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The ESC Textbook of Intensive and Acute Cardiovascular Care (2 ed.)

Edited by Marco Tubaro, Pascal Vranckx, Susanna Price, and Christiaan Vrints

Latest update

This online textbook has been comprehensively reviewed for the February 2018 update, with revisions made to 28 chapters. Find out more about the updates made.

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Pulmonary embolism

Chapter: Pulmonary embolism

Author(s): Adam Torbicki, Marcin Kurzyna, and Stavros Konstantinides
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Update:

2 new references

Simplified approach which allows withholding of treatment despite clinical suspicion of PE (YEARS clinical algorithm) by adjusting D-dimer threshold according to clinical presentation of the patient and decreasing the need of CT angiography has been presented.

The concept of multidisciplinary Pulmonary Embolism Response Teams (PERT) for assisting in rapid clinical decision-making in complex pulmonary embolism cases has been introduced.

Updated on 22 Feb 2018. The previous version of this content can be found **here**.

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Summary

Pulmonary embolism is usually a consequence of deep vein thrombosis, and together the two conditions are known as venous thromboembolism. Non-thromboembolic causes of pulmonary embolism are rare. Pulmonary thromboembolism is a potentially life-threatening disease, if left untreated. This is due to a natural tendency towards early recurrence of pulmonary emboli which may lead to fatal right ventricular failure. In more severe cases, secondary right ventricular failure may result from myocardial ischaemia and injury caused by systemic hypotension and adrenergic overstimulation. Clinical presentation of pulmonary embolism is non-specific and may include dyspnoea, chest pain, haemoptysis, syncope, hypotension, and shock. Patients with suggestive history, symptoms, and signs require an immediate triage which determines further management strategy. Computerized tomographic angiography has become the mainstay of diagnosis. However, depending on the clinical presentation, treatment decisions may also be made based on results from other tests. In particular, in high-risk patients with persistent hypotension or shock, bedside echocardiography may be the only available test to identify patients in need of primary thrombolysis, surgical embolectomy, or percutaneous intervention which will stabilize the systemic cardiac output. For most normotensive patients, anticoagulation is sufficient as initial treatment. However, to prevent early haemodynamic collapse and death, primary thrombolysis may be considered also in the presence of signs of right ventricular dysfunction and myocardial

injury monitoring is recommended to allow prompt rescue reperfusion therapy in case of haemodynamic decompensation.

Contents

Epidemiology

Morbidity and mortality associated with pulmonary embolism (PE) remain high, despite important advances in cardiovascular diagnosis and treatment. The reported annual incidence rate of venous thromboembolism (VTE) ranges between 23 and 69 cases per 10 000 population [1, 2], with approximately one-third of patients presenting with

acute PE and two-thirds with deep vein thrombosis (DVT) [3]. Case fatality rates vary widely, depending on the source of information, being higher in registries than in randomized clinical trials [4–7]. It is estimated that about 10% of all patients with acute PE die during the first 1–3 months [8, 9]; 1% of patients admitted to hospital die of acute PE, and 10% of all hospital deaths are PE-related [10–13].

Predisposing factors and primary prevention

Classical elements predisposing to venous thrombosis and PE include injury to vessel walls, decreased blood flow, and a prothrombotic blood composition, and these are known as the Virchow's triad. Clinical situations leading to PEs are usually classified as acquired (either setting- or patient-related) or inherited [14, 15]. Recent surgery, trauma, sepsis, and immobilization, particularly due to acute medical diseases are examples of acquired setting-related predisposing factors. An episode of PE which follows exposure to a setting-related and transient predisposing factor is called 'provoked'. This is in contrast to 'unprovoked PE' which may be associated with patient-related predisposing factors. Most of those predisposing factors are well established and include advanced age, malignancy, obesity, pregnancy, the antiphospholipid syndrome, and inherited thrombophilia; others, such as the use of haemopoietic factors, blood transfusions, and *in vitro* fertilization, have been identified more recently [16]. Similarities between the risk factors of arterial (athero)thrombosis and VTE have also been suggested [17, 18]. The concomitant presence of several predisposing factors further increases the risk of VTE [15, 19]. On the other hand, up to 25% of patients with confirmed PE have no, as yet, identifiable predisposing factors [4].

Primary prevention applied to patients with transient predisposing factors significantly reduces the risk of PE [20]. Pharmacological prophylaxis should be selected, depending on the risk of VTE disease and the risk of bleeding. Low molecular weight heparins (LMWH) or fondaparinux subcutaneous (SC) should be considered in acutely ill medical patients at high risk of VTE [21]; the new oral factor Xa or thrombin antagonists (non-vitamin-K-dependent oral anticoagulants; NOACs) are an alternative option for primary thromboprophylaxis following orthopaedic surgery [22]. Patients at exceptionally high risk of bleeding may benefit from mechanical methods, including graduated compression stockings and/or intermittent pneumatic compression to the lower limbs. Antithrombotic agents should be, however, introduced as soon as the bleeding risk lowers to acceptable levels. Central vein catheters (CVCs) clinically relevant consequence, particularly used for chemotherapy in cancer, increase the risk of upper body venous thrombosis and PE, but pharmacological prophylaxis was not found effective and therefore is not recommended in such a setting.

Pathophysiology and clinical presentation

The most clinically relevant consequence of PE is right ventricle (RV) failure, resulting from an acute increase of the RV afterload which is related not only to the volume and localization of pulmonary clots, but also to the individual compensatory reserve of the patient. Generally, however, small, isolated thromboemboli tend to be haemodynamically irrelevant, while multiple and large thrombi will disturb the RV performance during exercise or even at rest [23]. Low systemic output, shock, and sudden death, usually due to electromechanical dissociation, are the most feared consequences of a potential recurrent PE in patients who survived the initial embolic episode. However, even if recurrence is prevented and the patient appears to be stabilized, early secondary RV failure may result from relative myocardial ischaemia and injury caused by compensatory sympathetic stimulation necessary for haemodynamic stabilization. Chest pain (CP) in acute PE may be due also to pleural irritation, particularly if distal pulmonary arteries are blocked and so-called pulmonary infarction develops, frequently presenting with mild haemoptysis.

