REVIEW ARTICLE

Where to treat patients with acute pulmonary embolism?

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ABSTRACT
Acute pulmonary embolism (PE) is one of the major causes of in-hospital mortality, and the short-term prognosis of patients is strongly related to its hemodynamic consequences. Therefore, a stepwise risk-stratification approach has been proposed, using a combination of clinical data, imaging, and biochemical markers to define the risk of an early adverse outcome. Patients should be managed according to PE severity: some of them require urgent primary reperfusion; for most patients, anticoagulation alone is sufficient; and selected low-risk patients are potential candidates for early discharge and continuation of treatment on an outpatient basis. We present the current risk-adapted approach to management strategies in acute PE.

Introduction Acute pulmonary embolism (PE) remains one of the major causes of in-hospital mortality. The short-term prognosis of patients is strongly related to hemodynamic consequences of PE.[1] Importantly, PE may lead to a wide spectrum of clinical manifestations ranging from mild dyspnea on exertion to fully developed cardiogenic shock or even sudden cardiac death.[2-4] Therefore, according to the current guidelines of the European Society of Cardiology (ESC), a proper management strategy in patients with acute PE predominantly depends on assessing the risk of early mortality.[5] In patients with low cardiopulmonary reserve, even a relatively small embolic burden can result in acute right ventricular (RV) dysfunction (RVD) with systemic hypotension or shock, while in those without preexisting cardiopulmonary disorders, it is possible that the total occlusion of one pulmonary artery will not alter RV function.[6]

A stepwise risk-stratification approach has been proposed, using a combination of clinical data, imaging, and biochemical markers to define the risk of an early adverse outcome. Importantly, the management of patients depends on the severity of PE: some of them require urgent primary reperfusion; for most patients, anticoagulation alone will be sufficient; and selected low-risk patients are potential candidates for early discharge and outpatient treatment.[7]

Hemodynamically unstable patients with pulmonary embolism Approximately 5% of patients with PE are hemodynamically unstable at presentation, showing cardiac arrest or obstructive shock (TABLE 1). These criteria define high-risk PE, with PE-related early mortality exceeding 15%.[5] The risk of in-hospital death is especially high during the first hours after admission; therefore, urgent primary reperfusion therapy should be started immediately. Systemic thrombolysis is the treatment of choice in the majority of patients with high-risk PE, while invasive treatment including catheter-directed therapy or surgical embolectomy should be performed if thrombolysis is contraindicated or has failed.[5,8] Moreover, hemodynamically unstable patients may require intensive hemodynamic support with intravenous vasopressors, and mechanical ventilation is needed in selected cases.[9-11] Thus, patients with high-risk PE, similar to individuals with various other life-threatening acute cardiovascular conditions, should be managed in an intensive care unit.

Management of intermediate-risk pulmonary embolism Anticoagulation is sufficient for most hemodynamically stable patients

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TABLE 1 Criteria for high-risk pulmonary embolism[5]

Diagnosis of acute PE	
Clinical manifestation	Cardiac arrest: cardiopulmonary resuscitation; or
	Obstructive shock: systolic BP <90 mm Hg or vasopressors required to achieve a BP ≥90 mm Hg despite adequate filling status and end-organ hypoperfusion (altered mental status, cold and clammy skin, oliguria / anuria, increased serum lactate levels); or
	Persistent hypotension: systolic BP <90 mm Hg or systolic BP drop ≥40 mm Hg, lasting longer than 15 min and not caused by new-onset arrhythmia, hypovolemia, or sepsis
Right ventricular dysfunction on CTPA or TTE	

Abbreviations: BP, blood pressure; CTPA, computed tomography pulmonary angiography; PE, pulmonary embolism; RVD, right ventricular dysfunction; TTE, transthoracic echocardiography

with acute PE. However, it should be emphasized that the population of initially normotensive patients with PE is not homogeneous. It includes individuals with a favorable and benign clinical course with a near-zero risk of PE-related mortality, but also those with a risk of early mortality of up to 5% to 10% despite adequate anticoagulation.[12] Acute pressure overload caused by a rapid thromboembolic occlusion of pulmonary arteries results in RV dilation and increased stretching of the RV wall. Decreased cardiac output and coronary blood flow, with resulting imbalance between oxygen supply and demand, leads to RV myocardial injury. Elevated levels of markers of myocardial injury, especially cardiac troponin, predict an early adverse outcome even in normotensive patients with PE.[13-15] Progressive damage to cardiomyocytes further reduces RV systolic function and may lead to progressive irreversible RV failure with all related consequences, including hemodynamic collapse and cardiogenic shock. Thus, initially normotensive patients with PE with at least one indicator of elevated PE-related risk (TABLE 2) constitute a group with intermediate-risk PE and should be hospitalized.

