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Progress in the treatment of acute pulmonary embolism and chronic thrombo-embolic pulmonary hypertension/disease

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The combination of an initial clinical approach aimed at evaluating the early risk of mortality with subsequent diagnostic and therapeutic approaches articulated on the overall patient's profile is recommended in acute pulmonary embolism (PE). The presence of pulmonary hypertension associated with the persistence of chronic vascular obstructions in the pulmonary arteries after one or more acute thrombo-embolic events identifies a condition defined as chronic thrombo-embolic pulmonary hypertension (CTEPH). The evolution of technology and knowledge in the field of imaging has allowed us to qualify the computed tomography angiography of the pulmonary arteries as the gold standard for the diagnostic confirmation of both acute PE and CTEPH. In both these conditions, the first therapeutic step is the immediate initiation of anticoagulant therapy. In acute high-risk PE, in addition to anticoagulant therapy, thrombolytic therapy is recommended; in the event of contraindications to thrombolysis, surgical embolectomy or percutaneous catheter-directed treatment represents viable treatment options. In CTEPH, the combination of data collected from cardiac catheterization, computed tomography angiography, and conventional angiography of pulmonary arteries allows a team of experts to identify candidates for pulmonary endarterectomy surgery. Inoperable patients should be considered for percutaneous balloon angioplasty of the pulmonary arteries which can improve patients' symptoms, quality of life, and prognosis.

Acute pulmonary embolism

Epidemiology and definitions

Venous thrombo-embolism (VTE), which includes deep vein thrombosis (DVT) and/or acute pulmonary embolism (PE), globally represents the third most frequent acute cardiovascular disease after myocardial infarction and stroke. The overall incidence is estimated at ~60–70 cases per 100 000 person-years but increases with age, in cancer patients, during prolonged bed rest and after surgery.[1] In the European Union, it has been estimated that the annual number of deaths related to acute PE may exceed 500 000 cases per year, confirming the epidemiological relevance and the severity of this condition.[2] The increase in the incidence of PE and the reduction of fatal cases observed in the last 15 years seem to be due to the improvement in the therapeutic strategy and, possibly, due to the increase in the number of diagnoses associated with the larger use of the latest generation 'imaging' tools which are characterized by a higher sensitivity. The European Society of Cardiology (ESC) guidelines for the diagnosis and management of PE of 2019,[3] when compared with the previous ones, represent an updated document aimed at addressing and improving both diagnosis and effectiveness of treatment of acute PE.[1] The diagnostic work-up proposed in the ESC 2019 guidelines[3] allows to limit the number of false-positive diagnosis and to favour the appropriateness of the treatment. The now obsolete terms 'massive' and

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Table 1 Definition of haemodynamic instability and high-risk pulmonary embolism

(1) Cardiac arrest	(2) Obstructive shock	(3) Persistent hypotension
Need for cardiopulmonary resuscitation	Systolic blood pressure (SBP) < 90 mmHg or vasopressors required to achieve SBP ≥ 90 mmHg despite adequate filling status and end-organ hypoperfusion (altered mental status, cold, clammy skin, oliguria/anuria, increased serum lactate)	SBP < 90 mmHg or SBP drop ≥40 mmHg, lasting more than 15 min and not caused by new-onset arrhythmia, hypovolaemia, or sepsis

'non-massive' acute PE adopted in the first ESC 2000 guidelines are still improperly used in common clinical practice. In fact, even if this terminology was intended to characterize the clinical severity of acute PE at presentation, over the years has lent itself to potentially misleading interpretations being confused with 'the volume of the embolic mass' identifiable on the computed tomography angiography of the pulmonary arteries (CT-PA). Indeed, cases of angiographically 'massive' PE that are functionally well tolerated and, on the contrary, cases of 'non-massive' PE with critical haemodynamic impairment due to pre-existing cardio-respiratory comorbidities are commonly experienced in clinical practice.[4] With ESC 2008 guidelines, the terms 'massive and non-massive' have been replaced by the assessment of the risk of hospital mortality related to acute PE. The ESC 2019 guidelines, in the wake of the previous ones, underline the importance of the clinical as well as radiological evaluation, reinforcing the relevance of the overall clinical and haemodynamic picture of the patient with suspected PE.[4]

Risk of hospital mortality and diagnostic strategies

The ESC 2019 guidelines[3] confirm the importance of distinguishing between high-risk and non-high-risk patients based on the haemodynamic picture at presentation, providing for the first time a detailed description of three clinical profiles defined as high risk and illustrated in *Table 1*.