While dyspnoea is the most frequent symptom in acute PE, and some degree of respiratory failure is common, it is usually less prognostically relevant than haemodynamic instability. Respiratory failure is secondary to haemodynamic changes and mostly due to an excessively decreased O_2 saturation of mixed venous blood returning from hypoperfused tissues. Such desaturated blood is redistributed to the pulmonary arterial bed which has remained non-occluded by emboli. The reduced duration of contact with the alveolar air, due to blood overflow through the restricted pulmonary capillary bed, contributes to systemic hypoxaemia. In patients with PE and RV dysfunction, increased right atrial pressure may reopen an otherwise functionally closed patent foramen ovale, with resultant right-to-left shunt and further systemic desaturation.

Initial prognostic triage

Acute PE covers a wide spectrum of clinical severity, with in-hospital mortality rates ranging between <1% and >50% [4–9, 24]. The principal factor which determines prognosis in PE is the presence or absence of haemodynamic instability, defined as a systolic blood pressure of <90 mmHg, or an otherwise unexplained drop in systolic pressure by at least 40 mmHg persisting for at least 15 min, or frank cardiogenic shock (CS) [25].

It is of crucial importance to make this simple clinical distinction between patients at high and not high-risk of early death already, when being confronted with a patient *suspected* of having acute PE, as it will allow a risk-adjusted diagnostic strategy and guide the initial therapeutic management (see Figure **66.1**).

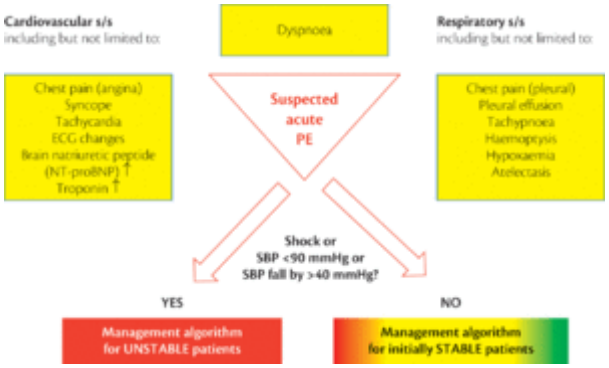

Figure 66.1
Main symptoms and signs and initial prognostic triage in suspected PE.
PE, pulmonary embolism; s/s, symptoms and signs; SBP, systolic blood pressure.

Diagnosis

Suspected high-risk pulmonary embolism (hypotensive patients)

The diagnostic strategy is different in the minority of patients presenting with hypotension or shock (suspected high-risk PE) [13] (see Figure **66.2**A). Regardless of the cause of haemodynamic instability, such patients are at very high risk of early death, and an immediate differential diagnosis is an absolute priority. While emergency computer tomography (CT) angiography (see Chapter 22) provides diagnostic information on the presence of PE, as well as on aortic dissection, cardiac tamponade, or pneumothorax, it may not be feasible in a highly unstable patient. Under such circumstances, bedside echocardiography is an acceptable alternative [13]. Although usually it does not provide a definite diagnosis or exclusion of PE [26], echocardiography (see Chapter 20) can confirm or exclude severe RV pressure overload and dysfunction. Considering its recognized value for diagnosing cardiac tamponade, aortic dissection, LV and acute valvular dysfunction, and even hypovolaemia, echocardiographic examination should suffice for the initial management decision in critically ill patients. However, as RV pressure overload is not specific for acute PE, additional diagnostic testing should still be considered. If the patient can be stabilized, computed tomography pulmonary angiography (CTPA) should be attempted. If only bedside tests are feasible, immediate compression ultrasonography (CUS) to search for proximal DVT should be considered, if performed as an extension of echocardiographic examination, without delaying treatment decisions [27]. In selected cases, particularly when surgical pulmonary embolectomy is considered on the basis of echocardiographic signs of RV only, TOE [28] may be useful to confirm proximal pulmonary artery clots.

Mobile thrombi found at echocardiography within right heart chambers directly confirm venous thromboembolism and justify aggressive therapy [29].

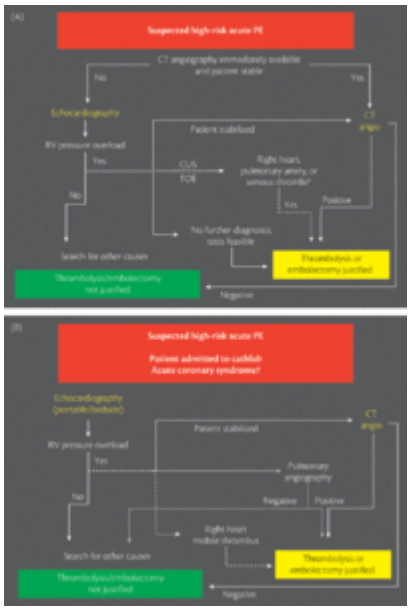

Figure 66.2
(A) Suggested diagnostic algorithm for hypotensive (high-risk) patients with suspected acute PE. RV, right ventricle; CT, computed tomography; CUS, compression venous ultrasound; TOE, transoesophageal echocardiography. (B) Suggested diagnostic algorithm for hypotensive (high-risk) patients admitted to the catheterization laboratory, because of an initial diagnosis of ACS. CT, computed tomography; RV, right ventricle.