Importantly, patients with signs of RVD on echocardiography or computed tomography pulmonary angiography (CTPA) and with elevated troponin levels (intermediate high-risk group) should be monitored in the first hours due to the risk of early hemodynamic decompensation. In the randomized PEITHO trial

TABLE 2 Clinical, imaging, and laboratory indicators of severity of pulmonary embolism in normotensive patients[5]

Clinical
Age >80 years
Heart rate >100 bpm
BP, 90–100 mm Hg
SaO_2 <90%
Comorbidities
Chronic heart failure
Chronic lung disease
Other serious conditions including active cancer, gastrointestinal bleeding in the previous 14 days, stroke in the previous 4 weeks, surgery in the previous 2 weeks, bleeding disorder or thrombocytopenia (platelet count <75 × 10^9/l), severe renal impairment (calculated CrCl <30 ml/min), and severe hepatic impairment
Imaging
Echocardiography (at least 1): RV / LV >1.0, TAPSE ≤16 mm, McConnell sign (hypokinesis of RV free wall), septal shift, D-shaped left ventricle, TR >2.8 m/s, congested IVC
CTPA: RV / LV >1
Laboratory
Elevated cardiac troponin levels
Other potential biomarkers: BNP and NT-proBNP; H-FABP, copeptin, lactate

Abbreviations: BNP, B-type natriuretic peptide; CrCl, creatinine clearance; H-FABP, heart-type fatty acid-binding protein; IVC, inferior vena cava; LV, left ventricle; NT-proBNP; N-terminal fragment of the prohormone brain natriuretic peptide; RV, right ventricle; SaO_2, oxygen saturation; TAPSE, tricuspid annulus plane systolic excursion; TR, peak systolic velocity of the tricuspid regurgitant jet; others, see TABLE 1

(Pulmonary Embolism International Thrombolysis Study) comparing tenecteplase plus heparin with placebo plus heparin in normotensive patients with intermediate high-risk PE, 5% of initially anticoagulated patients deteriorated and required rescue thrombolysis.[16] Therefore, the risk of decompensation mandates close monitoring, preferably in an intensive care unit. On the other hand, primary reperfusion is not recommended in these patients, as the risk of potentially life-threatening bleeding complications, especially intracranial hemorrhage, appears to outweigh potential benefits of this treatment.[16] On the other hand, rescue thrombolytic therapy, or, alternatively, surgical embolectomy or percutaneous catheter-directed treatment, should be considered in patients who develop signs of hemodynamic instability.[5]

Predictive role of right ventricular dysfunction Echocardiography can detect RV dysfunction in at least 25% of unselected patients with acute PE.[17] It was reported that RVD on echocardiography is associated with an elevated risk of short-term mortality even in initially hemodynamically stable patients.[18,19] However, the positive predictive value for PE-related mortality is low.[18] Moreover, there is no generally accepted echocardiographic definition of RVD used for risk stratification (TABLE 2).[18,20] However, despite these limitations, echocardiography is widely used in clinical practice for the assessment of prognosis in normotensive patients with acute PE.[21]

Potential candidates for early discharge and outpatient treatment Since acute PE is a potentially life-threatening cardiovascular disease, the decision on discharge shortly after establishing the diagnosis should be based on validated criteria and preferably supported by the results of prospective outcome trials. Early discharge of a patient with acute PE and continuation of anticoagulant treatment at home should be considered not only when the PE event itself has a low risk of early PE-related mortality and serious complications, but also when no serious comorbidity is present. Moreover, a sufficiently high level of outpatient care is necessary to ensure anticoagulant therapy and to provide adequate education regarding the management of venous thromboembolism and prompt medical support when needed.[22-24]

As mentioned above, apart from clinical, imaging, and laboratory data that help assess PE severity and PE-related early death, comorbidities should be considered to evaluate the overall mortality risk and early outcome. The Pulmonary Embolism Severity Index (PESI) and especially its simplified version, sPESI,[25,26] have been validated and are widely used mostly for identification of patients at low risk of 30-day mortality (sPESI score = 0; TABLE 1).[25,27-29]

Although the PESI was not developed as a tool to identify candidates for home treatment, it was used in a clinical trial in which 344 patients with PE were randomized to inpatient versus ambulatory treatment. One patient (0.6%) in each treatment group died within 90 days. Importantly, 3 patients (1.8%) receiving ambulatory treatment developed major bleeding, while no such complications occurred in inpatients.[30]

A group of Dutch investigators developed the so called Hestia criteria for assessing eligibility for home treatment of PE.[31] These criteria consist of clinical parameters that asses not only PE severity but also evaluate comorbidities and feasibility of home treatment (TABLE 4). If the answer to all the questions is "no," the patient can be treated at home. Single-arm management trials used these criteria for patient selection for home treatment. The recurrence rate of venous thromboembolism during 3 months was 2% in patients with PE who were discharged within 24 hours.[31]

TABLE 3 Simplified Pulmonary Embolism Severity Index (sPESI)[26]

Parameter	sPESI
Age >80 years	1 point
Cancer	1 point
Chronic heart failure	1 point
Chronic pulmonary disease	
Pulse rate ≥110 bpm	1 point
Systolic BP <100 mm Hg	1 point
SaO_2 <90%	1 point
0 points = 30-day mortality risk of 1% (95% CI, 0.0–2.1)	≥1 point(s) = 30-day mortality risk of 10.9% (95% CI, 8.5–13.2)

