Review Article

Management of Acute Pulmonary Embolism: A Contemporary, Risk-Tailored Approach

Georgios K. Chalikias, Dimitrios N. Tziakas, Dimitrios A. Stakos, Stavros V. Konstantinides

Department of Cardiology, Democritus University of Thrace School of Medicine, Alexandroupolis, Greece

Key words:
Pulmonary embolism, anticoagulation, thrombolysis, heparin.

Manuscript received:
April 17, 2010;
Accepted:
June 21, 2010.

Address:
Stavros V. Konstantinides

Department of Cardiology Democritus University of Thrace, University General Hospital 681 00 Alexandroupolis, Greece
e-mail: skonst@med.duth.gr

Pulmonary embolism (PE)-associated morbidity and mortality remain high despite important advances in cardiovascular diagnosis and treatment. The reported annual incidence of venous thromboembolism ranges between 23 and 69 cases per 100,000 population,[1,2] with approximately one third of patients presenting with acute PE and two thirds with deep vein thrombosis.[3] Case fatality rates vary widely depending on the clinical severity of the thromboembolic episode,[4-7] but it is estimated that approximately 10% of all patients with acute PE die within the first 1-3 months.[8,9] In the United States, the estimated venous thromboembolism-related annual mortality amounts to approximately 100,000 deaths.[10] Overall, 1% of hospitalised patients die of acute PE, and 10% of all hospital deaths are PE-related.[11-13] These epidemiological data underline the importance of an effective approach to acute PE in clinical practice.

The present review summarises our current state of knowledge concerning the management of acute PE. It is in agreement with the recommendations included in the recently updated guidelines of the European Society of Cardiology (ESC),[14] but also presents the most recent evidence and states the authors' opinion on some practically relevant issues in which conclusive evidence, particularly in the setting of acute and critical care, is still lacking. Finally, a particular focus of the present article is the identification of both the intermediate-risk patients, who may need immediate thrombus removal from the pulmonary circulation, and the low-risk patients who might safely be treated as outpatients.

A paradigm shift in PE severity classification

Acute PE covers a wide spectrum of clinical severity, and the mortality rates during the acute phase range between less than 1% and well over 50% in different studies.[4-9,15] The principal pathophysiological factor that determines disease severity and short-term prognosis is the presence or absence of right ventricular (RV) dysfunction and failure resulting from acute pressure overload.[16] Importantly, the extent of RV dysfunction, and of the resulting haemodynamic instability, is only roughly related to thrombus burden and the severity of anatomical obstruction.[17,18] This complexity is due to the involvement of additional pathophysiological factors, such as pulmonary vasoconstriction, platelet activation, and persistent myocardial injury, despite maintained coronary flow to the right ventricle.[19-22] Because of these considerations, contemporary clinical assessment of PE severity is focused on PE-related *early death risk* rather than reflecting the overall volume, shape or distribution

of intrapulmonary emboli on pulmonary angiography, computed tomography or lung scan. To emphasise this important change in paradigm, the recently updated ESC guidelines have insisted on replacing potentially misleading terms such as "massive", "submassive", and "non-massive" PE, with "high-risk", "intermediate risk", and "low-risk" PE.[14,23] Parameters useful for risk stratification are: i) clinical markers of haemodynamic instability; ii) markers of RV dysfunction; and iii) markers of myocardial injury.[14] Appropriate use of these markers may help classify PE patients as being at high (>15%), intermediate (3-15%) or low risk (<1%) of early death (Table 1).

Clinical markers associated with haemodynamic status

High-risk PE is defined by the presence of overt RV failure that results in haemodynamic instability, i.e. persistent arterial hypotension (systolic blood pressure <90 mm Hg, or a pressure drop by ≥40 mm Hg for at least 15 minutes) and shock (Figure 1). This condition accounts for almost 5% of all cases of acute PE and constitutes a medical emergency, since it is associated with a risk of in-hospital death of at least 15%, particularly during the first few hours after admission.[5,24-26] On the other hand, the absence of haemodynamic collapse indicates non-high-risk PE, which is generally associated with a more favourable outcome, provided that the disease is diagnosed correctly and anticoagulation can be instituted without delay.[15,24,25] For the physician, it is of crucial importance to make this simple clinical distinction directly when confronted with a patient suspected of having acute PE, as it will both permit a risk-adjusted diagnostic strategy and guide the initial therapeutic management (Figure 1). The necessity of a rapid initial risk stratification is underlined by the observation that 65% of PE-associated deaths occur during the first hour, and 85% of deaths during the first 2.5 hours after admission.[26]

Markers of right ventricular dysfunction

Echocardiography

As already emphasised, high-risk patients with acute PE are identified by clinical assessment during initial evaluation. However, normotensive, "non-high-risk" patients represent a more challenging subgroup since they may also have an elevated risk of death or major complications if they present with RV dysfunction. Echocardiography is capable of detecting the changes occurring in the morphology and function of the right ventricle as a result of acute pressure overload. A number of registries and cohort studies have demonstrated an association between various echocardiographic parameters—i.e. RV dilatation (right ventricle > left ventricle, or RV end-diastolic diameter >30 mm), RV free wall hypokinesia, paradoxical septal wall motion, pulmonary hypertension (gradient between right ventricle and right atrium >30 mm Hg, or pulmonary acceleration time <80 ms)—and a poor in-hospital outcome in terms of PE-related death and complications.[15,25,27-29] Moreover, the *post hoc* analysis of a large international registry suggested that echocardiographically detected RV dysfunction is an independent predictor of adverse outcome in normotensive patients.[30] Nevertheless, the potential prognostic and, particularly, therapeutic implications of cardiac ultrasound findings for the large group of

Table 1. Classification of disease severity in acute pulmonary embolism.