Currently, the recommended diagnostic algorithms for PE avoid invasive tests [13]. However, despite the lack of controlled data, invasive diagnosis of PE may represent an option in patients directly referred for cardiac catheterization, because of an initial suspicion of an ACS. Some of these patients present with hypotension or shock but fail to show culprit lesions requiring primary coronary angioplasty. Ideally, during preparation for coronary angiography, such patients should be evaluated by portable echocardiography to assist in the differential diagnosis, including acute PE [30, 31]. A decision of whether to proceed to conventional pulmonary angiography (with the option of percutaneous catheter intervention) (see Figure **66.2**B), or rather discontinue invasive assessment and transfer the patient for CT angiography (see Chapter 22), should be taken on a case-by-case basis. Importantly, the presence of right heart thrombi should be excluded with portable echocardiography, prior to passing an angiographic catheter into the pulmonary artery, in order to avoid catheter-induced thrombus dislodgement and further embolization. Moreover, if echocardiography (see Chapter 20) detects thrombi in one

of the right heart chambers, no further testing for PE is necessary, and the patient should be treated without delay, in view of the high early mortality risk [32]

Suspected not high-risk pulmonary embolism (normotensive patients)

Several diagnostic tests are useful for making therapeutic decisions in patients with a clinical suspicion of PE. Their interpretation usually requires previous assessment of clinical (pretest) probability of PE [33–35]. Such assessment should account for predisposing factors (particularly recent surgery, fracture, malignancy, advanced age, previous VTE), as well as symptoms and signs suggestive of PE (particularly dyspnoea of recent onset, CP, haemoptysis, tachycardia, unilateral leg pain, or oedema). An evaluation, based on clinical judgement and simple, routinely performed diagnostic tests (electrocardiogram (ECG), CXR (see Chapter 18), arterial blood gas (ABG) (see Chapter 19)), is sufficient, particularly if done by an experienced clinician. However, structured prediction rules give an opportunity to better standardize the probability assessment. The Wells and Geneva scores have been prospectively validated in large populations of mostly normotensive (not high-risk) patients with suspected PE [36, 37] and continue to be simplified for easier application [38–41]. This simplification has resulted in a reduction of the clinical probability levels, from three (low, intermediate, high) to two (PE-unlikely and PE-likely) [42]. The assessment of PE probability, with the help of the Wells or Geneva score, may be particularly useful when the local team experience with PE is limited.

While helpful, prediction rules do not suffice to confirm or exclude PE with the reliability required for therapeutic decisions. In most cases, such decisions are based on CT angiography. However, in normotensive (not high-risk) patients, with low or intermediate clinical probability (non-high probability) of PE, the diagnostic assessment may be limited to the D-dimer (see Chapter 38). If found negative with a highly sensitive test, it justifies withholding anticoagulation [43, 44] (see Figure **66.3**A). Such decision is also justified when the intermediate-sensitivity D-dimer tests are used, but only in patients with low clinical probability or qualified as PE-unlikely, according to the more recently introduced binomial probability scale.

Figure 66.3
(A) Suggested diagnostic algorithm for normotensive (not high-risk) patients with suspected acute PE. PE, pulmonary embolism; MDCT, multidetector CT angiography. (B) Suggested diagnostic algorithm for normotensive (not high-risk) patients with high clinical probability of acute PE, but a negative CT angiography result. PE, pulmonary embolism; MDCT, multidetector CT scan; CUS, venous compression ultrasound; V/Q scan, ventilation/perfusion lung scintigraphy.

Because D-dimer levels increase with age, comorbidities, or pregnancy [44–47], the test is more useful for the evaluation of outpatients in the ED [45, 47–49], particularly if the clinical probability is low [50]. Higher cut-off values, which would account for the physiological increase of D-dimer levels with age or during pregnancy, have been suggested [51, 52]. Age-adjusted D-dimer threshold calculated as age × 10 in patients ≥ 50 years old was associated with a 5% (from 28 to 33%) absolute increase in the proportion of patients with suspected PE in whom imaging could be safely withheld compared with fixed D-dimer testing. This strategy seemed safe across different high-risk subgroups such as with cancer, suffering from COPD, or more than 74 years old [53]. A positive proximal venous CUS is found in 1 out of 7 patients with suspected acute PE and is fully specific, justifying treatment [54]. However, its diagnostic yield in patients without clinical symptoms or signs of DVT is low [55]. Extending CUS to distal veins improves sensitivity but is not reliable enough to justify treatment [54]. Negative CUS may reinforce the controversial decision to withhold anticoagulation in a patient with a high clinical probability of PE, but with no clots detected at multidetector CTPA [35, 56] (see Figure **66.3**B).

Strategies based on lung scintigraphy may be useful in pregnancy, renal dysfunction, or cases of allergy to contrast media [57]. Preliminary reports on the potential role of thoracic ultrasound in suspected PE remain to be validated by larger studies [58–60]. Magnetic resonance angiography (see Chapter 23) is not, at present, a diagnostic option for suspected acute PE, due to the high (20–25%) rate of technically inadequate examinations and inadequate sensitivity [61–65].

The diagnostic strategies suggested for normotensive (not high-risk) patients have been validated by several outcome trials [66] and verified by a large accuracy study [35]. They have shown an efficacy of management similar to that of decisions based on pulmonary angiography, which was once considered as the gold standard of PE diagnosis. Particularly, the 3-month rate of symptomatic VTE episodes remained below 2–3% in patients left without anticoagulation treatment, despite a clinical suspicion of PE [13]. A recent meta-analysis of six prospective trials including 7268 patients with PE considered unlikely according to Wells score suggests that such strategy is also valid when using D-dimer threshold adjusted to age [53].

Recently, a simplified algorithm based on D-dimer thresholds adjusted according to the presence of one or more clinical markers extracted from the Wells probability score (YEARS clinical decision rule) was prospectively tested. Three clinical items (signs of deep vein thrombosis, haemoptysis, and whether pulmonary embolism is the most likely diagnosis), and D-dimer concentrations were considered. In patients without YEARS items and D-dimer less than 1000 ng/mL, or in patients with at least one YEARS item and D-dimer less than 500 ng/mL pulmonary embolism was considered excluded.

Of the 2946 patients (85%) in whom pulmonary embolism was ruled out at baseline and remained untreated, 18 patients were diagnosed with symptomatic venous thromboembolism during 3-month follow-up (0·61%, 95% CI 0·36–0·96) including six with fatal pulmonary embolism (0·20%, 0·07–0·44). Compared to standard approach including Wells score and fixed D-dimer threshold the YEARS strategy would decrease the number of patients not requiring CT angiography by 14% [173].

