Pulmonary embolism (PE) is a common and potentially lethal condition. The incidence of PE in the USA is 2 to 3 cases per 1000 persons per year, and accounts for 200,000 to 300,000 hospitalizations in a year.\(^1, 2\) The short-term mortality of acute PE varies from < 2% in those with nonmassive PE to > 65% in those who develop hemodynamic shock.\(^3, 4\) PE is also the direct cause of 5% to 10% of all in-hospital deaths.\(^5, 6\)

PE is the complication of deep vein thrombosis (DVT) in most cases, and about 50% of patients with proximal DVT have usually asymptomatic PE at lung scan.\(^7\) DVT has also been documented in lower limbs in about 70% of patients with PE.\(^8\) Early diagnosis and appropriate treatment considerably reduces the morbidity and mortality in acute PE.

**Definitions**

PE is traditionally divided into 3 categories: massive, submassive, and low-risk PE. The massive PE was originally defined on the basis of angiographic burden of emboli\(^9\) but it has not been proven of much clinical relevance. In patients with acute PE, the age and clinical comorbidities significantly influence the prognosis.\(^10, 11, 12\) A patient with submassive PE may have a high-risk for complications in the presence of comorbidities.\(^13\) Similarly, patients with low-risk PE who are elderly or have other clinical illnesses may still have increased PE-related complications.\(^13, 15\)

The American Heart Association (AHA) has recently proposed to define these different categories of PE as follows.\(^15\)

(a) **Massive PE:** Acute PE in patients with sustained hypotension (BP <90 mm Hg for > 15 min or requiring inotropic support), or persistent profound bradycardia (heart rate < 40/min with shock).

(b) **Submassive PE:** Acute PE in patients without systemic hypotension but with either right ventricular (RV) dysfunction or evidence of myocardial necrosis. The RV dysfunction is defined by the presence of at least 1 of the followings: 1) RV dilation (RV diameter/LV diameter >0.9) or RV systolic dysfunction on echocardiography; 2) RV dilation on CT; 3) Elevation of BNP (>90 pg/mL); 4) Elevation of N-terminal pro-BNP (>500 pg/mL); or 5) New RBBB, anteroseptal ST elevation or depression, or anteroseptal T-wave inversion on ECG. Myocardial necrosis is present if Troponin I is >0.4 ng/mL or troponin T is >0.1 ng/mL.

(c) **Low risk PE:** Acute PE in patients who are normotensive with normal biomarker levels and no RV dysfunction on imaging studies.

**Diagnosis of PE**

A major problem in the diagnosis of PE is that symptoms and signs are often non-specific, and most patients suspected of PE do not have it. In the diagnostic strategies in patients with suspected PE, the initial focus is on identifying those in whom PE can be ruled out.\(^16, 17\)

A patient with suspected PE should first have assessment of the probability of PE, so as to identify those with a high or intermediate clinical probability for PE needing prompt anticoagulant treatment while awaiting their diagnostic results including imaging studies.\(^18\) The estimate of pretest probability (PTP) for PE has a significant impact on choice and interpretation of diagnostic
tests as well. For example, a patient with high probability for PE should directly be subjected to imaging studies without D-dimer test. Also patients with a low PTP for PE and a negative D-dimer result need no further studies.\textsuperscript{16,17,19}

The pretest probability for PE can be assessed empirically using either empirical clinical assessment or with prediction rules or scores.

**Clinical Prediction Rules**

Before proceeding with the testing for suspected pulmonary embolism, the pretest probability of PE is estimated. It is recommended that validated clinical prediction rules (CPRs) be used to estimate pretest probability of PE and to interpret test results. These rules have improved the diagnostic work-up of patients with suspected PE. PE can be safely excluded in most patients with normal D-dimer result, if a clinical prediction rule suggests “PE unlikely”, without the need for further testing with computed tomographic pulmonary angiography (CTPA) or ventilation-perfusion (V/Q) scintigraphy.