High-risk patients represent 3–5% of those with confirmed PE and have an in-hospital mortality ranging from 14 to 30%. Non-high-risk subjects with PE are the majority, with a prevalence ranging from 93 to 95% and an in-hospital mortality between 0.5 and 11%, thus requiring, as we will see, a further prognostic stratification.

From a pathophysiological standpoint, the haemodynamic instability of high-risk patients is due to the rapid increase in right ventricular afterload which, despite the compensatory mechanisms of the adrenergic response (tachycardia and increased contractility), causes a reduction of cardiac output, varying degrees of systemic hypotension, and right atrial pressure increase. In the face of an acute increase in afterload, a normal right ventricle fails to develop a systolic pressure above 50–60 mmHg. Accordingly, if similar or higher values are documented by echocardiography, pre-existing conditions characterized by pulmonary hypertension (PH) such as left heart diseases, respiratory diseases, or chronic thrombo-embolic pulmonary hypertension (CTEPH) should be excluded.

Diagnostic algorithms[3]

The overall management of patients with acute PE is illustrated in *Figure 1*.

Patients with suspected PE and haemodynamic instability with high-risk characteristics require hospitalization in intensive care settings for initial treatment of right ventricular failure (inotropic drugs, oxygen therapy, diuretics, etc.) and a timely diagnostic approach. The bedside echocardiogram allows us to identify the presence of right ventricular dysfunction (dilatation and hypokinesia) and, in accidental cases, to detect mobile thrombi in right heart cavities (right atrium, right ventricle, and proximal pulmonary arteries). In the absence of right ventricular dysfunction, PE can be reasonably excluded as the cause of haemodynamic instability and the search for other causes has to be pursued. If right ventricular dysfunction is present, PE diagnosis has to be confirmed by CT-PA to start reperfusion treatments with the highest level of diagnostic accuracy. The identification of recent proximal DVT by bedside Doppler ultrasonography with compression of the lower extremities can be used for supporting PE diagnosis in an emergency setting.

In non-high-risk subjects with suspected PE, who are the vast majority, the diagnostic algorithm is more articulated and aimed to prevent the excessive use of CT-PA. The key element is the definition of the pre-test probability of PE through the use of validated scores (Wells, Geneva) or according to clinical judgement based on clinical evaluation and available preliminary investigations. In subjects with a low or intermediate probability of PE, plasma high-sensitivity D-dimer measurement is recommended since normal value reasonably excludes PE diagnosis. As an alternative to the fixed D-dimer cut-off, the ESC 2019 guidelines suggest the use of cut-off values of D-dimers adjusted for age or clinical probability. In subjects with positive D-dimers or with a high pre-test probability of PE, CT-PA is recommended.

Computed tomography angiography of the pulmonary arteries represents the gold standard for PE diagnosis although perfusion or ventilation-perfusion lung scintigraphy may be used for PE diagnosis in particular in subjects with severe renal failure to prevent contrast medium nephrotoxicity.

Further risk stratification in non-high-risk individuals[3–5]

The management of patients with PE is based on risk stratification and the early detection of signs of haemodynamic instability identifies patients at high risk of in-hospital mortality. In non-high-risk subjects, the initial