PE-related early mortality risk		Risk Markers: Clinical: shock or hypotension	RV dysfunction (echo, MDCT, natriuretic peptides)	Myocardial injury (troponin, H-FABP elevation)
High (> 15%)		+	(+)	(+)
			+	+
	Intermediate (3-15%)	-	+	+
Non-high			-	+
	Low (< 1%)	-	-	-

Modified from reference 14 and updated according to recent data. H-FABP – heart-type fatty acid binding protein; MDCT – multidetector computed tomography; PE – pulmonary embolism; RV – right ventricle.

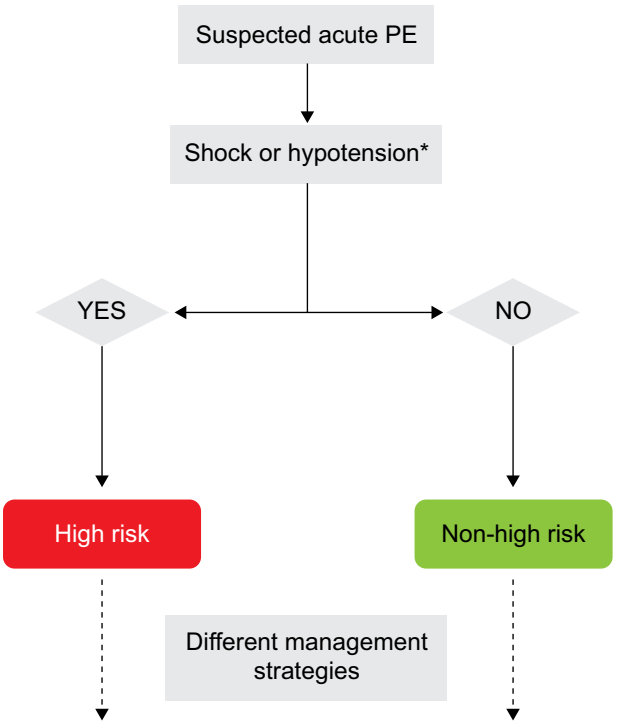

Figure 1. Initial risk stratification of acute pulmonary embolism. Modified from reference 14. *Defined as systolic pressure <90 mm Hg or a pressure drop by >40 mm Hg for ≥15 minutes.

non-high-risk patients with PE remain the subject of debate. The persisting uncertainty is mainly due to the lack of standardisation of the echocardiographic criteria and the absence of adequately powered, controlled studies focusing on normotensive (rather than unselected) patients with PE.[31] Furthermore, the differential diagnosis between acute and chronic pulmonary hypertension and RV dysfunction may be difficult, even though some echocardiographic criteria have been proposed to distinguish between these two entities.[32] Not surprisingly, a recent meta-analysis of five studies including a total of 475 normotensive patients with PE reported that echocardiography had only a moderate overall negative (60%; 95% confidence interval, CI: 55-65%) and positive (58%; 95% CI: 53-63%) predictive value for early death, while also emphasising the limitations due to the clinical and methodological diversity of the pooled publications.[33]

The largest randomised thrombolysis trial in PE to date, which included 256 normotensive patients with right ventricular dysfunction (mainly) detected by echocardiography, reported a significantly reduced incidence of the primary endpoint (30-day mortality or need for treatment escalation) in patients who underwent early thrombolysis as opposed to those treated with heparin alone. However, there was no significant influence of the type of treatment on mortality rates during the acute phase of PE.[34] It is thus likely that additional information (apart from echocardiographic findings) may be needed before the decision can be made to treat aggressively (for example, with thrombolytic agents) a normotensive patient with acute PE. Recent preliminary reports suggest that the prognostic value of echocardiography with regard to risk assessment can be improved if this modality is combined with biomarkers of myocardial injury,[35] or integrated into risk scores that also include clinical parameters and natriuretic peptides (see below).[36]

Computed tomography (CT scan)

Four-chamber views of the heart on the multidetector-row CT, which is currently the preferred method for diagnosing PE in most institutions, may detect RV enlargement due to PE. In a large retrospective series of 431 patients, 30-day mortality was 15.6% in patients with RV enlargement (reconstructed 4-chamber views), defined as right/left ventricular dimension ratio >0.9, on multidetector-row chest CT, compared to 7.7% in those without this finding.[37] Multivariate analysis revealed that RV enlargement independently predicted 30-day mortality (hazard ratio, HR: 5.17; 95% CI: 1.63-16.35). Another retrospective study of 120 patients evaluated the prognostic value of a predefined right/left ventricular short-axis diameter ratio of 1.0 (axial 4-chamber views without post-processing) during 3-month follow up.[38] The negative predictive value of a small right ventricle on helical CT was excellent, reaching 100%, whereas the positive predictive value of an RV/LV ratio of >1.0 was rather low (10.1%) for PE-related mortality and appeared to be inferior to a pulmonary artery obstruction index of 40% or higher. A meta-analysis of two studies (with two different RV/LV diameter thresholds, 1.5 and 1.0), including 191 normotensive patients with PE, reported a 58% (95% CI: 51-65%) overall negative and a 57% positive (95% CI: 49-64%) value of RV dilatation on CT for predicting early death.[33]