Special diagnostic challenges

CT angiography (see Chapter 22) is a first-choice test in patients presenting with haemoptysis. In such patients, the decision to start anticoagulation must be particularly well justified, because of the possibility of lung cancer as an alternative or concomitant diagnosis. The differentiation between an exacerbation of chronic obstructive pulmonary disease (COPD) and an episode of PE also usually requires CT angiography, as D-dimers tend to increase in both conditions and ventilation perfusion (V/Q) scans are rarely diagnostic [44, 67, 68]. Controversy persists on the clinical significance of isolated asymptomatic

subsegmental clots reported on CT. While most experts agree that, if found in cancer patients, they justify standard treatment for PE, no consensus exists for non-cancer patients [69–72].

Pregnancy poses particularly difficult problems. While being one of the predisposing factors for PE, normal pregnancy may also mimic several of its symptoms and signs: breathlessness (sometimes with hypoxaemia in the supine position), unilateral (usually left-sided) lower limb oedema, and even syncope [73]. The accuracy of the clinical probability scores has not been validated in pregnancy [74]. D-dimers (see Chapter 38) are rarely low, particularly during the second and third trimester, but, if negative, they are sufficient to withhold anticoagulation also in pregnant women, except in the high clinical probability category [46]. Venous clots may be confined to the iliac vein and therefore may be missed on standard CUS evaluation, even in a symptomatic patient [73]. Echocardiography may justify therapeutic decisions only in critically unstable patients. Therefore, diagnostic tests based on ionizing radiation often have to be considered. Contrary to common belief, the radiation absorbed by the fetus remains well below the dose considered as dangerous, even if the V/Q scan, CT scan, and contrast pulmonary angiography were to be sequentially performed [73]. Even so, a reduction of the radiation dose is always a high priority in pregnancy. Based on expert opinion, a useful approach consists of a CXR, followed, if normal, by lung perfusion scintigraphy [75, 76]. CT angiography delivers slightly less radiation to the fetus but seems to increase the whole-life risk of maternal breast cancer by approximately 15% [77]. Also, up to a quarter of CT examinations suffer from suboptimal opacification of pulmonary arteries. This is due to mixing of the injected contrast with an increased volume of non-contrast blood returning from the inferior vena cava due to placental flow [75]. However, a recent outcome trial showed that, while 20% were ‘technically limited’, they could be safely used for the decision to withhold anticoagulation, despite suspected PE. Only 1% of multidetector CT angiographies in pregnant women were inconclusive [78]. For reasons already described and because of uncertain long-term effects of gadolinium on the foetus, as well as the magnetic field effects on the DNA integrity, MR pulmonary angiography is not a recommended alternative in suspected PE in pregnancy.

Comprehensive severity assessment

Clinical assessment

As already mentioned, clinical assessment may be sufficient to raise a suspicion of high-risk PE through the presence of either persistent arterial hypotension (systolic blood pressure <90 mmHg, or a pressure drop by ≥40 mmHg for at least 15 min) or shock. About 5% of all cases of acute PE fall into this category, with a >15% risk of in-hospital death, particularly during the first few hours after admission [5, 79–81]. Not

high-risk PE has a much more favourable outcome, provided that anticoagulation is instituted without delay [24, 79, 80].

In-hospital mortality is particularly low (<1%) in patients without tachycardia and tachypnoea, if they are free from significant comorbidities and other aggravating factors such as advanced age.

The pulmonary embolism severity index (PESI) has been designed to allow a standardized comprehensive prognostic evaluation, based on clinical parameters (see Table 66.1). It was successfully validated in large populations of patients with PE [82, 83]. The index gives individual prognostic weight to each of clinical or simple laboratory variables (such as pulse oximetry) [84]. A randomized prospective trial successfully used low PESI (risk class I or II) for the selection of patients suitable for early discharge and home treatment, despite an objectively confirmed acute PE [85]. A simplified score (sPESI), limited to five equally weighted clinical variables and pulse oximetry, seems to have similar accuracy but awaits validation in an outcome trial focusing on the safety of home treatment [86] (see Table 66.2).

Table 66.1 The pulmonary embolism severity index: calculation

Variable	Points
Age	1/year
Male	10
History of cancer	30
History of heart failure	10
History of chronic lung disease	10
Pulse rate >110 beats/min	20
Systolic blood pressure <100 mmHg	30
Respiratory rate ≥30 breaths/min	20
Body temperature <36°C	20
Altered mental status (disorientation, confusion, somnolence)	60

Arterial oxyhaemoglobin saturation <90%	20

From [83].

Table 66.2 The simplified PESI (sPESI): calculation

Parameter	**Points**
Age >80 years	+1
Cancer	+1
Chronic cardiopulmonary disease	+1
Heart rate ≥110 beats/min	+1
Systolic blood pressure <100 mmHg	+1
Arterial oxyhaemoglobin saturation <90%	+1
Dichotomized: cut-off ≥1 indicates increased early mortality risk	

From [88].

Others prognostic scores, such as HESTIA or IMPACT, have similar accuracy in identifying low-risk patients as PESI and sPESI. In a cohort of 807 hospitalized PE patients, out of which 21 (2.6%) died before discharge, 26–38 % of patients were qualified by prognostic scores as low-risk for early mortality. Fatality among low-risk patients was 0% for sPESI and Hestia, 0.4 % and 0.6 % for IMPACT and PESI, respectively. All those four scores showed very low positive predictive value (3.5–3.8%) for in-hospital death [87].

Risk categories (with % rate of 30-day all-cause mortality) are as follows:

<65 points (0%)
Class II, 66–85 points (1%)
Class III, 86–105 points (3.1%)
Class IV, 106–125 points (10.4%)
Class V, >125 points (24.4%)

Patients in risk classes I and II are defined as low-risk.

Laboratory assessment

While high-risk and low-risk patients with acute PE can be identified on clinical grounds alone, several laboratory variables may help to further stratify the remaining intermediate-risk patients, according to their expected outcome. The ESC guidelines identify two main categories of risk markers, useful for such risk stratification in PE and widely available in the acute cardiovascular care setting: signs of humoral biomarkers indicating myocardial injury or strain and imaging indicating RV dysfunction. This was based on evidence suggesting that the combined presence of risk markers from both categories mentioned is related to an increased risk of death or a complicated clinical course of PE (intermediate-high risk category).

Comprehensive laboratory assessment has been suggested to reach optimal management decisions.

