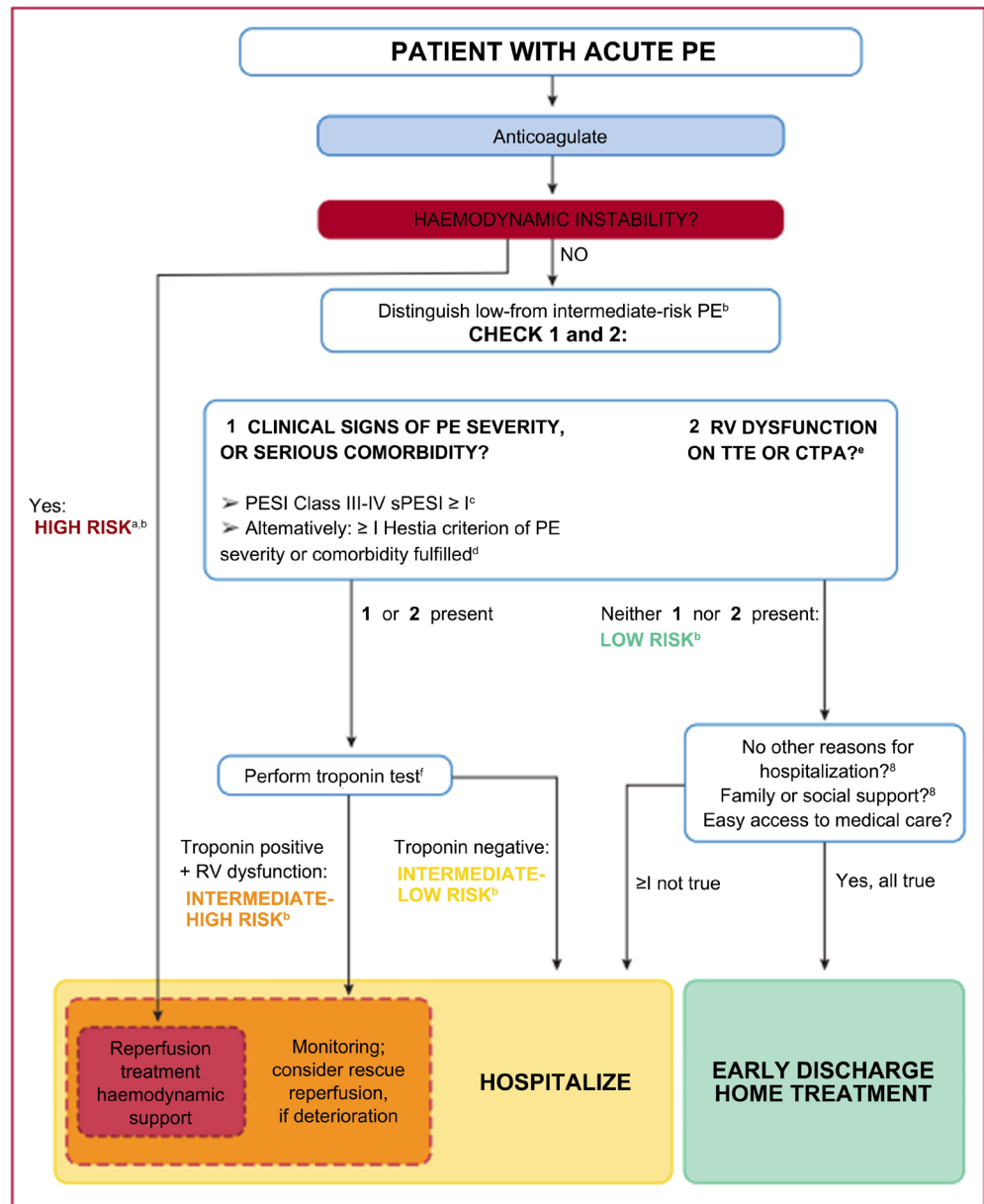

Figure 6. Risk-adjusted management strategy for acute pulmonary embolism (ESC-2019). CTPA = computed tomography pulmonary angiography/angiogram; PE = pulmonary embolism; PESI = Pulmonary Embolism Severity Index; RV = right ventricular; sPESI = simplified Pulmonary Embolism Severity Index; TTE = transthoracic echocardiogram. [a]emergency management algorithm. [b]high, intermediate-high-, intermediate-low-, and low-risk PE. [c]Cancer, heart failure and chronic lung disease are included in the PESI and sPESI. [d]the Hestia criteria. [e]Prognostically relevant imaging (TTE or CTPA) findings in patients with acute PE. [f]A cardiac troponin test may already have been performed during initial diagnostic work-up. [g]Included in the Hestia criteria.