Natriuretic peptides

Natriuretic peptides are released as a result of cardiomyocyte stretch and are very sensitive indicators of neurohormonal activation due to ventricular dysfunction. The biologically active C-terminal peptide 77-108 (BNP) and the inactive N-terminal fragment 1-76 (NT-proB-

NP) are detectable in human plasma, and their levels have been determined and evaluated in patients presenting with acute PE.[39-42] In general, both BNP and NT-proBNP are characterised by extreme prognostic sensitivity and a negative prognostic value that is probably even higher than that of the cardiac troponins.[43] On the other hand, they exhibit a very low specificity and positive prognostic value, in the range of 12 to 25%.[43] Furthermore, the appropriate cut-off levels for distinguishing between a "positive" and a "negative" BNP or NT-proBNP test have not yet been prospectively validated.[44] A recent meta-analysis of 13 studies found that 51% of the 1132 patients included had elevated BNP or NT-proBNP levels, and these were associated with an increased risk of early death (odds ratio, OR: 7.6; 95% CI: 3.4-17) and a complicated in-hospital course (OR: 6.8; 95% CI: 4.4-10).[45] However, the relative risk for an adverse outcome could not be adjusted for confounding factors, and the authors concluded that elevation of natriuretic peptides alone does not appear to justify more invasive treatment regimens. Evolving concepts of risk stratification suggest that the prognostic value of natriuretic peptides may be improved if they are combined with echocardiography,[35] or integrated into risk scores that also include clinical parameters and echocardiography.[36]

Markers of myocardial injury

Cardiac troponins

Elevated cardiac troponin I or T levels, a sensitive and specific indicator of myocardial cell damage and microscopic myocardial necrosis, are found in up to 50% of patients with acute PE.[46] Twenty studies published since 1998, with a total of 1985 patients, were included in a meta-analysis that was able to show that cardiac troponin elevation was associated with an increased risk of death (OR: 5.24; 95% CI: 3.28-8.38) and major adverse events (OR: 7.03; 95% CI: 2.42-20.43) in the acute phase.[47] Cardiac troponins appear to possess a high negative predictive value of 97-100%, and it has thus been proposed that normal troponin levels may rule out an adverse outcome in patients with PE.[16] Recently, however, it was suggested that a (negative) troponin test may not be necessary to confirm the favourable prognosis in normotensive patients with PE, if they have already been classified into a low risk category based on clinical scores, particularly the Pulmonary Embolism Severity Index (PESI).[48] At the other end of the severity spectrum, the positive predictive value of cardiac troponin I or T elevation has been consistently low in cohort studies, so that troponin elevation does not necessarily indicate a poor prognosis.[43] Moreover, a recent meta-analysis which focused only on normotensive patients (a total of 1366 patients included in 9 studies) was unable to confirm the prognostic value of cardiac troponins in non-high-risk PE.[49] Thus, based on the available data, the current opinion is that troponin elevation *alone* does not suffice to risk stratify normotensive patients with PE, and particularly to identify intermediate-risk patients who might require early aggressive (for example, thrombolytic) treatment. A large ongoing randomised trial is currently investigating whether normotensive patients with right ventricular dysfunction, detected by echocardiography or CT, *plus* evidence of myocardial injury indicated by a positive troponin test, may benefit from early thrombolytic treatment.[50]

Other biomarkers

Fatty acid-binding proteins (FABPs) are small cytoplasmic proteins that are abundant in tissues with active fatty acid metabolism, including the heart.[51] Heart-type FABP (H-FABP) is particularly important for myocardial homeostasis, since 50-80% of the heart's energy is provided by lipid oxidation, and H-FABP ensures the intracellular transport of insoluble fatty acids. Following myocardial cell damage, this small protein diffuses much more rapidly than troponins through the interstitial space and appears in the circulation as early as 90 minutes after symptom onset, reaching its peak within 6 hours.[52] These features make H-FABP an excellent candidate marker of myocardial injury,[53] and preliminary data suggest that it may provide prognostic information superior to that of cardiac troponins in acute PE.[54,55] These data were recently confirmed by a study focussing on non-high-risk patients with acute PE.[56]

Growth-differentiation factor-15 (GDF-15), a distant member of the transforming growth factor-β cytokine family, is an emerging biomarker for patients with cardiovascular disease. Cardiac expression of GDF-15 sharply increases after pressure overload or myocardial ischaemia,[57,58] and thus GDF-15 might be capable of integrating information about both RV dysfunction and myocardial injury in patients with acute PE. In a cohort study of 123 consecutive patients with confirmed PE, elevated levels of GDF-15 on admission were strongly and independently related with an increased risk of death or major complications during the first 30 days after diagnosis. More-

over, the prognostic information provided by GDF-15 appeared to be additive to that of cardiac troponins and natriuretic peptides, and to echocardiographic findings of RV dysfunction. GDF-15 also emerged as an independent predictor of long-term mortality.[59]

