Acute phase treatment of venous thromboembolism: advanced therapy
Systemic fibrinolysis and pharmacomechanical therapy

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Summary
Venous thromboembolism, which encompasses deep-vein thrombosis and acute pulmonary embolism (PE), represents a major contributor to global disease burden worldwide. For patients who present with cardiogenic shock or persistent hypotension (acute high-risk PE), there is consensus that immediate reperfusion treatment applying systemic fibrinolysis or, in the case of a high bleeding risk, surgical or catheter-directed techniques, is indicated. On the other hand, for the large, heterogeneous group of patients presenting without overt haemodynamic instability, the indications for advanced therapy are less clear. The recently updated guidelines of the European Society of Cardiology emphasise the importance of clinical prediction rules in combination with imaging procedures (assessment of right ventricular function) and laboratory biomarkers (indicative of myocardial stress or injury) for distinguishing between an intermediate and a low risk for an adverse early outcome. In intermediate-high-risk PE defined by the presence of both right ventricular dysfunction on echocardiography (or computed tomography) and a positive troponin (or natriuretic peptide) test, the bleeding risks of full-dose fibrinolytic treatment have been shown to outweigh its potential clinical benefits unless clinical signs of haemodynamic decompensation appear (rescue fibrinolysis). Recently published trials suggest that catheter-directed, ultrasound-assisted, low-dose local fibrinolysis may provide an effective and particularly safe treatment option for some of these patients.

Keywords
Pulmonary embolism, risk-adjusted treatment, fibrinolysis, catheter-directed treatment, pharmacomechanical therapy

Introduction
Venous thromboembolism, which encompasses deep-vein thrombosis, acute pulmonary embolism (PE), is the third most frequent cardiovascular disease and an important contributor to global disease burden. Studies from Western Europe, North America, Australia, and Southern Latin America (Argentina) have yielded consistent results with annual incidences ranging between 75 and 269 cases per 100,000 individuals in the population; among individuals 70 years of age or more, the reported incidence was as high as 700 per 100,000 (1).

Acute PE is a major cause of mortality, morbidity, and hospitalisation: according to an epidemiological model, over 370,000 deaths were related to PE in six countries of the European Union (with a total population of 454.4 million) in 2004. Of these cases, 34% presented with sudden fatal PE and 59% were deaths resulting from PE that remained undiagnosed during life (2). However, not all PE cases are life-threatening; in fact, PE has been shown to cover a wide spectrum of clinical severity and death risk, with early (30-day or in-hospital) mortality rates ranging between less than 1% and well above 50% (3–9). This review discusses recent advances in our understanding of the determinants of outcome, and the progress in risk stratification and risk-adapted management of acute PE. We review the scientific background supporting the recommendations of the updated (2014) European Society of Cardiology (ESC) Guidelines on the Management of Pulmonary Embolism, focusing on the risk-benefit ratio and current indications for advanced reperfusion treatment, notably fibrinolysis and percutaneous catheter-directed pharmacomechanical approaches.

Risk stratification and contemporary management algorithms
The principal pathophysiological factor which determines disease severity, and consequently the patient’s clinical course and risk of death over the short term, is the presence or absence of right ventricular (RV) dysfunction and failure resulting from acute pressure overload (10). As recently reviewed (11), pulmonary artery pressure begins to increase when thromboemboli occlude approximately 30–50% of the total cross-sectional area of the pulmonary
arterial bed. PE-induced vasoconstriction, mediated by thromboxane A2 and serotonin, contributes to the initial increase in pulmonary vascular resistance after PE. The acute increase in afterload results in RV dilation via the Frank-Starling mechanism. In parallel, the combination of neurohumoral activation (inotropic and chronotropic stimulation of the heart) and systemic vasoconstriction increase pulmonary artery pressure, temporarily improving flow through the obstructed pulmonary vasculature. However, the extent of adaptation of a non-preconditioned, thin-walled right ventricle (RV) is limited, and persisting pressure overload eventually results in a spiral of increased myocardial oxygen demand, ischemia, leftward septal displacement and left ventricular preload reduction, which ultimately lead to cardiogenic shock and death (11).

