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INVITED REVIEW

Pulmonary embolism: whom to discharge and whom to thrombolyze?

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Summary. Patients with pulmonary embolism can be divided in two groups according to their risk of death or major complication: a small group of high-risk patients defined by the presence of systemic hypotension or cardiogenic shock and a large group of normotensive patients. Among normotensive patients, further risk stratification, based on clinical grounds alone or on the combination of clinical data, biomarkers, and imaging tests, allows selection of low-risk patients and intermediate-risk patients. The safety of outpatient treatment for low-risk patients has been established mainly on the basis of retrospective and prospective cohorts using different selection tools. In most studies, about 50% of the patients have been safely treated at home. Although thrombolytic therapy has a favorable benefit to risk profile in patients with high-risk pulmonary embolism, the risk of major and especially intracranial bleeding outweighs the benefits in terms of hemodynamic decompensation in patients with intermediate-risk pulmonary embolism.

Keywords: anticoagulants; outpatient; prognosis; pulmonary embolism; thrombolytic therapy.

Anticoagulant treatment achieves remarkably low incidences of recurrent venous thromboembolism (VTE) or bleeding complications in the vast majority of patients with acute pulmonary embolism (PE). A few patients still have a poor outcome and require more aggressive treatment. Recent work helps to resolve a longstanding debate on the role of thrombolytic therapy in the so-called intermediate-risk (or submassive) PE. Conversely, recent data suggest that some patients with PE can be treated safely at home. The choice between these different therapeutic options can nowadays be based on risk stratification, but whether risk stratification can be based solely on clinical findings or on the combination of clinical findings, biomarkers, and imaging remains to be defined.

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Description of the different risk-stratification tools for patients with pulmonary embolism

The aim of risk stratification is to assess the outcome of patients with PE in order to select the most appropriate candidates for outpatient treatment, hospitalization, and more intensive treatment. Relevant outcome may, however, differ between these two goals: all-cause mortality, recurrent VTE and major bleeding for the selection of low-risk patients who might benefit from outpatient therapy, and PE-related mortality and non-fatal PE-related complications for the selection of intermediate-risk patients who might benefit from escalated therapy. This can be performed using a simple set of clinical criteria, clinical prognostic scores, or the combination of clinical findings, cardiac biomarkers, and imaging data.

Rules based on a simple set of clinical criteria

Several sets of criteria have been proposed for selecting the appropriate candidates for outpatient treatment (Table 1) [1–6]. The safety of these criteria was assessed in several studies where low-risk patients were treated directly at home or after a short hospitalization lasting < 72 h (Table 2). In these studies, the proportion of patients with PE treated on an outpatient basis varied from 10% to 68%, and recurrent VTE, major bleeding, and overall death at 3 months varied from 0% to 6.1%, from 0% to 1.9%, and from 0% to 5%, respectively (Table 2). The rate of hospital readmissions during the initial phase was 1.5% and 1.9% in the two studies with available data [1,4].

Prognostic rules based on clinical findings

Several clinical rules have been derived for the risk-assessment of patients with PE and were mainly designed to select low-risk patients who may be appropriate candidates

Table 1 Different simple sets of clinical criteria used for the selection of patients treated entirely at home or after early discharge

Study	Outpatient treatment criteria
Erkens [1]	systolic blood pressure > 100 mmHg oxygen saturation ≥ 92% and no need for oxygen no contraindications for the use of low molecular weight heparin no other comorbidities requiring hospitalization
Kovacs [6]	hemodynamic stability no requirement of oxygen no need for parenteral narcotics no high risk for major hemorrhage
Zondag [3]	hemodynamic stability no need for thrombolysis or embolectomy no active bleeding or high risk of bleeding no oxygen supply to maintain oxygen saturation > 90% no PE diagnosed during anticoagulant treatment no severe pain needing intravenous pain medication for more than 24 h no medical or social reason for treatment in the hospital for more than 24 h creatinine clearance ≥ 30 mL min^{-1} no severe liver impairment no pregnancy no documented history of heparin induced thrombocytopenia
Davies [4]	no other disease requiring hospitalization no need for additional monitoring no need for oxygen therapy or for intravenous drugs no history of previous PE or further PEs developing while currently on anticoagulation treatment no co-existing major deep venous thrombosis no bleeding disorders or active bleeding no pregnancy no likelihood of poor compliance patient preference
Rodríguez-Cerrillo [5]	PE affecting less than two lobar branches no contraindications for low molecular weight heparin absence of moderate to severe renal failure hemodynamic stability O2 saturation > 92% no signs of heart failure no arrhythmia no hemoptysis
Wells [35]	no illness unrelated to venous thromboembolism requiring hospitalization no active bleeding hemodynamic stability no pain requiring intravenous narcotics no need for oxygen age ≥ 18 years no likelihood of poor compliance