Integrated clinical scores

Several clinical and laboratory variables may be of value in PE management, since they appear to have prognostic significance. Many of them are related to the pre-existing condition and comorbidities of the individual patient, rather than to the severity of the PE episode itself. For example, in a large international registry, age >70 years, cancer, congestive heart failure, and chronic obstructive pulmonary disease were identified as prognostic factors.[60] More recently, the Pulmonary Embolism Severity Index or PESI (Table 2) was proposed and successfully validated in large populations of patients with PE.[61,62] The index appears capable of reliably identifying patients with very low rates of adverse events, and it was reported to be superior to the Geneva prediction rule in this regard.[63] On the other hand, it remains uncertain, as will be explained below, whether a low PESI (corresponding to risk classes I or II; Table 2) is by itself sufficient to permit early discharge and home treatment of low-risk patients with acute PE.

Treatment of acute PE

Initial anticoagulation

Anticoagulant treatment (Table 3) should be administered to all patients upon clinical suspicion of acute PE, i.e. without awaiting definitive confirmation by imaging procedures. Intravenous unfractionated heparin is the preferred mode of initial anticoagulation: 1) for patients with severe renal impairment (creatinine clearance <30 ml/min); 2) for patients at high risk of bleeding; 3) for high-risk, hypotensive patients; and, as a rule, 4) for extremely overweight, underweight, or old patients. A weight-adjusted bolus injection of 80 U/kg is followed by an infusion rate of 18 U/kg per hour. Subsequent infusion rates are adjusted using activated partial thromboplastin time (aPTT)-based nomograms in order to achieve and maintain therapeutic aPTT prolongation.[65] The aPTT should be measured 4 to 6 hours after the bolus injection, and subsequently 3 hours after each dose adjustment, or once daily when the target dose has been reached.

With the exception of the above circumstances, unfractionated heparin has largely been replaced by low molecular-weight heparin (LMWH), given subcutaneously in weight-adjusted doses. A meta-analysis of 12 trials confirmed that LMWH is at least as efficacious and at least as safe as unfractionated heparin.[66] Tinzaparin, at the dose of 175 U/kg once daily, is explicitly approved for acute PE, while enoxaparin, 1 mg/kg every 12 h, is approved for deep vein thrombosis with or without PE (the regimen of 1.5 mg/kg once daily is also approved in some countries). The pentasaccharide fondaparinux can be given, 5 mg (for body weight <50 kg), 7.5 mg (body weight 50-100 kg), or 10 mg (body weight >100 kg) once daily. Routine anticoagulation monitoring, i.e. 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

Table 2. The Pulmonary Embolism Severity Index.

Variable	Points
Age	1/year
Male sex	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 mm Hg	30
Respiratory rate ≥30 breaths/min	20
Body temperature <36˚C	20
Altered mental status (disorientation, confusion, somnolence)	60
Arterial oxyhaemoglobin saturation <90%	20

Adapted from reference 64, the Index is based on routinely collected clinical parameters at presentation. Risk categories (30-days all-cause mortality %): Class I, <65 points (0%); class II, 66-85 points (1%); class III, 86-105 points (3.1%); class IV, 106-125 points (10.4%); and class V, >125 points (24.4%). Patients in risk classes I and II are defined as low-risk.

Table 3. Initial anticoagulation for acute pulmonary embolism.

	Dosage	Interval	Remarks
Unfractionated heparin (intravenous infusion)	80 IU per kilogram of body weight as an intravenous bolus, followed by infusion at the rate of 18 IU/Kg/h	Continuous infusion	1) Adjust infusion rate to maintain aPTT between 1.5 and 2.5 times control, corresponding to therapeutic heparin levels (0.3 to 0.7 IU per millilitre by factor Xa inhibition). 2) Monitor platelet count at baseline and every other day from day 4 to 14 or until heparin is stopped. Investigate for HIT if platelet count falls by ≥50 percent and/or a thrombotic event occurs.
Low molecular-weight heparins (subcutaneous injection)			1) LMWH not tested and thus not recommended for patients with arterial hypotension or shock. 2) Monitoring of anti-factor Xa levels may be helpful in patients at increased risk of bleeding, particularly those with moderate or severe renal impairment. The need for monitoring anti-Xa levels in pregnancy remains controversial. 3) Monitor platelet count at baseline and every 2 to 4 days from day 4 to 14 or until heparin is stopped.*
Enoxaparin	1.0 mg/kg or 1.5 mg/kg	every 12 h once daily	If creatinine clearance <30 mL/min, reduce enoxaparin dosage to 1 mg/kg once daily; consider unfractionated heparin infusion as an alternative.[10]
Tinzaparin	175 U/kg	once daily	
Fondaparinux	5 mg (body weight <50 kg); 7.5 mg (body weight 50-100 kg); 10 mg (body weight >100 kg)	once daily	1) Contraindicated if creatinine clearance <20 mL/min. 2) No routine platelet monitoring.[26]

Adapted from reference 23 with permission. aPTT – partial thromboplastin time; HIT – heparin-induced thrombocytopenia; LMWH – low-molecular-weight heparins.
*This recommendation applies to postoperative patients and to medical or obstetric patients recently (within 100 days) exposed to unfractionated heparin.[67,68] For medical or obstetric patients who have only received low-molecular-weight heparin, some authorities recommend no routine platelet count monitoring.[68]

hours after the morning injection; the proposed target range is 0.6 to 1.0 IU/ml for twice-daily and 1.0 to 2.0 IU/ml once-daily administration.