The clinical classification of the severity of an episode of acute PE begins with the estimated PE-related early mortality risk. Based on the pathophysiological considerations summarised above, high-risk PE is diagnosed (or suspected) in a patient presenting with shock or persistent arterial hypotension as a result of acute RV pressure overload and overt RV failure. This type of clinical presentation is infrequent, however, as the vast majority (over 95%) of patients with acute PE are not at high risk, i.e. appear haemodynamically stable at presentation. A substantial body of evidence suggests that advanced risk stratification should be considered in this latter group, in order to distinguish between intermediate and low clinical risk and adapt monitoring needs as well as reperfusion and anticoagulation management accordingly. Consequently, the next step after diagnosing PE in a normotensive patient should consist of further risk assessment based on clinical findings at diagnosis and the presence of significant comorbidity. Of the prognostic tools currently available, the Pulmonary Embolism Severity Index (PESI) is the most extensively validated clinical prediction rule to date (Table 1) (12). Of note, the principal strength of the PESI lies in the reliable exclusion of an elevated risk for 30-day mortality (indicated by PESI classes I and II); these patients will not need advanced therapy and may be candidates for early discharge and home treatment (13). The simplified version of the PESI (sPESI) (14, 15) also possesses a high prognostic value for ruling out an adverse early outcome (16).

If, on the other hand, the PESI is elevated (or the sPESI ≥1), suggesting intermediate-risk PE, assessment of RV (dys)function and myocardial injury should be considered as the third step of risk assessment. Echocardiographic findings indicating RV dysfunction have been reported in at least 25% of patients with PE (17). Despite its limitations, echocardiographic assessment of the morphology and function of the RV remains a valuable bedside tool in the advanced prognostic stratification of not-high-risk patients with acute PE. Frequently used parameters include RV dilatation, an increased right-to-left ventricular diameter ratio (with the cutoff value usually set at 0.9 or 1.0), hypokinesia of the free RV wall, increased velocity of the jet of tricuspid regurgitation, decreased tricuspid annulus plane systolic excursion, or various

Table 1: Original and simplified Pulmonary Embolism Severity Index (PESI).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Original version (12)</th>
<th>Simplified version (14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Age in years</td>
<td>1 point (if age &gt; 80 years)</td>
</tr>
<tr>
<td>Male sex</td>
<td>+10 points</td>
<td>–</td>
</tr>
<tr>
<td>Cancer</td>
<td>+30 points</td>
<td>1 point</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>+10 points</td>
<td>1 point</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>+10 points</td>
<td></td>
</tr>
<tr>
<td>Pulse rate ≥110 b. p. m.</td>
<td>+20 points</td>
<td>1 point</td>
</tr>
<tr>
<td>Systolic BP &lt; 100 mm Hg</td>
<td>+30 points</td>
<td>1 point</td>
</tr>
<tr>
<td>Respiratory rate &gt; 30 breaths/min</td>
<td>+20 points</td>
<td>–</td>
</tr>
<tr>
<td>Temperature &lt; 36 °C</td>
<td>+20 points</td>
<td>–</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>+60 points</td>
<td>–</td>
</tr>
<tr>
<td>Arterial oxyhaemoglobin saturation &lt; 90 %</td>
<td>+20 points</td>
<td>1 point</td>
</tr>
</tbody>
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Risk strata*

- Class I: ≤65 points – very low 30-day mortality risk (0 to 1.6%)
- Class II: 66–85 points - low mortality risk (1.7 to 3.5%)
- Class III: 86–105 points – moderate mortality risk (3.2 to 7.1%)
- Class IV: 106–125 points – high mortality risk (4.0 to 11.4%)
- Class V: > 125 points – very high mortality risk (10.0 to 24.5%)

0 points – 30-day mortality risk 1.0% (95% CI 0.0–2.1%)

≥1 point(s) – 30-day mortality risk 10.9% (95% CI 8.5–13.2%)

b. p. m. = beats per minute. *based on the sum of points.
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combinations of the above (18, 19). Four-chamber views of the heart on computed tomographic (CT) angiography may also detect RV enlargement as an indicator of RV dysfunction. A recent meta-analysis of 36 studies, eight of which were prospective, confirmed the high negative predictive value of the absence of RV enlargement on CT angiography, which reached 99% with regard to PE-related mortality at 30 days (20). The majority of the included studies used a right-to-left ventricular dimensional ratio of either 0.9 or 1.0 as the cutoff point; these values were also among the inclusion criteria of recently published fibrinolysis trials (21–23).