for outpatient treatment [7]. The original Pulmonary Embolism Severity Index (PESI) includes 11 clinical variables. According to this rule, patients are divided into five risk classes for 30-day mortality. Usually, patients in class I and II are categorized as low risk, and patients in class III, IV, or V are categorized as high risk [8]. The simplified PESI (sPESI) includes seven clinical variables from the original score [9]. In a recent meta-analysis including 21 studies, the pooled sensitivity and specificity of the original PESI for the outcome of death were 0.90 (95% CI: 0.89–0.91) and 0.41 (95% CI: 0.41–0.41), respectively. The corresponding figures for the sPESI were 0.92 (95% CI: 0.91–0.93) and 0.38 (95% CI: 0.38–0.39). The pooled sensitivity and specificity of the original PESI for PE-related complications were 0.83 (95% CI: 0.79–0.86) and 0.41 (95% CI: 0.41–0.42), respectively. The corresponding figures for the sPESI were 0.82 (95% CI: 0.78–0.85) and 0.37 (95% CI: 0.36–0.37) [10].

Using the original PESI and the sPESI, 45% (95% CI, 42–49) and 35% (95% CI, 31–39) of patients were categorized as low risk, respectively [11]. In the studies using the original PESI, the risk of death at day 30 in low-risk patients varied from 0.0% to 7.7% and the risk of adverse outcome varied from 1.0% to 8.3% [10]. In patients classified as low risk using the sPESI, the risk of death at day 30 varied from 0.0% to 2.7% and the risk of adverse outcome varied from 1.0% to 2.9% [10].

The Spanish score includes recent severe bleeding, metastatic or non-metastatic cancer, serum creatinine values > 2 mg dL^{-1}, immobilization due to a recent medical condition, absence of surgery in the past 2 months and age > 60 years. In a large cohort of PE patients, the Spanish score classified 62% of patients as low risk, but the mortality in the low-risk group was higher for the Spanish score than for the PESI (4.2% vs. 1.1%) [12].

The Geneva score includes cancer, previous venous thrombosis, heart failure, systolic blood pressure < 100 mmHg, PaO2 < 8.5 kPa, and venous thrombosis [13]. Patients with a score ≤ 2 are assigned to the low-risk category and those with a score ≥ 3 points to the high-risk category. The risk of death among low-risk patients varies from 1.9% to 16.8% in validation studies [11].

Prognostic rules combining clinical data, biomarkers, and imaging data

Right ventricular dysfunction (RVD) assessed by echocardiography or spiral computed tomography angiography and biomarkers including brain natriuretic peptide (BNP) N terminal pro-BNP (NT-proBNP) and troponin have been associated with an increased risk of death or PE-related complications including death due to PE, cardiogenic shock, and recurrent PE. Several prediction rules combine these data with clinical findings, and most were designed to select patients with an intermediate risk among normotensive patients with PE.