Several statistically derived scores or clinical prediction rules (CPRs) have been developed in the past that provide estimates of the probability of PE using clinical information. A prediction rule for acute PE was first described by Hoellerich and colleagues in 1986 \textsuperscript{20} however it was not validated in large clinical studies. Subsequently, several CPRs have been described, of these, the Wells score \textsuperscript{21} and the Geneva score \textsuperscript{22} are the most widely validated. Many of these CPRs have also been modified so as to make them simpler and easier to use in clinical practice, such as modified Wells score \textsuperscript{23}, revised Geneva score \textsuperscript{24}, and simplified revised Geneva score.\textsuperscript{25}

The most widely used CPRs are Wells score and the revised Geneva score for suspected PE. Although all scores have been validated in outpatients, only the Wells score has been validated in hospitalized patients.\textsuperscript{26} Several meta-analyses performed in patients with acute PE have documented that different CPRs have similar accuracy in assessing clinical probability of PE, but are not totally equivalent.\textsuperscript{17,26} In high prevalence situation for PE, a rule with higher specificity is desirable, whereas in a lower prevalence situation, a rule with higher sensitivity is advisable.\textsuperscript{17}

**D-dimer Testing**

D-dimer is a degradation product of cross-linked fibrin. It is highly sensitive for the diagnosis of acute thrombotic process including PE, but lacks specificity.

PE can be safely excluded in those who have a low or intermediate pretest probability (PTP) which is derived from one of the clinical prediction rules as discussed earlier, and a negative D-dimer result.\textsuperscript{16,17,19} These patients do not require anticoagulant treatment as two meta-analyses have also confirmed these results.\textsuperscript{27,28} The recurrence rate of subsequent venous thromboembolism (VTE) in those not treated on the basis of low pretest probability (PTP) and a negative D-dimer testing is < 1%.

The main limitation of D-dimer is its low specificity. Apart from acute PE and deep vein thrombosis (DVT), it is also elevated in other conditions, including surgery, malignancy, infection, pregnancy and acute myocardial infarction.\textsuperscript{29}

**Compression ultrasonography (CUS)**

A high percentage of proximal DVT progresses to PE. The contrast venography has traditionally been considered the gold standard for the diagnosis of DVT, however in recent years CUS has largely replaced it in the diagnosis of DVT of lower extremities. CUS reliably confirms or rules out proximal DVT. It may also be performed as initial imaging modality for evalu
ation of suspected PE in critically ill unstable patients and pregnant women. In patients with indeterminate ventilation/perfusion (V/Q) scan, CUS plays an important role. The presence of proximal DVT in a symptomatic patient with contraindications for CT pulmonary angiography (CTPA) is considered sufficient to rule in PE. However, a negative CUS does not rule out PE, as > 50% of patients with confirmed PE have a negative CUS.

**Ventilation/perfusion (V/Q) scanning**

For many decades, radionuclide V/Q scanning was the modality of choice for the diagnosis of PE. In recent years, it has been largely supplanted by CT pulmonary angiography (CTPA). Both CTPA and V/Q scanning can safely rule out PE if the results are negative. V/Q scan may be preferable in premenopausal women (only perfusion scintigraphy in pregnancy advocated), and patients with renal insufficiency or dye allergy. V/Q scan is conventionally reported as normal, high probability, or non-high probability scan. A normal V/Q scan essentially excludes PE. A high-probability scan is one in which there is at least one segmental defect on perfusion scintigraphy with normal ventilation scintigraphy. However a large number of V/Q scans are reported as non-high or indeterminate probability scan. In a prospective study directly comparing CTPA with V/Q scan in patients with suspected PE, 54% of V/Q scans were reported as non-diagnostic. A nondiagnostic V/Q scan combined with a negative venous ultrasound excludes PE if clinical suspicion is not high, however, CTPA should be considered in those with high clinical likelihood for PE.

In recent years, the single-photon-emission CT (SPECT) scan appears to be a promising modality in the diagnosis of PE. Some studies have even suggested that SPECT may have a higher sensitivity compared to CTPA for diagnosis of acute PE than CTPA, although such observations need further evaluation.

**Multidetector Computed Tomographic Pulmonary Angiography (CTPA)**

CTPA has replaced conventional pulmonary angiography as the reference test for PE. CTPA is highly sensitive (96% to 100%) with a specificity of about 98% for the diagnosis of PE. A normal CTPA safely rules out PE if clinical pretest probability is low or intermediate. In a study, only 1.3% of patients with high pretest probability of PE but a negative CTPA subsequently developed PE during a 3-month follow-up period. In normotensive patients, the CTPA may also allow risk stratification before echocardiography results. A further advantage of CTPA is that it may provide alternative diagnoses or detect unsuspected lung pathology.

**Medical Resonance Angiography (MRA)**

The role of magnetic resonance pulmonary angiography (MRA) in acute PE is under investigations, however, it has a much less sensitivity and specificity compared to CTPA. In the recent PIOPED III study, the sensitivity of MRA was only 78% with an overall specificity of 99%. Presently, MRA and thigh vein MR venography is considered only in patients in whom other imaging studies can not be performed.