excellent prognosis and carries a risk of significant bleeding 1.8% - 6.3% and Intra Cerebral haemorrhage (ICH) 1.2%. It produces faster clot lysing, dissolves obstruction, reverses RV failure, dissolves much of source, and decreases recurrence risk.

Risk-adjusted management strategy for acute PE

Efficacy and safety of systemic thrombolysis in acute PE well proven in Meta-analysis with the reduction in all-cause mortality, PE mortality, PE recurrence with low bleeding complications. Therapeutic doses and contraindications are given in Table 5.

Plasminogen Activator Italian Multicenter Study II (PAIMS-II) included 36 patients with acute PE treated with rtPA 10 mg bolus followed by 90 mg over 2 hours' period and showed reduced angiographic severity of PE, mean pulmonary artery pressure, and increase of the cardiac index [7]. A randomized, double-blind trial assessing RV function and pulmonary function compared Alteplase Vs Heparin which included 101 stable patients with acute PE showed improvement of RV function, reduction in RV dimensions, improvement of pulmonary function and no PE occurrence in rtPA group [8]. Another randomized control trial of rtPA (n = 22) vs Urokinase (n = 23) showed clot lysis in 82% of rtPA vs 48% Urokinase treated patients [9]. A European multicenter, double-blind trial showed a decrease in pulmonary vascular resistance at 2hours, *i.e.* 18% ± 22% in Urokinase vs 36% ± 17% in Alteplase treated patients [10]. RCT of STK vs Alteplase in massive PE with 50 patients showed significant RV ejection fraction and fall of PVR in Alteplase group compared to STK [11].

Table 5. Therapeutic doses and contraindications for acute PE.

Molecule	Regimen	Contraindications to fibrinolysis
Recombinant tissue-type plasminogen (rtPA)	100 mg over 2 h 0.6 mg/kg over 15 min (maximum dose 50 mg)	**Absolute:** ➢ History of hemorrhagic stroke or stroke of unknown origin ➢ Ischemic stroke in previous 6 months ➢ CNS neoplasm ➢ Major trauma, surgery, or head injury in previous 3 weeks ➢ Bleeding diathesis ➢ Active bleeding
Streptokinase	250,000 IU as a loading over 30 min, followed by 100,000 IU/h over 12 - 24 h Accelerated regimen: 1.5 million IU over 2 h	
Urokinase	4400 IU/kg as a loading dose over 10 min, followed by 4400 IU/kg/h over 12 - 24 h Accelerated regimen: 3 million IU over 2 h	**Relative:** ➢ Transient ischemic attack in previous 6 months ➢ Oral anticoagulation ➢ Pregnancy or first postpartum week ➢ Non-compressible puncture sites ➢ Traumatic resuscitation ➢ Refractory hypertension (systolic BP > 180 mmHg) ➢ Advanced liver disease ➢ Infective endocarditis ➢ Active peptic ulcer

All patients with massive PE should be tried with fluid expansion if no significant IVC and RV dilatation followed by IV Nor-epinephrine and IV Dobutamine infusion for hypotension correction inotropy. Volume loading saline or ringer's lactate up to 500 ml over 15 to 30 minutes can be considered in patients with average to low central venous pressure. It sometimes can be over distending the RV, worsen ventricular interdependence and reduce CO. Mechanical ventilation with Positive End Expiratory Pressure (PEEP) is to be avoided as far as possible which may worsen the clinical condition, and try to limit tidal volume plateau pressure due to decreasing venous return. Some high-risk PE patients may get benefited with additional mechanical circulatory support like ECMO along with thrombolysis treatment; catheter-directed PE therapy and surgical pulmonary embolectomy.