According to the score defined by the European Society of Cardiology (ESC score), PE patients with normal blood pressure are divided in intermediate-risk patients

Table 2 Three-month outcomes of patients with PE selected for outpatients on the basis of simple sets of clinical criteria

Study	*n*	Outpatient treatment	Death *n* (%; 95% CI)	Recurrent VTE *n* (%; 95% CI)	Major bleeding *n* (%; 95% CI)	Readmission *n* (%; 95% CI)
Erkens [1]	473	260 (55%)	13 (5.0%; 2.7–8.4%)	10 (3.8%, 1.9–7.0)	4 (1.5%; 0.4–3.9)	4 (1.5%; 0.4–3.9)
Kovacs [36]	158	108 (68%)	4 (3.7%)	6 (5.6%)	2 (1.9%)	0
Kovacs [6]	639	314 (49%)	9 (2.9%; 1.4–5.6)	3 (0.95%, 0.25–3.0)	3 (0.95%; 0.25–3.0)	NA
Davies [4]	NA	157	3 (1.9%; 0.4–5.5)	0 (0%; 0.0–2.3)	0 (0%; 0.0–2.3)	3 (1.9%; 0.4–5.5)
Rodríguez-Cerrillo [5]	286	30 (10%)	0	0	0	0
Zondag [3]	581	297 (51%)	3 (1.0%; 0.2–2.9)	6 (2.0%, 0.8–4.3)	2 (0.7%; 0.08–2.4)	NA

VTE, venous thromboembolism; NA, not available. The PESI and sPESI are discussed in the section about Prognostic rules based on clinical findings.

Table 3 Outcomes according to different risk-stratification models based on the combination of clinical data and biomarkers

Study	Clinical rule	Outcome* (%)
Lankeit 2014 [16]	sPESI = 0 (n = 258)	2 (0.8)
	sPESI = 0, NT-proBNP < 600 pg mL^{-1} (n = 172)	0 (0)
	sPESI = 0, NT-proBNP > 600 pg mL^{-1} (n = 86)	2 (2.3)
Jimenez 2014 [17]	sPESI = 0 (n = 313)	5 (1.6)
	sPESI = 0, BNP ≤ 100 pg mL^{-1} (n = 216)	2 (0.9)
	sPESI = 0, BNP > 100 pg mL^{-1} (n = 97)	3 (3.1)
Sanchez 2013 [23]	PESI I-II (n = 324)	7 (2.2)
	PESI I-II, BNP ≤ 100 pg mL^{-1} (n = 218)	2 (0.9)
	PESI I-II, BNP > 100 pg mL^{-1} (n = 106)	5 (4.7)
Moores 2010 [25]	PESI I-II (n = 192)	2 (1.0)
	PESI I-II, TnI ≤ 0.1 ng mL^{-1} (n = 149)	2 (1.3)
	PESI I-II TnI > 0.1 ng mL^{-1} (n = 43)	0 (0)

PESI, Pulmonary Embolism Severity Index; sPESI, simplified Pulmonary Embolism Severity Index; BNP, brain natriuretic peptide; NT-pro BNP, N terminal pro-brain natriuretic peptide; TnI, troponin I. *Outcome at 30 days was defined: as pulmonary embolism-related death or need for intravenous catecholamine administration, endotracheal intubation or cardiopulmonary resuscitation (Lankeit *et al.*); as death from any cause, hemodynamic collapse, or adjudicated recurrent pulmonary embolism (Jimenez *et al.*); as death, secondary cardiogenic shock, or recurrent venous thromboembolism (Sanchez *et al.*); as all-cause mortality (Moores *et al.*).

who have RVD or elevated troponin level and low-risk patients who have normal right ventricular function and normal levels of cardiac biomarkers. The risk of death varies between 0% and 5.6% in patients classified as low risk by the 'ESC score' and between 2.5% and 22.5% in those at intermediate risk [11].