Elevated plasma troponin I or T concentrations, which indicate myocardial injury and necrosis, have been associated with worse prognosis in acute PE. Cohort studies have shown that the negative predictive value of this biomarker is high and possibly independent from the assay or cut-off values used (24). Moreover, cardiac troponins are the only biomarkers prospectively evaluated as part of a risk-adapted management strategy for patients with acute PE: In a large randomised controlled trial, normotensive PE patients who had a positive troponin test in combination with evidence of RV dysfunction on echocardiography or CT angiography were found to be at “intermediate-high” (almost 6%) risk of death or haemodynamic decompensation during the first five days (22). These findings support the need for early monitoring and, in some cases, rescue fibrinolytic treatment of these patients.

RV pressure overload is associated with increased myocardial stretch, which leads to the release of brain natriuretic peptide (BNP) or N-terminal (NT)-proBNP. In a prospective multicentre cohort study that included 688 patients, NT-proBNP plasma concentrations of 600 pg/ml were identified as the optimal cut-off value for the prediction of elevated risk (25). Heart-type fatty acid-binding protein (H-FABP), an early marker of myocardial injury, also was reported to predict an adverse early outcome in acute PE (26, 27).

Various combinations of clinical findings, imaging modalities and laboratory biomarkers have been developed and tested in cohort studies in an attempt to optimise risk stratification and risk-adapted management of PE (26, 28–30). The evidence generated from these and further observational studies, and from a randomised controlled clinical trial (to be discussed in the following section) (22), provided the basis for an integrated management algorithm as proposed in the 2014 ESC Guidelines (Figure 1) (11).

**Systemic fibrinolysis – current regimens and uncontested indications**

In 1971, Miller et al. reported that streptokinase infusion over 72 hours (h) resulted in a significant reduction of systolic pulmonary artery pressure, total pulmonary resistance, and the angiographic index of PE severity (31). Subsequently, randomised trials (23, 32–41) confirmed that fibrinolytic therapy rapidly resolves thromboembolic obstruction and exerts beneficial effects on haemodynamic indicators of cardiac function. Registry data suggest that at least 90% of patients can be expected to respond favourably to

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**Figure 1:** Risk-adjusted management strategy in acute PE (adapted from [11]). A/C = anticoagulation; CT = computed tomographic pulmonary angiography; PE = pulmonary embolus; PESI = Pulmonary Embolism Severity Index; RV = right ventricular; sPESI = Simplified Pulmonary Embolism Severity Index.
fibrinolysis as indicated by clinical and echocardiographic improvement within 36 h (42). The greatest benefit is observed when treatment is initiated within 48 h of symptom onset, but fibrinolysis can still be useful in patients who have had symptoms for up to 14 days (43).

Tested and approved regimens of fibrinolytic agents for PE as well as the contraindications to fibrinolysis have been reviewed previously (11, 44) and are summarised in Table 2. To reduce the risk of bleeding complications, anticoagulation using unfractionated heparin infusion should be stopped during administration of streptokinase or urokinase, while it can be continued during recombinant tissue-type plasminogen activator (rtPA) infusion. Low-molecular-weight heparins (LMWH) have been administered in combination with fibrinolysis in recent randomised trials (22, 45), but they are not officially approved for use in this context in acute PE. In patients receiving LMWH or fondaparinux at the time that fibrinolysis is initiated, it is recommended to delay the infusion of unfractionated heparin until 12 h after the last LMWH injection (if given twice daily), or until 24 h after the last LMWH or fondaparinux injection (if given once daily). Furthermore, in view of the bleeding risk associated with fibrinolysis and the possibility that it may become necessary to immediately discontinue or reverse the anticoagulant effect of heparin, it appears reasonable to continue anticoagulation with unfractionated heparin for several hours after the end of fibrinolytic treatment before switching to LMWH or fondaparinux (11).