Rescue thrombolysis therapy is recommended for patients with hemodynamic deterioration in anticoagulation therapy. Alternatively, these patients can be treated with surgical embolectomy or catheter-directed thrombolysis or interventions percutaneously. Routine treatment is not recommended for intermediate or low-risk PE patients. Percutaneous catheter-directed thrombolysis treatment should be considered for high-risk PE patients whose thrombolytic therapy is contraindicated or has failed. ECMO should be considered in combination with surgical embolectomy or catheter-directed therapy in patients with high-risk PE associated with refractory collapse or cardiac arrest (Figure 7).

No clinical benefit of VA-ECMO in patients with PE unless combined with surgical embolectomy or catheter-directed therapies. Catheter-directed thrombolysis includes CDT, lytic assisted devices—pharmaco mechanical, sonic assisted, Mechanical thrombectomy devices like simple suction ± clot fragmentation, and large bore aspiration.
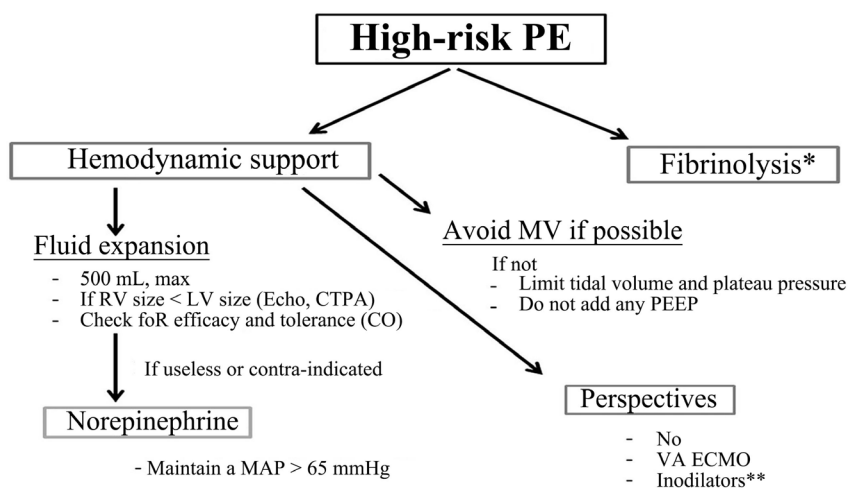
RV right ventricle, LV left ventricle, computed tomography pulmonary angiography (CTPA), cardiac output (CO), mechanical ventilation (MV), nitric oxide inhalation (NO), veno-arterial extracorporeal membrane oxygenation (VA ECMO)

Figure 7. Proposal for hemodynamic management in high-risk PE (Meyer G, *Ann. Intensive Care* 2016).

Surgical embolectomy is indicated in patients with massive PE with contraindication to thrombolytic therapy, failed thrombolytic treatment, pregnancy, right heart failure or cardiogenic shock.

European Society of Cardiology (ESC) 2019 guidelines recommended Hestia exclusion criteria for choosing outpatient management of PE (Table 6).

5. Risk Factors Associated with Recurrent Venous Thromboembolism (VTE) and Anticoagulant-Related Bleeding (Table 7)

Long-term PE management after discharge depends on the possibility of recurrent

Table 6. Hestia exclusion criteria for choosing outpatient management of PE by ESC 2019.

Criterion/question
Is the patient hemodynamically unstable?
Is thrombolysis or embolectomy necessary?
Active bleeding or high-risk of bleeding?
More than 24 h of oxygen supply to maintain oxygen saturation > 90%?
Is PE diagnosed during anticoagulation treatment?
Severe pain needing I.V. pain medication for >24 h?
Medical or social reason for treatment in the hospital for >24 h (infection, malignancy, no support system)?
Does the patient have a creatinine clearance < 30 mL/min?
Does the patient have severe liver impairment?
Is the patient pregnant?
Does the patient have a documented history of heparin-induced thrombocytopenia?
If at least one of the questions is answered with "yes", the patient can't discharged early.

Table 7. Risk factors associated with recurrent VTE and anticoagulant-related bleeding.