The LR-PED score includes age, chronic heart failure, atrial fibrillation, heart rate, troponin I, creatinine, blood glucose level, and C-reactive protein and was derived in clinically stable patients to identify low-risk patients [14]. Only 25 among the 142 patients (17.6%) included in the derivation study were considered as low-risk patients and none died during hospitalization or at one month [14]. The PREP score includes cancer, underlying cardiac or respiratory disease, cardiogenic shock, altered mental status, BNP, and right to left ventricle diameter ratio [15]. In the derivation study, 323 of 570 patients (56.7%) were classified in the lowest risk category and had a risk of adverse event at 30 days of 2.5%. In the subgroup of normotensive patients belonging to the highest risk category, the risk of PE-related adverse event was 22.9% [15]. In another cohort of 688 normotensive patients with acute PE, both NT-proBNP and echocardiography had a prognostic impact on top of that of the sPESI (Table 3) [16]. The PROTECT model includes the sPESI, cardiac troponin I, BNP, and lower limb ultrasound [17]. The combination of all modalities included in the model (i.e. sPESI, troponin, BNP, and venous ultrasound) had the highest positive predictive value for a complicated course during follow-up (25.8%; 95% CI, 10.4–41.2) [17]. The FAST score combines heart-type fatty acid binding protein (H-FABP) (≥ 6 ng mL^{-1}), heart rate (> 110 bpm), and syncope [18]. In normotensive patients with PE, the positive predictive value of the FAST score and sPESI for PE-related complications were 22% (95% CI, 14–33) and 11% (95% CI, 8–17), respectively [18].

Combining patient data from six studies involving 2874 normotensive patients with PE, Bova *et al.* developed a prognostic model for intermediate-risk PE. Predictors of the composite of PE-related death, hemodynamic collapse, or recurrent PE included systolic blood pressure between 90 and 100 mmHg, heart rate ≥ 110 bpm, elevated troponin, and RVD. A risk index based on these variables identified three stages with

complication rates of 4.2%, 10.8%, and 29.2%, respectively [19].

How to select appropriate candidates for outpatient treatment?

Risk-stratification models vs. simple clinical criteria

Five of the 11 studies included in a recent meta-analysis used risk-stratification models to select patients for outpatient treatment and the others used clinical gestalt with specific exclusion criteria. No difference was observed between these two groups of studies for recurrent VTE or major bleedings [20]. In one study, a simple set of clinical criteria selected a larger proportion of patients for outpatient treatment than the PESI or sPESI [21]. Among 115 patients safely treated as outpatients on the basis of the clinical criteria, 34 patients (29.6%) were classified as high-risk patients by the original PESI and 54 (47.0%) by the sPESI [21]. In the HESTIA study, 58 of the 247 patients (23%) treated at home according to the Hestia criteria were classified as low risk according to the sPESI. Conversely, among patients treated at hospital according to the Hestia criteria, 86 patients (39%) had a sPESI = 0. The Hestia criteria and the sPESI classified different patients eligible for outpatient treatment, with similar and low mortality rates [22]. Of note, HESTIA and the criteria described by Erkens *et al*. lack external validation yet, whereas PESI and sPESI have been assessed in several independent studies [11].

Clinical risk-stratification models vs. more complex models using biomarkers and imaging

The rates of PE-related complications or overall death have been reported to be higher in patients with low-risk PESI or sPESI and abnormal BNP, NT-proBNP, or troponin values, than in patients with a low-risk PESI or sPESI and normal values of biomarkers, but the absolute risk of adverse events was < 5%, even in the patients with elevated biomarkers (Table 3) [16,17,23,24]. In addition, this was not confirmed in all studies [25,26]. These results suggest that biomarkers and imaging data have probably a limited role in the selection of low-risk patients for outpatient treatment.

How to select intermediate-risk patients?

In clinically stable patients, the specificity of the PESI and sPESi for mortality was 0.49 (0.44–0.53) and 0.38 (0.32–0.44), respectively [11]. Recent cohort studies suggest that abnormal values of biomarkers and RVD increase the risk of death or PE-related complication in patients with normal blood pressure and sPESI ≥ 1 or PESI class III-IV. In one study, the risk of adverse event in clinically stable patients with PESI III-IV was 6% and 5% in patients with normal values of BNP and troponin, respectively. The corresponding figures in those with abnormal values of BNP and troponin were 10% and 17%, respectively [23]. In another study, the risk of adverse outcome in patients with sPESI ≥ 1 was 2.5% and 8.2% in patients with NT-proBNP < 600 and ≥ 600 pg mL^{-1}, respectively [16]. Similarly, in the PROTECT study, the risk of adverse outcome in patients with sPESI ≥ 1 was 6.1% and 13.8% in patients with BNP ≤ 100 pg mL^{-1} and BNP > 100 pg mL^{-1}, respectively [17]. In both studies, the addition of a positive troponin test or RVD further increased the risk of adverse outcome [16,17].