Markers of myocardial injury found of prognostic value in acute PE include cardiac specific troponins (cTns) (see  Chapters 35 and 36), h-FABP, and growth differentiation factor-15 (GDF-15).

cTns received the most attention as a marker of myocardial injury in acute PE. Elevated cTnI or cTnT levels were found in up to 50% of such patients [89]. A meta-analysis of 20 studies with a total of 1985 patients showed that cTn elevation was associated with an increased risk of death (odds ratio (OR) 5.24; 95% confidence intervals (CI) 3.28–8.38) and major AEs (OR 7.03; 95% CI 2.42–20.43) in the acute phase [90]. However, a more recent meta-analysis which focused only on normotensive patients (1366 patients in nine studies) was unable to confirm the prognostic value of cTns in not high-risk PE [91]. Thus, cTn elevation alone does not suffice to identify normotensive, intermediate-risk patients who require early aggressive (e.g. thrombolytic) treatment.

Fatty acid-binding proteins are small cytoplasmic proteins which are abundant in tissues with active fatty acid metabolism, including the heart [92]. Following myocardial cell damage, h-FABP appears in the circulation 90 min after symptom onset, reaching its peak within 6 hours [93]. It was suggested that h-FABP may provide prognostic information superior to that of cTns and echocardiography in acute PE [94, 95] also in not high-risk patients [96, 97].

GDF-15 is a member of the transforming growth factor beta (TGF-β) cytokine family. Its cardiac expression increases sharply after pressure overload or myocardial ischaemia [98, 99], and thus GDF-15 might be capable of integrating information both on RV dysfunction and myocardial injury. Elevated levels of GDF-15 were associated with an increased 30-day risk of death or major complications in PE [100].

Markers of RV dysfunction and/or strain found of prognostic relevance in acute PE can be derived from echocardiography, CT angiography, and NT-proBNP. Echocardiography is capable of detecting both RV dilatation and its systolic dysfunction in PE, though generally accepted echocardiographic criteria are lacking [101, 102]. Despite the association between an abnormal RV on echocardiography and an adverse in-hospital outcome [24, 80, 103–105], a meta-analysis, including 475 normotensive patients with PE, reported an only moderate negative (60%) and a positive (58%) value of echocardiography for predicting early death [106]. Therefore, while an entirely normal RV on echocardiographic examination predicts a good outcome, the therapeutic implications of isolated RV dysfunction on cardiac ultrasound in otherwise not high-risk patients with PE remain unclear.

Four-chamber views of the heart on the multidetector-row CT (see Chapter 22), which is currently the preferred method for diagnosing PE, may detect RV enlargement due to PE. In a retrospective series of 431 patients, the 30-day mortality was 15.6% in patients with a right/left ventricular dimension ratio of >0.9 on multidetector-row chest CT, compared to 7.7% in those without this finding [107]. The prognostic value of an enlarged RV on CT angiography was confirmed by a joint analysis of two retrospective studies [106] and by a prospective multicentre cohort study of 457 patients. According to the latter, RV dysfunction was an independent predictor for an adverse in-hospital outcome in haemodynamically stable patients (HR 3.8; 95% CI 1.3–10.9; $P = 0.007$) [108].

NPs (see Chapter 37) are sensitive indicators of neurohormonal activation, due to ventricular dysfunction, and their levels have been determined in patients with acute PE [109–112]. Plasma biomarkers do not indicate which ventricle is acutely dysfunctional, and theoretically this should be resolved by imaging. Even so, a meta-analysis of 13 studies enrolling 1132 patients found that elevated BNP or NT-proBNP levels were associated with an increased risk of early death (OR 7.6; 95% CI 3.4–17) [113]. However, the authors concluded that elevation of NPs alone does not appear to justify more invasive treatment regimens.

In addition to markers of myocardial injury and RV dysfunction, other less specific markers were also related to prognosis after acute PE. This includes markers of renal dysfunction (see Chapter 39) or injury, such as decreased glomerular filtration fraction (GFR), elevated serum levels of creatinine, NGAL, and cystatin C [114]. Elevated D-dimer concentrations (see Chapter 38) were associated with an increased short-term mortality in some studies, while levels <1500 ng/mL had an negative predictive value (NPV) of 99% for excluding 3-month all-cause mortality.

At present, no individual clinical, imaging, or laboratory parameters have been shown to predict the risk of an adverse in-hospital outcome which is high enough to justify primary thrombolysis or another mode of pulmonary revascularization in not high-risk patients. Various combinations of clinical findings, echocardiography, and laboratory biomarkers have been tested in registries and cohort studies in an attempt to improve the risk stratification of PE [115–120].

The clinical relevance, particularly with regard to the therapeutic implications, of most of the suggested scores remains to be determined. The only combination of prognostic markers tested prospectively in a management trial was that of RV dysfunction on echocardiogram or CT angiogram with a positive cTn test. It was used as an inclusion criterion in a recently presented randomized thrombolysis trial which enrolled 1006 normotensive patients with acute PE. Patients treated with standard anticoagulation had a 5.6% incidence of death or haemodynamic decompensation within the first 7 days following randomization, and this was reduced by half in patients randomized to thrombolysis. With similarly low in-hospital mortality in the two groups (below 2%), the difference was almost entirely driven by the prevalence of secondary haemodynamic destabilization and came at a cost of an increased risk of haemorrhagic stroke [121].

Recent prospective validation of the prognostic approach suggested by ESC guidelines confirmed the presence of a mortality gradient between the four prognostic groups. This prognostic gradient was more obvious with respect to death due to PE, which occurred in 15% of high-risk patients, 5% in patients in intermediate–high, 2% in intermediate–low, and 0.5% of patients in the low-risk category [122]. Respective numbers for all cause mortality were 22%, 7.7%, 6.0%, and 0.5%, showing that the currently recommended prognostic strategy could still be improved in order to better risk-stratify normotensive patients who do not fall into the low-risk category. It might be useful to take into account not only RV imaging and laboratory markers but also borderline values of systolic blood pressure (90–100 mmHg) as well as the presence of tachycardia >100 bpm [123]. A score able to identify a subgroup of normotensive PE patients with 30-day PE-related mortality of 15% based on those signs awaits prospective validation in a management trial.