At present, the majority of experts (11, 46, 47) agree that systemic fibrinolysis is indicated in patients who present with high-risk PE, i.e. persistent arterial hypotension or shock. Pooled data from five trials which included haemodynamically unstable patients suggested a reduction of death or PE recurrence after fibrinolysis in this group (48). A recent meta-analysis of 15 trials which enrolled 2,057 patients (4 of these trials had included patients with high-risk PE) also found that fibrinolytic therapy was associated with a significant reduction of overall mortality (odds ratio [OR] 0.59, 95 % confidence intervals [CI] 0.36–0.96) and, particularly, PE-related death (OR 0.29, 95 % CI 0.14–0.60) (49). When translating these favourable data into clinical practice, it should be kept in mind that, in the early trials, patients had received fibrinolytic agents (for example, urokinase) and regimens which are no longer used in many countries, while the drugs used in some of the more recent trials (such as tenecteplase) are not (yet) approved for use in PE. On the other hand, the benefits of fibrinolysis are also supported by a large epidemiological study in the United States which reported that in-hospital mortality attributable to PE was lower in unstable patients who received fibrinolytic therapy compared with those who did not (relative risk [RR] 0.20, 95 % CI 0.19–0.22, p<0.0001) (50).

Uncontrolled data suggest that fibrinolysis might be a safe and effective alternative to surgery in patients with PE and free-floating thrombi in the right heart (51, 52).

Weighing the benefits against the risks of systemic fibrinolysis in not-high-risk PE – the end of a 40-year-old debate

In contrast to the consensus regarding the need for fibrinolysis in high-risk PE, the possible clinical benefits of this treatment modality in haemodynamically stable patients (not-high-risk PE) have
remained controversial for decades. When the haemodynamic benefits of fibrinolysis in acute PE are weighed against the risk of haemorrhagic complications, it needs to be taken into account that only patients with a ‘truly elevated’ risk of death or haemodynamic collapse during the first few (7 or less) days after diagnosis may be expected to have a net benefit. This is due to the observation that RV function ultimately also recovers in PE survivors who have been treated with heparin alone (23, 53). At the same time, fibrinolytic treatment carries a significant risk of major bleeding including intracranial haemorrhage. Pooled data from controlled fibrinolysis trials which either compared fibrinolysis to heparin alone or different fibrinolytic regimens with each other in patients with PE (32, 36, 38, 54–61), revealed a 13% cumulative rate of major bleeding and a 1.8% rate of intracranial/fatal haemorrhage (62). These rates were recently confirmed by the largest randomised fibrinolysis trial in acute PE (22). Increasing age and the presence of comorbidity have been associated with a higher risk of bleeding complications (22, 63), but a validated bleeding score is still lacking.

In a randomised comparison of heparin vs alteplase in 256 non-motorve patients with acute PE and evidence of RV dysfunction or pulmonary hypertension, fibrinolytic treatment reduced the incidence of escalation to emergency treatment (from 24.6% to 10.2%; p = 0.004), but it did not affect mortality which was low also in the heparin-only treatment group (34). More recently, the Pulmonary Embolism Thrombolysis Trial (PEITHO), a multicentre randomised European study, compared, in a double-blind manner, fibrinolysis with tenecteplase plus heparin vs placebo plus heparin in 1,006 patients with acute PE (22). Eligible patients had RV dysfunction, confirmed by echocardiography or CT angiography, plus myocardial injury confirmed by a positive troponin I or T test; i.e. they were at intermediate-high risk of an adverse early outcome based on the updated ESC classification (11). The primary efficacy outcome of the trial, a composite of all-cause death or haemodynamic decompensation/collapse within seven days of randomisation, was significantly reduced with tenecteplase (2.6% vs 5.6% in the placebo group; OR 0.44, 95% CI 0.23–0.88). The clinical benefit was driven mainly by a significant reduction in the rate of haemodynamic collapse (1.6% vs 5.0%, P = 0.002); all-cause mortality was 1.2% in the tenecteplase group and 1.8% in the placebo group (P = 0.43). On the other hand, there was a 2% incidence of haemorrhagic stroke after fibrinolytic treatment with tenecteplase (versus 0.2% in the placebo arm); major non-intracranial bleeding events were also increased in the tenecteplase group, compared with placebo (6.3% vs 1.5%; P < 0.001) (22).