Results of outpatient treatment for acute PE

Only one randomized controlled trial was included in the Cochrane review comparing outpatient and inpatient treatment for PE [27,28]. Authors of this review ranked the quality of the evidence as very low due to the small number of events with imprecision in the confidence intervals and the small sample size. Indeed, the confidence intervals were wide and included clinically significant effects in both directions regarding short-term mortality (30 days) (RR 0.33, 95% CI 0.01–7.98, $P = 0.49$), long-term mortality (90 days) (RR 0.98, 95% CI 0.06–15.58, $P = 0.99$), major bleeding at 14 days (RR 4.91, 95% CI 0.24–101.57, $P = 0.30$), and recurrent PE within 90 days (RR 2.95, 95% CI 0.12–71.85, $P = 0.51$) [27]. The authors of the review concluded that this trial did not provide sufficient evidence to assess the efficacy and safety of outpatient vs. inpatient treatment for acute PE adequately [27]. The safety of home treatment for PE has also been assessed in cohort studies. Both randomized controlled trials and cohort studies were included in a recent systematic review [20]. During the 3-month follow-up period, the rate of recurrent VTE in 1258 patients managed as outpatients was 1.47% (95% CI: 0.47–3.0), the rate of fatal PE was 0.47% (95% CI: 0.16–1.0), the rate of major bleeding was 0.81% (95% CI: 0.37–1.42), and the overall 3-month mortality rate was 1.58% (95% CI: 0.71–2.80) [20]. Although a higher level of evidence would be welcome, the current results strongly suggest that outpatient treatment of selected patients is feasible and safe for a significant proportion of patients with PE. Of note, most of the studies were undertaken in the context of a dedicated outpatient thrombosis clinic with close follow-up of patients managed as outpatients [1]. Outpatient treatment of low-risk patients with PE should be restricted to hospitals with an available dedicated thrombosis clinic including a 24-h service to follow patients and to rapidly re-admit them in case of complications and to patients with well-maintained living conditions, strong support from family or friends, phone access, and ability to quickly return to the hospital if there is deterioration [29].

Who should receive thrombolytic therapy?

Thrombolytic therapy should not be used in low-risk PE patients

Normotensive patients without signs of RVD or damage have a very low risk of mortality and of PE-related complication and do not deserve the use of thrombolytic treatment with its associated bleeding risk. Patients who either have a sPESI = 0, or no RVD and normal biomarkers have a risk of PE-related complication varying between 0% and 2.3% and between 0.9% and 6.1% in two recent cohort studies [16,17]. These complication rates are lower than the rate of major bleeding observed in recent thrombolytic trials in PE [30]. Thus, guidelines advise not using thrombolytic treatment in these patients [31].

Thrombolysis probably helps patients with cardiogenic shock

Although the evidence is limited, the use of thrombolytic therapy is recommended for high-risk PE patients because these patients have a high mortality risk when receiving anticoagulant treatment [31]. In this setting, the hemodynamic effects of thrombolytic treatment far outweigh its bleeding risk. A systematic review of randomized trials suggested that thrombolysis is associated with a reduction in mortality or recurrent PE in patients who present with hemodynamic instability [32]. In the studies including hemodynamically unstable patients (high-risk PE), thrombolytic therapy was associated with a non-significant reduction in mortality [odds ratio (OR): 0.48; 95% CI 0.20–1.15], a significant reduction in PE-related mortality (OR: 0.15; 95% CI: 0.03–0.78), and a significant reduction of the end-point of death or treatment escalation (OR: 0.18; 95% CI: 0.04–0.79)[32]. Noteworthy, only a minority of the patients included in these studies had systemic hypotension.

What about the use of thrombolytic therapy in patients with intermediate-risk PE?