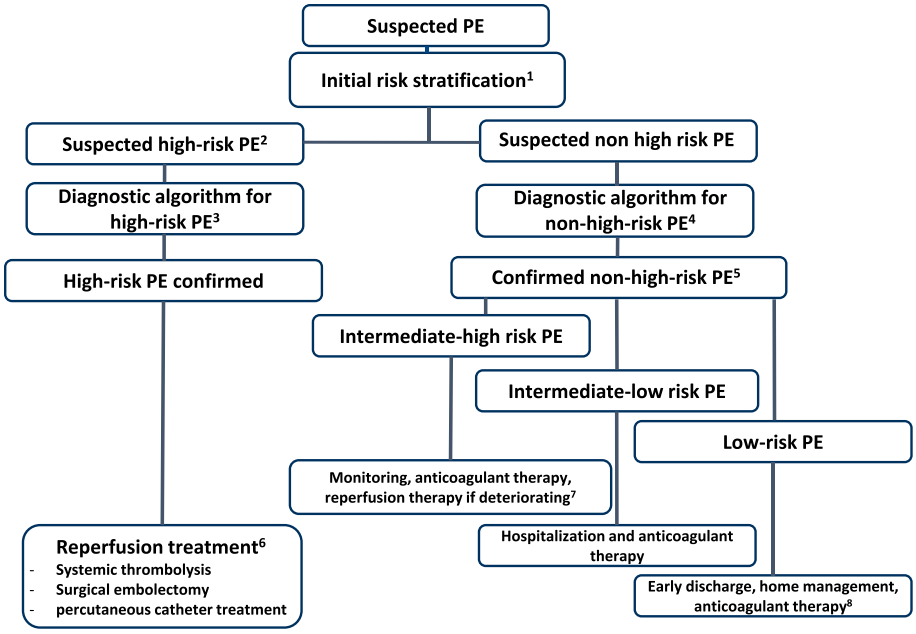

Figure 1 Management of patients with acute pulmonary embolism.

diagnostic assessment should be followed by a further distinction between intermediate-risk patients (~50% of the total number of PE patients, with in-hospital mortality ranging from 3.4 to 10.9%) and low-risk patients (~45% of the total number of patients with in-hospital mortality ranging from 0 to 1.5%). This distinction is obtained through clinical scores such as the Pulmonary Embolism Severity Index (PESI) which simplified version (sPESI) scores '0' only in low-risk subjects. Intermediate-risk patients are classified as high-intermediate risk when right ventricular dysfunction (detected by transthoracic echocardiography or CT angiography on cardiac scans) and increased circulating troponin levels are both present, while are classified as low-intermediate risk if only one of the two parameters is present (right ventricular dysfunction or circulating troponin levels). In subjects defined as low risk with clinical scores (calculated PESI of I-II or an sPESI of 0), signs of right ventricular dysfunction (36% of cases) or elevated cardiac troponin levels (26% of cases) may be present; these patients should be reclassified into the intermediate-low-risk category preventing possible early discharge.

In fact, in low-risk patients (calculated PESI of I-II or an sPESI of 0) without echocardiographic signs of right ventricular dysfunction or troponin elevation, early discharge may be considered (in the absence of other reasons for hospitalization). This recommendation is supported by the recent results of the Home Treatment of Pulmonary Embolism study in more than 500 PE patients.[6]

The most complex decision-making approach pertains to 'intermediate-high risk' patients (PESI III-IV or sPESI $\geq$ 1 with both right ventricular dysfunction and increased circulating troponin levels): currently, there is no indication for reperfusion therapy, but it is recommended to monitor the patient in an intensive care setting to promptly identify and treat early progression to the high-risk condition.

Treatment of acute pulmonary embolism

The therapeutic strategy of acute PE is based on the risk of in-hospital mortality in order to favour the appropriate use of the available resources according to their efficacy and potential side effects. In high-risk patients, reperfusion therapy with systemic thrombolysis is the treatment of choice. In case of contraindications to systemic thrombolysis, both surgical embolectomy and percutaneous catheter-directed treatment can be adopted. The use of systemic thrombolysis in acute PE has been known for >50 years and, in a meta-analysis of 15 randomized clinical trials involving a total of 2057 patients, this strategy resulted in a reduction in overall mortality and an improvement in combined endpoints of death/need for further treatment.[7] However, in haemodynamically stable patients, the mortality reduction was not statistically significant due to an increased risk of major haemorrhage, fatal bleeding, or intracranial bleeding in the overall study population. Similar results were observed in the Pulmonary Embolism Thrombolysis (PEITHO) study which assessed the efficacy and safety of systemic thrombolysis in 1005 patients with intermediate-risk acute PE reporting a significant reduction in the composite endpoint of death or haemodynamic deterioration in the treated group but associated with a 2.4% incidence of haemorrhagic stroke.[8]

Systemic thrombolysis is underused, as reported in the study by Keller *et al.*[9] which analysed the characteristics, comorbidities, treatment, and outcomes of 885 806 patients with acute PE followed up in Germany between 2005 and 2015. The following reasons may explain the reticence to the use of systemic thrombolysis: the increasing age and frailty of patients hospitalized for PE, the risk of cerebral haemorrhages, and the global reduced experience in the use of thrombolytic agents in the era of primary percutaneous revascularization for ST-elevation myocardial infarction.[10] Surgical embolectomy,

performed with cardiopulmonary bypass without aortic clamping and circulatory arrest, and percutaneous catheter-directed treatment are recommended in high-risk patients in whom thrombolysis is contraindicated or has failed.[3] Temporary use of venous-arterial circulatory support (extra corporeal membrane oxygenation) may be considered in patients with refractory shock associated with systemic thrombolysis, surgical or percutaneous embolectomy and not as an isolated treatment considering its high mortality burden.[11]