**Pulmonary angiography**

The catheter pulmonary angiography was traditionally considered the gold standard for the diagnosis of PE, and was the standard practice since late 1960s onwards. However, CTPA and V/Q scanning have almost replaced it in the evaluation of PE. It is now rarely performed as an isolated diagnostic procedure. Multiple studies have documented the superiority of CTPA over pulmonary angiography in the diagnosis of PE.
Risk Assessment and stratification
Current guidelines emphasize the importance of an early risk stratification of patients with acute pulmonary embolism (PE) to allow assessment of the individual prognosis and guide therapeutic decision-making. The Pulmonary Embolism Severity Index (PESI) and its simplified version (sPESI) are most widely used clinical scores to date.

Hemodynamic instability is an important indicator of poor prognosis. The evaluation of hemodynamic status, signs of RV dysfunction and myocardial injury, and the assessment of additional patient-related risk factors are required for optimal risk stratification. However, differentiating submassive PE from low-risk PE in patients may be difficult at times, particularly when they are hemodynamically stable.

Patients with acute PE who die have higher D-dimer levels compared to those who survive. Acute RV failure is the main cause of death in acute PE, and RV dysfunction on echocardiography is associated with high mortality. A recent meta-analysis has also confirmed this association.

Brain natriuretic peptides (BNPs) and N-terminal proBNP (NT-proBNP) are specific markers of stress on ventricular wall. A strong correlation exists between levels of these markers and RV dysfunction assessed by echocardiography. Patients with acute PE and high levels of BNP and NT-proBNP have a higher mortality or adverse events, including even those with normotensive PE.

Elevated values of cardiac troponins T and I are associated with increased risk of short-term mortality in patients with acute PE including those who are hemodynamically stable.

Treatment
Patients with acute PE are stratified according to prognosis. Although treatment strategies are UFH and LMWHs are equally effective without clearly defined for hypotensive, hemodynamically unstable patients with massive PE, stratifying normotensive patients into an intermediate-risk (submassive PE) and a low-risk subgroup is still problematic.

Acute massive PE with cardiogenic shock or severe RV dysfunction should be treated with immediate thrombolysis, percutaneous mechanical thrombectomy (PMT) or surgical embolectomy. Anticoagulation should be started in patients with intermediate or high clinical probability of PE while they are undergoing evaluation for PE. All patients with confirmed PE should receive prompt anticoagulant therapy with unfractionated heparin (UFH), a low-molecular weight heparin (LMWH), or fondaparinux.

Heparins
Heparins act by binding to antithrombin which inactivates thrombin and several other activated coagulation factors including factor Xa. Treatment with unfractionated heparin (UFH) should be initiated without delay in patients with high-risk PE as low molecular weight heparins (LMWHs) have not been evaluated in this setting.

Therapy in acute PE is usually started with 80 units/kg of UFH as bolus followed by 18 units/kg/hour by continuous IV infusion with monitoring of activated partial thromboplastin time (aPTT) between 1.5 to 2.5 times control. However, the dose of UFH should not be increased > 40,000 units/day despite aPTT ratio being in the subtherapeutic range, if the anti-factor Xa heparin level is > 0.35 IU/mL (51). UFH is also preferred over LMWHs in patients with severe renal impairment with creatinine clearance < 30 ml/min and in those at high-risk of bleeding.

In patients with submassive or low-risk PE, both
an increase in recurrent VTE or all-cause mortality in either group.\textsuperscript{52, 53} LMWHs have a more predictable dose-response effect, hence routine laboratory monitoring with anti-Xa levels is not necessary except in those with severe renal failure and in females during pregnancy.\textsuperscript{54} Compared to UFH, LMWHs have a lower risk of immune-mediated thrombocytopenia or osteoporosis. As LMWHs are primarily excreted by the kidneys, in patients with severe renal impairment (creatinine clearance < 30 mL/min), either UFH is used, or the dose of LMWHs is decreased with anti-Xa level monitoring.\textsuperscript{55}

Fondaparinux is a synthetic pentasaccharide. It has potent and specific antithrombin-mediated anti-Xa activity. It has an excellent bioavailability and a long half-life. It has been used in submassive and low-risk PE with equal efficacy and safety as UFH.\textsuperscript{4}