The risk of heparin-induced thrombocytopenia, a potentially fatal complication (mortality rate, 8 to 20%) of heparin treatment, depends on both the type of heparin used and the clinical setting.[23,67] The incidence is highest (3-5%) in patients who have undergone orthopaedic surgery and those who have received unfractionated heparin. On the other hand, in medical and surgical patients receiving LMWH the incidence is below 1%. For patients receiving fondaparinux, the risk is negligible. The current recommendations for platelet count monitoring under heparin treatment are summarised in Table 3, which also displays the anticoagulation regimens currently in use.[23,68] Upon clinical suspicion of heparin-induced thrombocytopenia, all sources of heparin should be discontinued and therapy with direct parenteral thrombin inhibitors, particularly argatroban or lepirudin, initiated; bivalirudin is approved for patients undergoing percutaneous coronary interventions.

Anticoagulation with unfractionated heparin or LMWH should be continued for at least 5 days. Oral anticoagulants (vitamin K antagonists) 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 international normalised ratio (INR) has been in the therapeutic range (between 2.0 and 3.0) on 2 consecutive days.

Thrombolysis

Randomised trials performed over a 30-year period[69] have consistently shown that thrombolytic therapy for PE effectively resolves thromboembolic obstruction and promptly reduces pulmonary artery pressure and

resistance with a concomitant increase in cardiac output. One of the largest trials also demonstrated a significant improvement in right ventricular function as assessed by echocardiography, three hours after treatment with recombinant tissue plasminogen activator.[29] In the only randomised thrombolysis trial with clinical endpoints, early thrombolytic treatment given to normotensive patients with evidence of RV dysfunction significantly reduced the need for emergency escalation of therapy during the hospital stay.[34]

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.[70] 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 to 14 days.[71] On the other hand, the haemodynamic benefits of thrombolysis over heparin alone appear to be confined to the first few days. In patients who are alive one week after treatment, the improvement in the severity of vascular obstruction and RV dysfunction appears to be similar in thrombolysis-treated and heparin-treated patients.[72] Moreover, thrombolysis also carries a significant bleeding risk. According to the data derived from thrombolysis trials in acute PE, a cumulative rate of major bleeding of up to 13% and a rate of intracranial and/or fatal haemorrhage reaching 2% should be anticipated,[73,74] although the risk of major or life-threatening bleeding may be lower if non-invasive imaging methods are used in the diagnostic workup of PE.[29,34] Taken together, these data underline that thrombolysis should be reserved for patients in whom a high risk of *early* PE-related death is anticipated.

Currently approved thrombolytic regimens for PE include:

1. streptokinase, 250,000 IU as a loading dose over 30 min, followed by an infusion of 100,000 IU/h over 12-24 hours;
2. urokinase, 4400 IU/kg as a loading dose over 10 minutes, followed by 4400 IU/kg/h over 12-24 hours; and
3. alteplase (recombinant tissue plasminogen activator), 100 mg infusion over 2 hours, with the first 10 mg usually given as a bolus injection.

A short (over 15 minutes) infusion regimen of alteplase at the dosage of 0.6 mg/kg (maximum dosage, 50 mg) can be used in emergency situations, e.g. during cardiopulmonary resuscitation. Satisfactory haemodynamic results have also been obtained with double-bolus reteplase, 2 injections (10 U) 30 minutes apart.[75] Furthermore, the results of a recent multicentre controlled trial appear to support the efficacy and safety of bolus tenecteplase in acute PE.[76] However, neither reteplase nor tenecteplase are officially approved for treatment of PE at present.

Surgical or catheter-based embolectomy

Pulmonary embolectomy remained a rarely performed rescue operation over several decades, and there were only limited data regarding its efficacy and safety. Recent technical advances in transportable extracorporeal assist systems, and particularly the timely involvement of the cardiac surgeon as part of an interdisciplinary approach to high-risk PE, may contribute to better postoperative outcomes.[77] Currently, pulmonary embolectomy is a recommended therapeutic option in patients with high-risk PE for whom there are absolute contraindications to thrombolysis, or if thrombolysis has failed. Alternatively, catheter embolectomy or thrombus fragmentation may be considered, provided that there is adequate experience with these modalities on site.

Inferior vena cava filters

Cava filters may be used as a means of primary or secondary PE prevention. However, the data about their relative safety and efficacy remain inconclusive. Comparison with therapeutic anticoagulation has to take into account the fact that the latter treatment is very effective in preventing recurrent thromboembolism in patients treated for symptomatic PE. For example, recurrence rates under effective anticoagulation are in the range of 3%, even in the presence of free-floating thrombi in the proximal leg veins,[78] and fatal PE occurs in 0.4-1.5% of patients during treatment with heparin or warfarin.[79] In one study, inferior *vena cava* filter placement increased the risk of recurrent leg vein thrombosis over the long term.[80] At present, temporary inferior *vena cava* filters have a role in the prevention of PE only if anticoagulation is absolutely contraindicated, or in cases of recurrence in spite of adequate medical treatment.