Despite its limitations (22), the PEITHO study provides the best evidence that we will probably ever be able to obtain in order to answer to the question ‘Is systemic fibrinolysis indicated in PE patients without haemodynamic instability at presentation?’ The trial showed that full-dose systemic fibrinolysis, given as primary reperfusion therapy, can prevent potentially life-threatening haemodynamic decompensation or collapse, but this benefit is counterbalanced by a high incidence of haemorrhagic stroke or major non-intracranial bleeding. Accordingly, systemic fibrinolysis cannot be recommended as routine primary treatment for patients with intermediate-risk PE, even if signs of both RV dysfunction and myocardial injury are present (intermediate-high risk). Instead, patients belonging to this risk group should receive parental heparin anticoagulation and be monitored closely over at least 48–72 h; rescue fibrinolysis should be considered if clinical signs of haemodynamic decompensation appear (11).

Can reduced-dose systemic fibrinolysis improve safety without a loss of efficacy? Preliminary evidence suggests that a reasonable strategy might consist of reducing by 50% (or even more) the dosage of the fibrinolytic agent used. In a randomised pilot trial of 118 patients with high- or intermediate-risk PE, half-dose rtPA was equally effective with the full dose in terms of improving pulmonary vascular obstruction, and it appeared to cause less bleeding (64). In another small study of 121 patients with (arbitrarily defined) ‘moderate’ PE, reduced-dose rtPA appeared to be safe in the acute phase and to reduce the persistence of echocardiographically assessed pulmonary hypertension at 28 ± 5 month follow-up (65). The safety and efficacy of reduced-dose regimens are also supported by recent findings in patients treated with fibrinolysis for acute myocardial infarction (66). Nevertheless, the available evidence is by no means conclusive and reduced-dose fibrinolysis remains off-label therapy in acute PE; accordingly, it cannot be recommended at present. As an alternative option for PE patients who necessitate advanced reperfusion treatment but present with absolute or relative contraindications to systemic fibrinolysis, pharmacomechanical approaches or other catheter-based techniques should be considered as explained in the following section.

From surgical embolectomy to percutaneous catheter-directed treatment and the ‘revival’ of pharmacomechanical approaches

Surgical pulmonary embolectomy remained a rarely performed procedure over several decades. Recent technical advances in transportable extracorporeal assist systems help to stabilise the patients perioperatively and improve outcomes. Today, involvement of cardiac surgeons and teams experienced in advanced haemodynamic support systems ensures, if locally available, an effective interdisciplinary approach to PE in compromised or deteriorating patients (67–71). Accordingly, surgical pulmonary embolectomy is recommended for haemodynamically unstable patients with PE, in whom fibrinolysis is contraindicated or has failed; it may also be considered as a rescue procedure in intermediate-to-high-risk patients in whom haemodynamic decompensation appears imminent and the anticipated bleeding risk under systemic fibrinolysis is high (11). Pulmonary embolectomy is the treatment of choice for patients with a patent foramen ovale and pending paradoxical systemic embolism (72). Catheter-directed techniques and modalities for the removal of obstructing thrombi from the main pulmonary arteries have also been available for several years; these procedures are considered an alternative to surgery for patients with absolute or relative contraindications to fibrinolysis provided that expertise is locally available (73). ‘Purely interventional’ options such as thrombus
fragmentation with pigtail or balloon catheter, rheolytic thrombectomy with hydrodynamic catheter devices, suction thrombectomy with aspiration catheters and rotational thrombectomy have been reserved for patients with absolute contraindications (▶ Table 2) to fibrinolysis. On the other hand, for patients with relative contraindications to fibrinolysis and (moderately) increased risk of bleeding, conventional catheter-directed fibrinolysis through a multi-sidehole catheter placed into the thrombus, or pharmacomechanical fibrinolysis, are preferred approaches. The rationale for the latter technique is based on experimental (although not clinically confirmed) data and assumes that ultrasound facilitates the penetration of the drug into the thrombus and also causes reversible disaggregation of uncrosslinked fibrin fibres which possibly create additional binding sites for the fibrinolytic agent (74–76).