<table>
<thead>
<tr>
<th>Table 1. Approved LMWHs and fondaparinux for treatment of acute PE\textsuperscript{41}</th>
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<tbody>
<tr>
<td><strong>Dose</strong></td>
</tr>
<tr>
<td>Enoxaparin 1 mg/kg</td>
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<tr>
<td>Enoxaparin 1.5 mg/kg</td>
</tr>
<tr>
<td>Tinzaparin 175 U/kg</td>
</tr>
<tr>
<td>Fondaparinux 5 mg (body wt &lt; 50 kg)</td>
</tr>
<tr>
<td>Fondaparinux 7.5 mg (B.W. 50-100 kg)</td>
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<tr>
<td>Fondaparinux 10 mg (B.W. &gt; 100 kg)</td>
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</tbody>
</table>

**Thrombolysis**

Thrombolysis should be promptly started in those with high-risk PE presenting with cardiogenic shock and/or persistent hypotension, severe RV dysfunction, or major myocardial necrosis.\textsuperscript{15, 41} With fibrinolytic agents the lung perfusion is rapidly restored with ~1/3rd reduction in total perfusion defect at 24 hours. However, by 1 week, both heparin and adjunctive thrombolytic therapy achieve similar reduction in perfusion effect of about 2/3rd. No definitive therapeutic advantage of catheter-directed thrombolysis has been documented when compared with intravenous thrombolysis. The approved thrombolytic drugs are enumerated in table 1.

**Table 2. Dosage of plasminogen activating fibrinolytics for acute PE**

<table>
<thead>
<tr>
<th>Fibrinolytic dose</th>
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<tbody>
<tr>
<td>Streptokinase</td>
<td>250,000-IU IV bolus over 30 min, followed by 100,000-IU/h infusion for 12-24 h</td>
</tr>
<tr>
<td>Urokinase</td>
<td>4400-IU/kg bolus over 10 min, followed by 4400-IU/kg/h infusion for 12-24 h, or, accelerated regimen: 3 million IU over 2 h</td>
</tr>
<tr>
<td>Alteplase</td>
<td>100-mg IV infusion over 2 h or, 0.6 mg/kg over 15 min (max 50 mg)</td>
</tr>
<tr>
<td>Reteplase</td>
<td>Double 10-U IV bolus 30 min apart</td>
</tr>
<tr>
<td>Tenecteplase</td>
<td>Weight-adjusted rapid IV bolus over 5 s (30-50 mg with a 5 mg step every 10 kg from &lt;60 to &gt; 90 kg)</td>
</tr>
</tbody>
</table>
Catheter-based Interventions and Surgical Embolectomy

Percutaneous mechanical thrombectomy (PMT) can be considered as an alternative when thrombolysis is contraindicated or has failed. In PMT, the thrombus removal is achieved via mechanical thrombus fragmentation, maceration, and/or aspiration. In a meta-analysis, the combined approach with catheter-based clot fragmentation and local thrombolysis was superior to PMT only. Surgical embolectomy is an option in those with massive or submassive PE with RV dysfunction when thrombolysis is contraindicated or has failed.

Oral anticoagulants

For many decades, Vitamin K antagonists (VKAs) were the only oral anticoagulant drugs available. Recently, other new oral drugs, namely the direct thrombin inhibitor dabigatran etexilate and direct factor-Xa inhibitor rivaroxaban have been approved for clinical use. These new compounds have the potential to replace VKAs and heparins in many patients. These drugs are used in fixed dose therapy without routine coagulation monitoring, and have few drug–drug or drug–food interactions. Presently, VKAs are the drug of choice for the prolonged anticoagulation, and have been documented to be effective and safe. VKAs include warfarin, acenocoumarol, phenprocoumon, and fluindione, however, warfarin is the most commonly used anticoagulant drug. VKAs can be started either simultaneously with or few days after starting heparin therapy. The meta-analyses of studies comparing VKAs with prolonged LMWH have documented equal efficacy in preventing VTE recurrences.

Vitamin K antagonist (VKA) therapy is used for at least 3 months in patients after initial therapy with injectable anticoagulant. In patients with high-risk for recurrent PE or DVT, an extended therapy is needed.

Conclusions

Acute PE is potentially a lethal problem. A
prompt diagnosis and immediate anticoagulation therapy improve patient outcome. Patients with massive PE should receive prompt thrombolysis, catheter-based surgical intervention, or surgical embolectomy. In non-massive and low-risk PE, a pretest clinical probability with one of the clinical prediction rules is important before clinical tests are ordered. The investigations for PE should be performed in sequences to avoid false-positive and false-negative results. Oral anticoagulants with VKAs are continued for at least 3 months. Selected patients may continue to receive VKAs for much longer period. Novel oral anticoagulants are in the pipeline and may change the therapeutic approach in acute PE.

References