The presence of proximal DVT at CUS [124] as well as thrombi within right heart chambers found at echocardiography in a patient with PE [29] is related to increased mortality but at present are not included into the panel of prognostic markers that drive the treatment algorithm.

Treatment in the acute phase of pulmonary embolism

In acute PE, cardiovascular mortality is highest during the first few hours after presentation [81]. In patients who survive the early phase, the cardiovascular risk is determined, at least in part, by the development of secondary RV failure, due to either recurrent thromboembolic events or the inability to chronically sustain a significantly increased afterload. Accordingly, the management of PE must focus on two major goals: (1) the early reversal of RV dysfunction, if present; and (2) the prevention of recurrent thromboembolism.

The first goal is particularly important in unstable, high-risk patients and can be achieved by thrombolysis, surgical embolectomy, or by percutaneous intravascular interventions Often clinical presentation, comorbidities or high bleeding risk make management decisions difficult. Moreover, local expertise and availability of different interventional methods such as thrombus fragmentation, suction, local thrombolysis or bridging to recovery using ECMO may differ. Multidisciplinary Pulmonary Embolism Response Teams (PERT) started to appear in clinical centers offering rapid web-based consultations assisting in decision-making by adjusting it to clinical presentation of individual patients and local availability of treatment options [174].

The second goal is of major importance for all patients with PE and can be achieved by the immediate institution of adequate anticoagulation [20, 125]. Implantable venous filters may be used to prevent recurrence of PE in patients with active bleeding and absolute contraindications to anticoagulation.

Anticoagulation

Anticoagulant treatment (see Figure **66.4**) should be initiated without delay in patients with an intermediate or a high clinical probability of acute PE, while awaiting confirmation by appropriate diagnostic evaluation. IV UFH is the preferred mode of acute phase anticoagulation for: (1) patients with severe renal impairment (creatinine clearance <30 mL/min); (2) patients at high risk of bleeding; (3) high-risk, hypotensive patients; and (4) extremely overweight patients. With the exception of these circumstances, UFH has largely been replaced by LMWH or fondaparinux, given SC at weight-adjusted doses. Routine anticoagulation monitoring, i.e. the measurement of anti-factor Xa levels, is not necessary in patients receiving LMWH, but it should be considered during pregnancy. In this case, anti-Xa levels should be determined 4 hours after the morning injection; the proposed target range is 0.6–1.0 IU/mL for twice-daily, and 1.0–2.0 IU/mL for once-daily, administration [20].

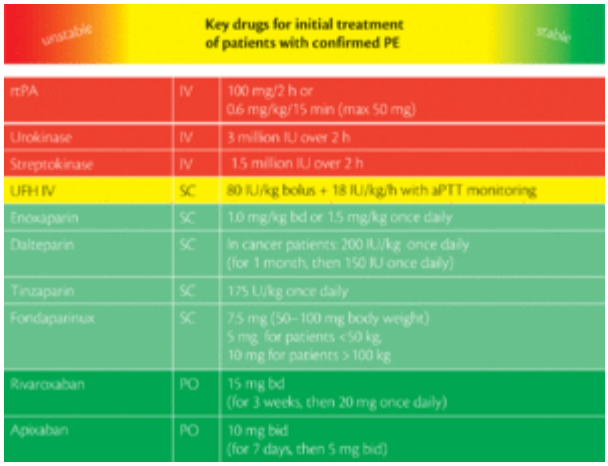

Figure 66.4
Drugs and their mode of administration suggested for the initial treatment of PE, according to haemodynamic stability and the risk of early death.

As an alternative to the initial parenteral treatment of acute PE with heparin, two new oral anticoagulants (NOACs)—the anti Xa agents rivaroxaban and apixaban—have been approved as an ‘oral drug only’ anticoagulation regimen in haemodynamically stable patients. Both showed an efficacy (prevention of symptomatic VTE or fatal PE) which was non-inferior to that of LMWH and were associated with less major bleedings [126, 127]. Of note, most of the patients in those trials received at least one dose of heparin, prior to randomization and initiation of the tested drug.

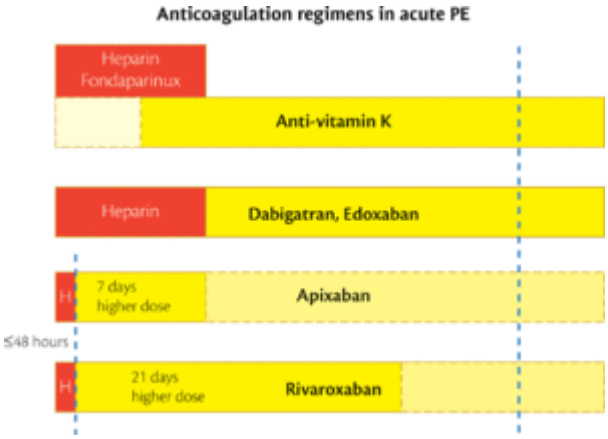

Figure 66.5
Anticoagulation regimens in acute PE

Anticoagulation with UFH or LMWH should be continued for at least 5 days. Oral anticoagulants (vitamin K antagonists (VKAs)) should be initiated as soon as possible in all haemodynamically stable patients,

preferably on the same day as heparin. Parenteral anticoagulation can be stopped as soon as the INR has been in the therapeutic range (between 2.0 and 3.0) for 2 consecutive days [20]. As an alternative to the heparin–VKA combination, rivaroxaban can be administered at a dose of 15 mg bd over the first 3 weeks, followed by a single daily dose of 20 mg thereafter [126]. A similar treatment pattern, but with a dose decrease after 7 days of initial therapy, has been approved for apixaban [127]. Initial treatment with anti-Xa drugs seem to shorten the hospital stay without increasing the complication rate [128]. Two other approved drugs—the DTI inhibitor dabigatran and the direct anti-Xa agent edoxaban—have been found useful as alternatives to VKAs for anticoagulant treatment after at least 5 days of prior parenteral LMWH therapy [129, 130]. Recently, the HAS-BLED score developed to assess bleeding risk in patients with atrial fibrillation has proven useful also in patients with pulmonary embolism during the first 6 months of anticoagulation [131].