Recurrent VTE	Serious or fatal bleeding	Both recurrent VTE and severe bleeding
Initial unprovoked VTE	Low platelet count	Increased age
Initial proximal DVT or PE	Previous bleeding	Cancer
Thrombophilia	Recent major bleeding	Immobilization
Residual proximal thrombosis	Previous stroke	Recent surgery (transient)
Male sex	Hepatic failure	Severe renal impairment
Elevated D-dimer concentrations	Diabetes	
When not receiving anticoagulation	Abnormal prothrombin time	
Pregnancy	Thrombocytopenia	
Anticoagulation lasting < 3 months	Poor anticoagulant control	
	Comorbidity	
	Anemia	

PE, fatal bleeding and balancing the risk vs benefit of preventing recurrence vs bleeding related events. Standard anticoagulation therapy for at least three months is recommended to all patients, and it can be stopped after three months for patients with 1st PE/VTE secondary to major transient/reversible risk factor.

Indefinite duration is recommended for recurrent VTE (*i.e.* with at least one previous PE or DVT) not related to a significant transient or reversible risk factor and patients with antiphospholipid antibody syndrome. It would be preferable to assess drug tolerance and adherence, hepatic and renal function, and the bleeding risk at regular intervals during follow-up. For patients with PE and cancer, weight-adjusted subcutaneous LMWH should be considered for the first six months over VKAs. Edoxaban and Rivaroxaban in patients without gastrointestinal cancer should be considered as an alternative treatment to LMWH. Routine use of IVC filter is not recommended, indicated to PE patients with absolute contraindication to anticoagulation and in case of PE recurrence despite therapeutic anticoagulation [5].

In a pregnant patient with suspected PE, venous CUS should be considered to avoid unnecessary irradiation. Perfusion scan or CTPA should be considered to rule out suspected PE. LMWH therapy should be considered for all pregnant women with PE, thrombolytic therapy or surgical embolectomy should be recommended for patients with high-risk PE. NOACs should be avoided during pregnancy or lactation period [5].

6. Pulmonary Embolism Response Team (PERT) Approach

With the prompt response, PE management with Pulmonary Embolism Response Team (PERT) improves patient outcomes using collaborative, multidisciplinary teams with the best therapeutic options available with well-ordination protocol-based services (Figure 8). It was observed that with PERT based management reduces delay in diagnosis and treatment, reducing mortality by choosing the best possible therapeutic options.
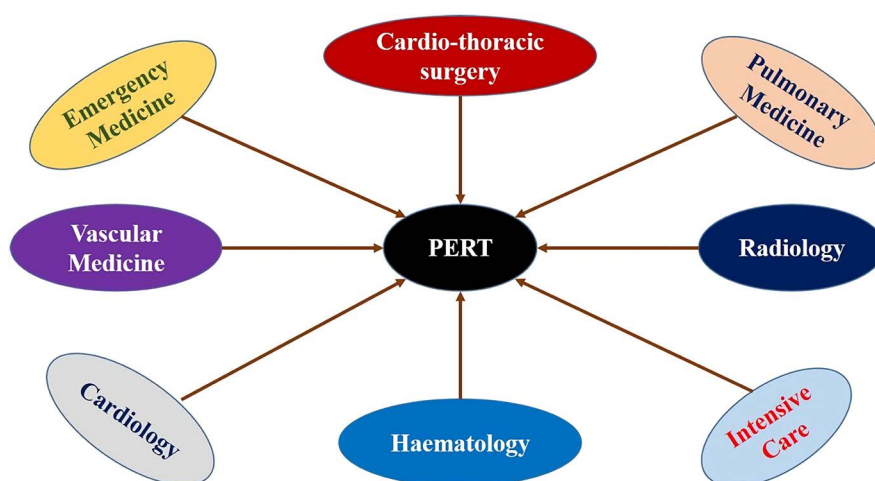

Figure 8. Pulmonary embolism response team.

7. Conclusion

VTE clinically presenting as DVT or PE, is globally the third most frequent acute cardiovascular syndrome behind myocardial infarction and stroke. Thrombolytic therapy is recommended in all patients with high risk PE, unless contraindicated. Routine use of primary systemic thrombolysis is not recommended in patients with intermediate-or low-risk PE. The assembly of a PERT can offer a way to expeditiously and simultaneously engage multiple experts to generate a thoughtful, coordinated, and comprehensive treatment plan for patients with PE.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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