Integrated, risk-adjusted management strategy

High-risk PE (Figure 2)

In view of the high early mortality and complication risk associated with high-risk PE,[5,24,26] existing guide-

lines[14,81] and the vast majority of clinicians agree that patients who present with persistent arterial hypotension or shock are in need of immediate pharmacological (e.g. thrombolysis) or mechanical (surgical or catheter-based) recanalisation of the occluded pulmonary arteries. The decision to implement such an aggressive treatment with potential life-threatening complications is usually made on the basis of emergency CT pulmonary angiography. However, CT angiography may not be readily available or feasible in a highly unstable patient. Under such circumstances, bedside echocardiography is an acceptable alternative.[14] Although echocardiography generally does not provide direct diagnosis or definite exclusion of PE in unselected patients,[82] in the unstable patient population it can confirm or exclude severe RV pressure overload and dysfunction. Thus, bedside echocardiographic examination may suffice for the initial management decision in critically ill patients. If the patient can be stabilised, CT pulmonary angiography should be reconsidered. If only bedside tests are feasible, venous ultrasound[83] and/or transoesophageal echocardiography[84] may be useful to identify venous or pulmonary artery clots, thus confirming the diagnosis of venous thromboembolic disease and assisting in otherwise difficult management decisions. Also, if a floating thrombus-in-transit from the venous system is detected in a right heart chamber by transthoracic echocardiography, immediate treatment is needed instead of further diagnostic testing.[85]

Pooled data from 5 trials that included haemodynamically unstable patients suggested a significant reduction of death or PE recurrence after thrombolysis in this group.[69] Thus, haemodynamically unstable patients with suspected high-risk PE should immediately receive a weight-adjusted bolus of unfractionated heparin 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 thrombus fragmentation or suction is a valuable alternative.

Non-high-risk PE (Figure 3)

Several diagnostic tests are useful for making therapeutic decisions in normotensive patients with clini-

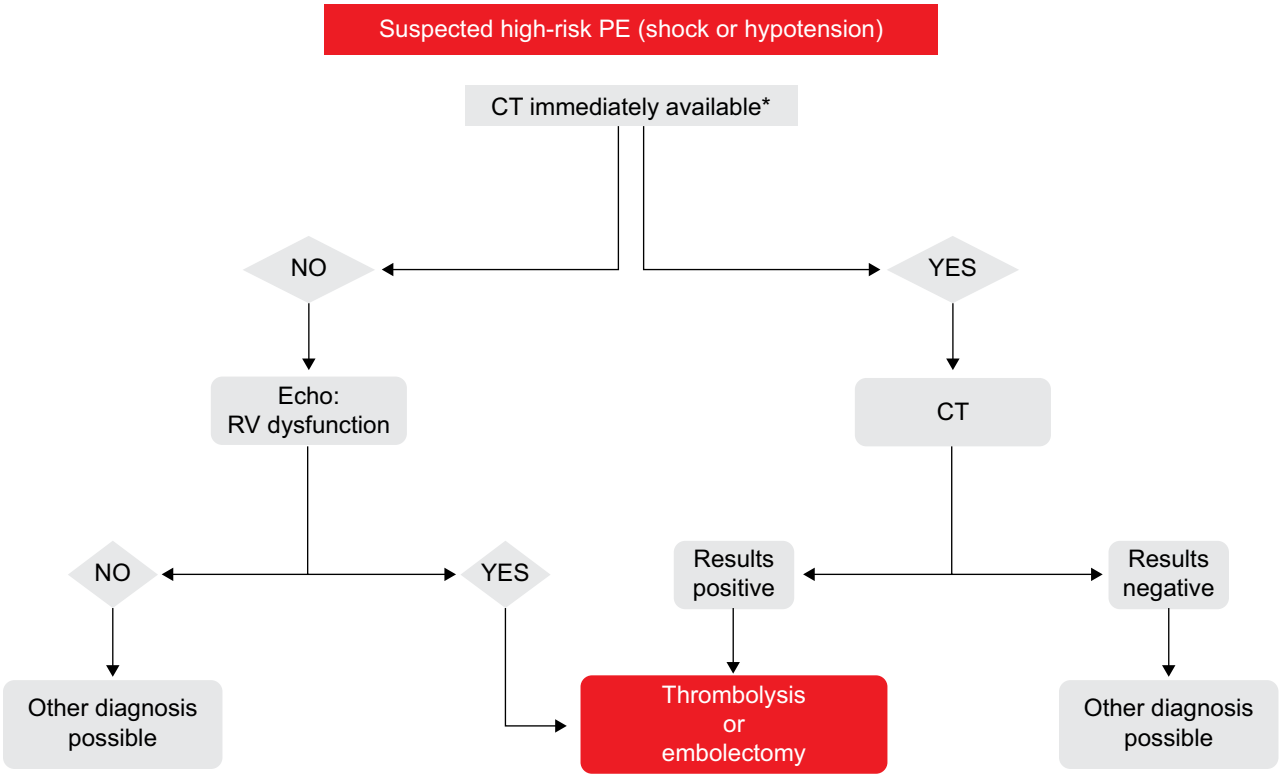

Figure 2. Diagnostic workup of suspected high-risk pulmonary embolism (PE) patients. Modified from reference 14. *If computed tomography or pulmonary angiography is available on site and the patient's haemodynamic status allows this diagnostic test. CT-computed tomography; RV-right ventricle.