A review of interventional treatment of acute PE identified 35 non-randomised studies (6 of which were prospective and 29 retrospective) including a total of 594 patients (77). The pooled clinical success rate, based on stabilisation of haemodynamic parameters, resolution of hypoxia, and survival to discharge, was approximately 87%. The contribution of the mechanical catheter intervention per se to clinical success is unclear because 67% of patients also received adjunctive local fibrinolysis. Publication bias possibly resulted in underreporting of major complications (reportedly affecting 2.4% of the interventions and including five peri-procedural deaths), which may include death from worsening RV failure, distal embolisation, pulmonary artery perforation with lung haemorrhage, systemic bleeding complications, pericardial tamponade, heart block or bradycardia, haemolysis, contrast-induced nephropathy, and puncture-related complications. The very high success rates may also have been the result, at least in part, of publication bias.

Recently, the results of the Ultrasound Accelerated Thrombolysis of Pulmonary Embolism Trial (ULTIMA), a phase 2 clinical trial using the only catheter system for intravascular ultrasound-assisted fibrinolysis which is commercially available at present, were published (21). The study was preceded by a number of uncontrolled series, the pooled data of which had suggested a low (3.6%) risk of major bleeding and no intracranial or fatal haemorrhage (73). In ULTIMA, which was performed in two European countries, 59 patients with acute main- or lower-lobe PE and echocardiographic right-to-left ventricular dimension ratio ≥1.0 were randomised to receive unfractionated heparin and an ultrasound-assisted fibrinolytic regimen of 10–20 mg rtPA plus unfractionated heparin over 15 h as opposed to unfractionated heparin alone. Reduced-dose local fibrinolysis significantly reduced, compared to heparin anticoagulation alone, the subannular right-to-left ventricular dimension ratio between baseline and 24-h follow-up without an increase in bleeding complications (21). The efficacy and safety of pharmacomechanical thrombolysis appears to be further supported by the results of a recently presented prospective, single-arm multicentre trial from the United States which enrolled 150 patients with so-called ‘submassive’ (intermediate-risk) or ‘massive’ (high-risk) PE (ClinicalTrials.gov identifier: NCT01513759). On the other hand, the need for local expertise along with the high costs of the equipment and the lack of reimbursement by the health systems of most countries are currently limiting the widespread use of this technique outside selected specialised centres.

Conclusions

Although the modalities used for reperfusion of the pulmonary vasculature in acute PE have been available for many years, it was only recently that risk-adapted management strategies made significant progress thanks to the published results of prospective randomised or management trials. The evidence currently available is considered sufficient to support clear recommendations on advanced treatment such as those included in the 2014 update of the ESC guidelines. The risk-to-benefit ratio of primary systemic fibrinolysis for intermediate-risk PE could finally be determined and was found to be unfavourable. The principal concern is not the efficacy of fibrinolysis, which is high, but the safety of full-dose regimens and particularly the risk of intracranial or other major haemorrhage. Besides developing strategies which propose reduced intravenous dosages, pharmacomechanical catheter-directed approaches, and particularly ultrasound assisted low-dose intrapulmonary fibrinolysis, appear to be a promising therapeutic option for haemodynamically unstable patients with contraindications to systemic administration. This type of treatment may also be appropriate for intermediate-to-high-risk patients in whom haemodynamic decompensation appears imminent and the anticipated bleeding risk under full-dose intravenous fibrinolysis is high.

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Conflicts of interest

None declared.

References