All patients diagnosed with PE, regardless of the clinical severity, must receive anticoagulant therapy for at least 3 months. Currently, non-vitamin K-dependent direct oral anticoagulants (DOACs) are the drugs of choice. The use of vitamin K antagonists is still recommended in patients with contraindication for the use of DOACs, primarily severe renal failure and antiphospholipid antibody syndrome. Furthermore, patients with high-risk PE have not been enrolled in Phase III studies with DOACs; therefore, in these patients, their use should be individualized. The introduction of prognostic stratification combined with the wide use of DOACs led to a considerable reduction in the length of hospitalization for acute PE (12 days in 2005 and 8 days in 2015) as reported by Keller *et al.*[9]

Anticoagulants are highly effective in preventing the recurrence of VTE during treatment but do not abolish the risk of recurrence after discontinuation. For this reason, the duration of anticoagulant treatment has to be defined balancing the risk of both embolic recurrence and haemorrhagic events. Patient involvement in the decision-making process is essential to optimize and maintain treatment adherence. Currently, after the first 3 months of anticoagulant therapy, three scenarios can be identified: patients who can discontinuate treatment (risk of recurrence <3% per year), patients in whom extended treatment should be considered (risk of recurrence between 3 and 8% per year), and patients in whom extended treatment of indefinite duration is recommended (risk of recurrence >8% per year). Patients who can discontinuate treatment after 3 months are those with a major transient/reversible risk factor for VTE. Extended anticoagulant therapy beyond 3 months should be considered after a first episode of PE in the absence of identifiable risk factors, in case of persistent risk factors, and in patients with minor transient or reversible risk factors. Oral anticoagulant treatment of indefinite duration is recommended for patients with antiphospholipid antibody syndrome (and other thrombophilic conditions), for patients with recurrent VTE not related to a major transient or reversible risk factor, or in individuals with active malignancies.

Chronic thrombo-embolic disease and chronic thrombo-embolic pulmonary hypertension

The presence of chronic thrombo-embolic vascular obstructions in the pulmonary arteries identifies a condition defined as chronic thrombo-embolic pulmonary disease (CTEPD)[12] with or without PH (chronic thrombo-embolic pulmonary hypertension—CTEPH—remains the preferred term for patients with PH). This condition should be sought, after at least 3 months of therapeutic anticoagulant therapy, in all patients reporting persistent, new-onset dyspnoea, or exercise limitation after an episode of acute PE.

In CTEPH, the presence of PH is due to both chronic-organized embolic obstructions and distal vascular remodelling phenomena (similar to those described in pulmonary arterial hypertension) in non-obstructed areas.[13] When a CT-PA is performed for suspected acute PE, the evidence of increased diameter of the pulmonary artery, bronchial arteries hypertrophy, mosaic oligoemia, and moderate-to-severe dilatation of right heart sections should raise the suspicion of pre-existing CTEPH. Once the diagnosis is confirmed, patients with CTEPH should be evaluated by a 'multidisciplinary team' in order to define the best therapeutic strategy.

The therapeutic approach of the CTEPH includes the use of 'ad vitam' anticoagulant treatment in order to avoid recurrence of thrombo-embolic events or progression of *in situ* disease. Vitamin K antagonists are the drugs of choice in CTEPH, in particular in patients with antiphospholipid antibody syndrome (antiphospholipid syndrome testing is recommended at diagnosis in patients with CTEPH).

Pulmonary endarterectomy (PEA) is the treatment of choice in patients with CTEPH and technically operable fibrotic vascular obstructions.[14]

Pulmonary balloon angioplasty (BPA) is recommended in patients who are technically inoperable or have residual PH after PEA as long as the distal obstructions are amenable to percutaneous approach.[15] Pulmonary balloon angioplasty may also be considered for technically operable patients with a high proportion of distal disease and an unfavourable risk/benefit ratio for PEA.

Regarding medical therapy, riociguat is recommended for symptomatic patients with inoperable CTEPH or persistent/recurrent PH after PEA. The level of evidence and the grade of recommendation are lower for the other approved drugs for pulmonary arterial hypertension and their 'off-label' use can be considered only in symptomatic and inoperable patients. Regardless of the initial therapeutic strategy, a long-term follow-up is recommended. In CTEPD patients without PH, long-term anticoagulant therapy should be considered on an individual basis. Pulmonary endarterectomy or BPA, in subjects with CTEPD without PH, should also be considered on an individual basis and only in symptomatic patients.

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Data availability

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