Thrombolysis

Thrombolytic therapy of PE resolves the thromboembolic obstruction and, within 1–2 hours, reduces pulmonary artery pressure and resistance, with a resulting increase in cardiac output [105, 132]. Overall, up to 92% of patients with PE appear to respond favourably to thrombolysis, as indicated by clinical and echocardiographic improvement within the first 36 hours [133]. The greatest benefit is observed when treatment is initiated within 48 hours of symptom onset, but thrombolysis can still be useful in patients who have had symptoms for 6–14 days [134].

The haemodynamic benefits of thrombolysis over heparin appear to be confined to the first few days. In survivors, the improvement in the severity of vascular obstruction and RV dysfunction after 1 week appeared to be similar in thrombolysis-treated and heparin-treated patients [135]. Accordingly, thrombolytic treatment may be lifesaving in high-risk unstable patients with shock or hypotension. When given to normotensive patients with evidence of RV dysfunction and myocardial injury, thrombolysis significantly reduced the frequency of secondary haemodynamic destabilization during the hospital stay, but not of death [136]. More recently, a large multicentre, randomized, double-blind trial compared thrombolysis with tenecteplase plus heparin vs placebo plus heparin in 1006 patients with RV dysfunction, confirmed by echocardiography or CT angiography, and myocardial injury, confirmed by a positive cTnI or cTnT test. The primary efficacy outcome, a composite of all-cause mortality or haemodynamic decompensation/collapse within 7 days of randomization, was significantly reduced with tenecteplase (2.6%, compared to 5.6% in the placebo group; $P = 0.015$; OR 0.44; 95% CI 0.23–0.88). There was a significant reduction in the rate of haemodynamic collapse (1.6% vs 5.0%; $P = 0.002$); however, all-cause mortality was similar and low: 1.2% in the tenecteplase group, and 1.8% in the placebo group ($P = 0.43$). This was at the cost of 2% incidence of haemorrhagic

stroke after thrombolytic treatment with tenecteplase compared to 0.2% in the placebo arm. The incidence of major non-intracranial bleeding events was also increased (6.3% vs. 1.5%; P < 0.001) [121].

These results are consistent with those of earlier trials which also indicated a cumulative rate of up to 13% for major bleeding and a 2% rate of intracranial and/or fatal haemorrhage [105, 136–138]. Taken together, these data indicate that thrombolysis should be used as primary therapy only in haemodynamically unstable patients. Its administration to patients with PE, signs of RV overload, and myocardial injury, but without shock or hypotension, should be considered as rescue treatment. Consequently, those patients require close monitoring for early signs of haemodynamic decompensation.

While currently approved thrombolytic regimens for PE still include the older agents urokinase and streptokinase, alteplase, either as an IV infusion of 100 mg over 2 hours (with an initial 10 mg bolus) or a short infusion of 0.6 mg/kg (not exceeding 50 mg), is most widely used at present.

Surgical or catheter-based thrombus removal

Pulmonary embolectomy remained a rarely performed rescue operation over several decades, and limited data existed regarding its efficacy and safety. Recent technical advances in transportable extracorporeal assist systems (see  Chapter 30) may help to stabilize the patient perioperatively and improve outcome. Therefore, the involvement of cardiac surgeons and a team experienced in advanced haemodynamic support systems should be considered in compromised or deteriorating patients, as part of an interdisciplinary approach to PE [139–143]. Pulmonary embolectomy is the treatment of choice for patients with pending paradoxical systemic embolism [144], those with hypotension or shock but with contraindications to thrombolysis, and cases where thrombolysis has failed [13, 133].

Alternatively, transcatheter interventions may be considered, provided that there is adequate equipment and expertise on site [145, 146]. For patients with absolute contraindications to thrombolysis, interventional options include: (1) thrombus fragmentation with pigtail or balloon catheter; (2) rheolytic thrombectomy with hydrodynamic catheter devices; (3) suction thrombectomy with aspiration catheters; and (4) rotational thrombectomy [147]. Emerging ‘hybrid therapies’ include catheter-directed, pharmacomechanical (ultrasound-enhanced) thrombolysis; a phase 2 randomized trial and a prospective cohort study have yielded promising results [148, 149].

Vena cava filters

Caval filters may be used successfully for the prevention of PE recurrence. However, inferior vena caval filter placement may increase the risk of recurrent leg vein thrombosis over the long term [150]. Thus, filters have a role in the prevention of PE only if anticoagulation is absolutely contraindicated or in cases of recurrence, in spite of an adequately prescribed medical treatment. In the former case, anticoagulation should be resumed as soon as the bleeding risk can be lowered. Whenever filters are used in a patient with transient risk factors for PE, a retrievable device should be placed, and retrieval should be attempted after the elimination of the predisposing factors [151].

Data from the United States have shown a 3-fold increase in the use of (retrievable or permanent) cava filters between 2001 and 2006 [152]. However, recent trial data do not appear to support the liberalization of their use beyond the strict indications mentioned above. In a randomized, open-label, blinded endpoint trial with 6-month follow-up, hospitalized patients with acute, symptomatic PE associated with lower limb vein thrombosis and at least one criterion for severity were assigned to retrievable inferior vena cava filter implantation plus anticoagulation (n = 200) or anticoagulation alone with no filter implantation (n = 199). By 3 months, recurrent PE had occurred in six patients (3.0%; all events fatal) in the filter group and in three patients (1.5%; two fatal) in the control group (RR with filter: 2.0; 95% CI 0.51–7.89); results were similar at 6 months, providing no evidence in favour of filter placement [153].

There is anecdotal experience with superior vena cava filters for the prevention of PE recurrence in cases of DVT of the upper extremities [154, 155].