In the most comprehensive meta-analysis published before 2014, studies including clinically stable patients only (combining low-risk and intermediate-risk patients) were analyzed separately and did not demonstrate significant difference between thrombolysis and heparin for the risk of death (OR: 1.16; 95% CI, 0.44–3.05) nor in the combined end-point of death or recurrent PE (OR: 1.07; 95% CI, 0.50–2.30) [33]. Biomarkers were not measured in any study and most did not report on echocardiography. Thus, most of the patients included in these trials probably had low-risk PE and the role of thrombolytic therapy for patients with intermediate-risk PE cannot be defined on this basis.

More recently, the PEITHO study randomized 1006 patients with normal blood pressure and both RVD and elevated troponin to receive either heparin and tenecteplase or placebo and heparin [30]. The main clinical composite end-point of death from any cause or hemodynamic decompensation (or collapse) occurred in 13 patients (2.6%) in the tenecteplase group and in 28 patients (5.6%) in the placebo group (OR, 0.44; 95% CI, 0.23–0.87; $P = 0.02$). This increase in efficacy was, however, obtained at the expense of an increase in major bleeding and intracranial bleedings. Major bleeding occurred in 58 patients (11.5%) in the tenecteplase group and 12 patients (2.4%) in the placebo group. Overall, 12 patients (2.4%) in the tenecteplase group and one patient (0.2%) in the placebo group had a stroke ($P = 0.003$). Mortality was 1.2% and 1.8% in the tenecteplase and placebo group, respectively ($P = 0.42$) [30].

A recent meta-analysis analyzed for the first time the results of thrombolytic therapy in patients with intermediate-risk PE [32]. In these patients, thrombolysis is associated with a non-significant reduction in overall mortality (OR: 0.42; 95% CI, 0.17–1.03), with a significant reduction in PE-related death (OR: 0.17; 95% CI, 0.05–0.67), a non-significant reduction in PE recurrence (OR: 0.25; 95% CI, 0.06–1.03), a significant increase in the risk of major bleeding (OR: 2.91; 95% CI: 1.95–4.36), and fatal or intracranial hemorrhage (OR: 3.18; 95% CI: 1.25–8.11) [32]. According to the recent guidelines from the European Society of Cardiology, this narrow benefit to risk ratio precludes the use of thrombolytic therapy in all patients with intermediate-risk PE but thrombolysis should be considered if clinical signs of hemodynamic decompensation appear [31]. Preliminary findings suggest that lower doses of thrombolytic therapy may have the same efficacy with lower bleeding risks, but this has to be confirmed in larger trials [34].

Conclusion

Outpatient treatment appears feasible and safe for a substantial proportion of patients with PE, but current evidence is mainly based on cohort studies and on one small-sized randomized controlled trial. Selection of the appropriate candidates for outpatient treatment can be based on simple clinical criteria or on clinical risk-stratification tools. Among them, the PESI and sPESI have been assessed in a large number of studies, whereas most of the lists of clinical criteria lack validation studies; only the PESI has been used to randomize patients between outpatient treatment and hospitalization. A head to head comparison between these two selection processes may be helpful. Although biomarkers may select a subset of patients with a lower risk of adverse outcome among those at low risk according to clinical rules, their role in the selection of candidates for outpatient treatment is probably limited. Conversely, abnormal values of cardiac

biomarkers and evidence of RVD help selecting patients with a high risk of PE-related complication among those with sPESI ≥ 1 and normal blood pressure. Thrombolytic therapy is associated with a decrease in the risk of death or PE recurrence in patients with cardiogenic shock or sustained hypotension and is the first-line treatment in these patients. Thrombolytic treatment should not be given in patients with normal blood pressure classified as intermediate-high risk on the basis of abnormal cardiac biomarkers and RVD, because the risk of major bleeding outweighs its hemodynamic benefit in this context. The search for thrombolytic regimens having the same efficacy and carrying a lower bleeding risk may help decreasing the rate of adverse events related to pulmonary embolism, which remain significant in these patients.

Disclosure of Conflict of Interests

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