cal suspicion of PE. Interpretation of imaging studies (V/Q scan, CT angiography) requires previous assessment of the clinical (pre-test) probability of PE.[86-88] Such assessment should account for predisposing factors (particularly recent surgery, fracture, malignancy, advanced age, previous venous thromboembolic disease) as well as symptoms and signs suggestive of PE (particularly dyspnoea of recent onset, chest pain, haemoptysis, tachycardia, unilateral leg pain or oedema). While implicit assessment is acceptable, validated prediction rules such as the Wells and Geneva score may help to standardise probability assessment.[89-93] Thus, in normotensive (non-high-risk) patients with a low or intermediate clinical probability (non-high probability) of PE, the diagnostic assessment may be limited to a D-dimer test. If negative, a highly sensitive test justifies withholding anticoagulation.[27,28] If positive, CT pulmonary angiography should be performed as the next step to confirm or reject the diagnosis and further treatment should then be initiated (see below) or withheld, respectively. On the other hand, in normotensive patients with a high clinical probability, the clinician should proceed directly to CT pulmonary angiography. At present, it remains unclear whether patients with a high clinical probability of PE and negative CT angiography may require additional testing to safely withhold anticoagulation.[94,95] Strategies based on ventilation-perfusion lung scintigraphy are still useful for exclusion or confirmation of PE in some institutions and particularly in specific clinical situations such as pregnancy, renal dysfunction or allergy to contrast media.[14,96]

At present, LMWH or fondaparinux is considered adequate treatment for most normotensive patients with pulmonary embolism. Routine thrombolysis is generally not recommended as a first-line therapeutic option, irrespective of the echocardiographic (or CT) findings or the biomarker levels. However, based on the results of the largest randomised thrombolysis trial to date,[34] early thrombolysis may be considered in selected intermediate-risk patients (i.e. those with evidence of RV dysfunction or myocardial injury), if they have a high risk of death (due, for example, to pre-existing heart or respiratory failure) and an absence of contraindications for thrombolytic agents. A large multinational randomised trial has set out to de-

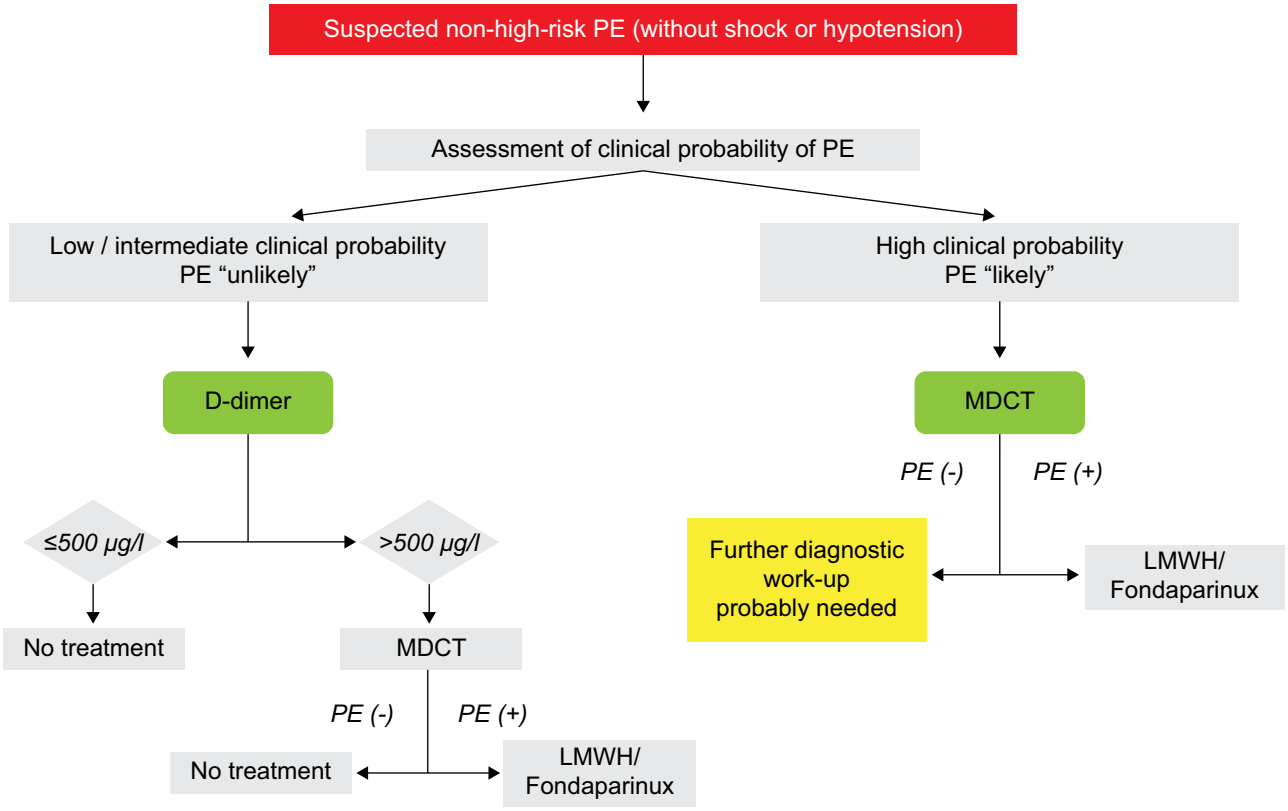

Figure 3. Diagnostic workup of suspected non-high-risk pulmonary embolism (PE). Modified from reference 14. LMWH - low molecular weight heparin; MDCT - multidetector computed tomography