Abbreviations: see TABLES 1 and 2

TABLE 4 Hestia exclusion criteria for outpatient management of pulmonary embolism[31]

Criterion / question
Is the patient hemodynamically unstable?[a]
Is thrombolysis or embolectomy necessary?
Active bleeding or high risk of bleeding?[b]
More than 24 h of oxygen supply to maintain oxygen saturation >90%?
Is PE diagnosed during anticoagulant treatment?
Severe pain requiring administration of intravenous pain medication for more than 24 h?
Medical or social reason for hospital treatment for more than 24 h (infection, malignancy, no support system)?
Does the patient have a CrCl of <30 ml/min?[c]
Does the patient have severe liver impairment?
Is the patient pregnant?
Does the patient have a documented history of heparin-induced thrombocytopenia?

a Systolic BP <100 mm Hg with heart rate >100 bpm or a condition requiring admission to an intensive care unit

b Gastrointestinal bleeding in the previous 14 days, stroke in the previous 4 weeks, surgery in the previous 2 weeks, bleeding disorder or thrombocytopenia (platelet count $<75 \times 10^9$/l), uncontrolled hypertension (systolic BP >180 mm Hg or diastolic BP >110 mm Hg)

c CrCl calculated according to the Cockroft–Gault formula

Abbreviations: see TABLES 1 and 2

Important questions remain of whether the assessment of RVD (RV pressure overload and / or myocardial injury) has a prognostic value in low-risk patients and whether individuals with low-risk PE assessed solely with clinical criteria can be safely treated on an outpatient basis. It was reported that high-sensitivity troponin T levels of 14 pg/ml or lower, together with clinical indicators of low-risk PE, predict an excellent prognosis, and the combination of both modalities may be used to identify possible candidates for out-of-hospital treatment.[13] Barco et al[32] performed a meta-analysis assessing whether the presence of RVD may aggravate the early prognosis, notably all-cause mortality at 30 days or during hospitalization in low-risk patients. The diagnosis of RVD was based on echocardiography or CTPA. The prognostic value of elevated troponin levels in patients with low-risk PE was also assessed. The authors found that the odds ratio for early all-cause mortality in patients with vs without RVD was 4.19 (95% CI, 1.39–12.58) with a morality rate of 1.8% (95% CI, 0.9–3.5) and 0.2% (95% CI, 0.03–1.7), respectively. For troponin levels, the mortality rates were 3.8% (95% CI, 2.1–6.8) and 0.5% (95% CI, 0.2–1.3), respectively (OR, 6.25; 95% CI, 1.95–20.05). The conclusion was that in low-risk patients with acute PE, the presence of RVD on admission is associated with early mortality. Thus, since RVD indicated by imaging findings or laboratory markers was associated with increased mortality also in patients who appeared to be at low risk based on clinical criteria alone, these results may influence the management also of low-risk patients.[32]

Such an approach was investigated in a recent trial, HoT-PE (Home Treatment of Pulmonary Embolism).[33] The study was designed to assess if early discharge and ambulatory treatment with rivaroxaban is effective and safe in patients with acute low-risk PE. Importantly, patients were selected not only on the basis of clinical criteria but also the absence of RVD or intracardiac thrombi on admission.[33] Symptomatic recurrent venous thromboembolism (VTE) or PE-related death within 3 months of enrollment was a primary endpoint. Of the 525 consecutive patients included in the trial, 3 (0.6%) experienced symptomatic recurrence of nonfatal VTE, while major bleeding occurred in 6 patients (1.2%). Hospital discharge was scheduled within 48 hours after the presentation, and up to 2 nights of hospital stay were permitted, as per the trial protocol. The median hospitalization length was 34 hours, and the median time from PE diagnosis to discharge, 31 hours. Only 11 patients (2.1%) required prolonged hospitalization due to early adverse events, mostly acute infection. This trial confirmed that early discharge and home treatment with rivaroxaban is effective and safe in carefully selected patients with acute low-risk PE.[33]

The current ESC guidelines on the management of acute PE recommend that patients with low-risk PE and absence of serious comorbidity should be considered for early discharge and continuation of treatment at home if proper

outpatient care and anticoagulant treatment can be provided. In this context, the guidelines recommend that the RV should be assessed by imaging methods or measurement of laboratory biomarkers even in the presence of a low PESI or a negative sPESI.[5]

Summary In the current ESC guidelines, the management strategy in patients with acute PE depends on an individual risk assessment.[5] Hemodynamically unstable patients should be treated with primary reperfusion therapy in an intensive care unit, while normotensive individuals with at least one predictor of PE-related mortality or with significant comorbidity should be hospitalized. Moreover, due to the risk of hemodynamic collapse, normotensive patients with RVD on echocardiography or CTPA as well as elevated troponin levels should be initially monitored, and in the case of decompensation, rescue reperfusion should be started. On the other hand, patients with low-risk PE without any indicator of complicated clinical course, with preserved RV function and no signs of myocardial injury, and with access to high-level outpatient care are potential candidates for a short hospital stay or even comprehensive outpatient management.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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