Risk-adjusted management strategy in the acute phase

High-risk pulmonary embolism

In view of the high early mortality and complication risk associated with high-risk PE, existing guidelines [13, 20] and the majority of experts agree that patients who present with persistent arterial hypotension or shock are in need of immediate ‘primary’ pharmacological or mechanical recanalization of the occluded pulmonary arteries. Thus, haemodynamically unstable patients with suspected high-risk PE should immediately receive a weight-adjusted bolus of UFH, while awaiting the results of further diagnostic work-up; if PE is confirmed, thrombolysis should be administered without delay. If thrombolysis is absolutely contraindicated or has failed, surgical embolectomy or catheter-based interventions are valuable alternatives (see Figure **66.6**).

Figure 66.6
Suggested management algorithm for patients with suspected and confirmed PE.

Not high-risk pulmonary embolism

Heparin, fondaparinux, rivaroxaban, apixaban, dabigatran, and edoxaban are all approved for treatment of normotensive patients with PE (see Figure **66.4**). In these patients, thrombolysis is reserved for ‘rescue’ in cases of haemodynamic destabilization, due to recurrence or secondary RV failure. In order to detect haemodynamic destabilization and respond to it immediately, patients with signs of RV dysfunction and myocardial injury, shown to be at the highest risk of decompensation, should be closely monitored.

Patients with confirmed PE and a low PESI score (≤85 points), an sPESI score of 0, or the absence of HESTIA criteria of the need for hospitalization can be considered for early discharge and home treatment, in view of the very low risk of an early adverse outcome [84, 156]. It is, at present, questionable whether a negative cTn test and/or an echocardiogram excluding RV dysfunction are also required to further increase the safety of home treatment [157–159]. If a CT angiogram has been used for the diagnosis of PE, the assessement of the RV/LV ratio may exclude the possibility of asymptomatic RV dysfunction, without any additional delay or expenses [108].

Pulmonary embolism: recurrence and extended secondary prophylaxis

Anticoagulation after an episode of PE provoked by transient risk factors can be discontinued usually after 3 months, with an acceptable low risk of subsequent recurrence. Unprovoked PE carries an increased lifetime risk of recurrent episodes of VTE, in most cases also presenting as PEs. The

long-term recurrence rate may be >30% after 8–10 years [160–162]. Prolonging anticoagulation from 6 months to 18 months has no effect on cumulative prevalence of recurrent VTE [163]. Extended, long-term anticoagulation has been shown to reduce the risk for recurrent thromboembolism by approximately 80% but is associated with considerable major bleeding risk [164]. Therefore, the duration of secondary prophylaxis should be determined individually and continuously reassessed with the help of specifically developed scores predicting bleeding risk in survivors of VTE on stable anticoagulation therapy [164–167]. While patients with high-risk thrombophilia or active cancer are likely candidates for long-term oral anticoagulation [168], other patients could benefit from an attempt to discontinue secondary prophylaxis. This is particularly reasonable in patients with unprovoked PE, in whom some of the predisposing conditions could be eliminated or modified (e.g. obesity, sedentary lifestyle, hormonal therapy).

Increased D-dimer plasma levels 1 month or later after the discontinuation of secondary prophylaxis may indicate an elevated risk of recurrence and thus present an argument in favour of resuming anticoagulation treatment [169, 170]; on the other hand, it is questionable whether anticoagulants can be withheld in patients with a negative D-dimer test, as this scenario does not appear to safely exclude recurrence [171] The patient’s informed opinion and her/his priorities play a growing role in the decision making regarding the duration of anticoagulation after PE. An important element in this context may be the presence of chronic or paroxysmal atrial fibrillattion or flutter, which, in almost all patients, constitutes a clear indication for lifetime anticoagulation. Therefore, before deciding about the discontinuation of secondary prophylaxis, taking a focused history, and possibly 24-hour ECG monitoring, may help to select the optimal strategy. NOACs may facilitate extended, or even indefinite, treatment [126, 127, 172].

Long-term consequences of PE: Chronic thromboembolic pulmonary hypertension

Thromboembolic deposits are progressively eliminated from the pulmonary circulation during the first 3 months after an acute PE episode. In those few patients in whom this process is not sufficiently effective, residual post-thrombotic occlusions may lead to chronic thromboembolic pulmonary hypertension (CTEPH). Redistribution of pulmonary flow and increased systemic bronchial supply to the lungs result in further remodeling of pulmonary vessels. Early diagnosis and specific treatment may prevent progressive increase of pulmonary vascular resistance otherwise leading to fatal right ventricular failure. Screening of asymptomatic survivors of acute PE is not an option due to low (1–2%) prevalence of CTEPH [173]. Also, persistent dyspnoea after a PE episode is usually related to comorbidities such as COPD or left heart failure. Risk factors for CTEPH include but are not limited to central, recurrent, haemodynamically significant non-provoked PE episodes. Hypothyroidism with replacement hormonal therapy seem to increase the risk of CTEPH. Splenectomy, persistent right heart catheters, and electrodes predispose to smaller, distal post-thrombotic deposits, are more difficult to manage by surgical pulmonary endarterectomy, which is the treatment of choice. Thrombolytic treatment does not seem to influence the incidence of CTEPH after an acute episode. In some cases this may be due to chronic changes already present in patients clinically considered as having acute PE. Diagnosis requires comprehensive chest imaging, including selective pulmonary angiography, but starting with a V/Q scan, which is the most sensitive screening test in suspected cases [173]. An experienced multidisciplinary CTEPH team is required to qualify the patient to surgical treatment, or in cases of non-operability or pulmonary hypertension persisting despite the operation to medical therapy and/or percutaneous balloon angioplasty [173].

Personal perspective

The management of acute PE continues to evolve. Easier access to CTA improves detection, and primary pulmonary reperfusion treatment is lifesaving in hypotensive, high-risk patients. Prognostic staging of initially normotensive patients helps to identify those in need of close monitoring and possibly rescue thrombolytic treatment. Catheter-directed methods, with/without low-dose thrombolytics, may emerge as an alternative to full-dose systemic thrombolytic treatment, as the haemorrhagic risk of the latter is not counterbalanced by the survival benefit in normotensive patients. While NOACs may facilitate the management of stable patients, heparin remains the key anticoagulant in the intensive cardiovascular care setting. Long-term outcome in survivors may be complicated by

progressive chronic thromboembolic pulmonary hypertension, which requires management in specialized pulmonary hypertension referral centres [13].

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