termine whether normotensive, intermediate-risk patients with right ventricular dysfunction, detected by echocardiography or CT, *plus* evidence of myocardial injury indicated by a positive troponin test, may benefit from early thrombolytic treatment (EudraCT number, 2006-005328-18). The primary efficacy endpoint is a clinical composite endpoint of all-cause mortality or haemodynamic collapse within the first 7 days. Safety endpoints are total strokes (intracranial haemorrhage or ischaemic stroke) within 7 days, and major bleeds (other than intracranial haemorrhage) within 7 days. A six-month follow up is also being conducted. This study, which is already underway in 10 European countries, plans to enrol a total of 1000 patients and will be completed in 2011.

It has been proposed that selected patients with low-risk PE (i.e. normotensive patients with neither RV dysfunction nor myocardial injury) can be discharged early and treated as outpatients.[97] In particular, the Pulmonary Embolism Severity Index appears to reliably identify patients with very low rates of adverse events.[63] However, excessive optimism is not warranted at present, since a randomised study of home treatment versus hospitalisation of low-risk patients with PE was recently discontinued because of high mortality in the early discharge group.[98] Indeed, current evidence suggests that only a very small proportion (less than 10%) of patients with PE may be eligible for home treatment,[99] and this management option cannot be recommended at present until further data become available regarding its safety and practicability.

PE recurrence and long-term secondary prophylaxis

Pulmonary embolism, and particularly unprovoked PE, is considered a lifelong disease; thus chronic secondary prophylaxis is necessary. Without continuing anticoagulation, as many as 50% of patients with symptomatic proximal deep vein thrombosis or PE may suffer a recurrent episode within the first 3 months.[100] The frequency of recurrence appears to be independent of the initial clinical manifestation of venous thromboembolism, but recurrent venous thromboembolism is three times more likely to present as PE if the initial clinical event was PE than if it was deep vein thrombosis.[101] This fact emphasises the need for effective secondary prophylaxis in patients who have suffered PE. To date, most of the studies addressing recurrence prophylaxis for venous thromboembolism have included patients with deep vein thrombosis, rather than focusing on PE alone. The available data indicate that the long-term recurrence rate may be 30% or even higher after 8-10 years,[102-104] and it was found that indefinite treatment might be capable of reducing the risk of recurrent thromboembolism by up to 90%.[105] Thus, oral anticoagulants (vitamin K antagonists) are highly effective in preventing recurrent thromboembolism, but they do not eliminate the risk of subsequent recurrence after their discontinuation, regardless of the duration of treatment.[106,107] On the other hand, the benefits of chronic oral anticoagulation are partly offset by the increased risk of major bleeding.[105,108]

In view of these considerations, the recommended duration of oral anticoagulation after an episode of acute PE weighs the risk versus the benefits of vitamin K antagonists.[14,81] As a rule, treatment with vitamin K antagonists should be continued for 3 months after a first episode of PE triggered by a transient risk factor (trauma, surgery, immobilisation, pregnancy, contraceptive use or hormonal replacement therapy), and for *at least 3 months* for patients with unprovoked PE. Indefinite oral anticoagulation should be considered and discussed on an individual basis for patients with a first manifestation of unprovoked PE and a low risk of bleeding, and it is clearly recommended for most patients with a second unprovoked episode of venous thromboembolism. Patients with high-risk thrombophilia or active cancer are also candidates for long-term oral anticoagulation. On the other hand, it is at present unclear whether, and to what extent, the severity of the initial event and possibly other clinical and haemodynamic factors, such as persistent pulmonary hypertension on echocardiography, may determine recurrence-related fatality rates and affect long-term therapeutic decisions. It also remains to be confirmed whether D-dimer testing one month after discontinuation of vitamin K antagonists may be used to resume or definitely terminate therapy in patients who have received oral anticoagulants for 3 months after the first episode of idiopathic vein thrombosis or pulmonary embolism.[109]

Novel, vitamin K-independent, oral anticoagulants are currently under investigation for both prophylaxis and treatment of venous thromboembolism. In particular, the selective oral thrombin inhibitor dabigatran and the oral factor Xa inhibitor rivaroxaban have yielded promising data in phase III clinical trials and have obtained approval in Europe for postoperative (primary) prophylaxis of venous thromboembolism following elective orthopaedic surgery (hip or knee replace-

ment). Very recently, dabigatran, at a dose of 150 mg twice daily, was tested against warfarin, at an INR-adjusted dose, for the treatment of patients who had suffered venous thromboembolism and had received parenteral anticoagulation for a median of 9 days. The primary outcome was the 6-month incidence of symptomatic recurrence of venous thromboembolism and related deaths. The efficacy and safety of dabigatran was similar to that of warfarin.[110] If eventually approved for the treatment and long-term secondary prophylaxis of venous thromboembolism, the new oral anticoagulants may simplify chronic anticoagulation and increase patient compliance.

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