# The diagnostic and therapeutic management of pulmonary embolism

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# CHAPTER 2

## Recent developments in the diagnosis and treatment of pulmonary embolism

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## ABSTRACT

Due to the nonspecific symptoms of the condition, a diagnosis of acute pulmonary embolism (PE) is frequently considered. However, PE will only be confirmed in 10–20% of patients. Because the imaging test of choice, computed tomography pulmonary angiography (CTPA), is costly and associated with radiation exposure and other complications, a validated diagnostic algorithm consisting of a clinical decision rule and D-dimer test should be used to safely exclude PE in 20–30% of patients without the need for CTPA. Recently, the age-adjusted D-dimer threshold has been validated, and this has increased the proportion of patients at older age in which PE can be excluded without CTPA. Initial therapeutic management of PE depends on the risk of short-term PE-related mortality. Haemodynamically unstable patients should be closely monitored and receive thrombolytic therapy unless contraindicated because of an unacceptably high bleeding risk, whereas patients with low-risk PE may be safely discharged early from hospital or receive only outpatient treatment. The PESI score and Hestia decision rule are available to select patients in whom early discharge or outpatient treatment will be safe, although the safety of these strategies should be confirmed in additional studies. Standard PE therapy consists of low molecular weight heparin (LMWH) followed by vitamin K antagonists (VKAs). Recently, several nonvitamin K-dependent oral anticoagulants have been shown to be as effective as LMWH/VKAs, and maybe safer. Determining the optimal duration of treatment for a first unprovoked PE remains a challenge, although clinical prediction rules for estimating the risk of recurrence of venous thromboembolism and anticoagulation-associated haemorrhage are under investigation. Using these prediction rules may lead to both more standardized and more individualized long-term treatment of PE.

## INTRODUCTION

Acute pulmonary embolism (PE) is a relatively common disease with an annual rate of 1–2 per 1000 patients [1, 2]. The clinical presentation of acute PE is nonspecific and highly variable, ranging from incidentally diagnosed asymptomatic thrombi to sudden death [3]. As a result, a clinical suspicion of PE is frequently raised, whilst the diagnosis is only confirmed in 10–20% of patients [4, 5]. Diagnostic algorithms have been developed to ensure reliable and efficient management of patients with clinically suspected PE.

Once acute PE is diagnosed, prompt initiation of anticoagulant therapy is indicated to prevent thrombus extension and recurrent (fatal) PE. However, the risk of such an adverse outcome is highly variable, ranging from <1% to >15% [6]. Management decisions including early discharge or prescription of thrombolytic therapy should preferably be based on reproducible risk stratification of the individual patient [6, 7]. For the long-term treatment of acute PE, the decision to continue or stop anticoagulant therapy, after an initial period of 3 months, depends on the balance between the risk of recurrent venous thromboembolism (VTE) and of anticoagulant-associated haemorrhage.

Here, we will present an up-to-date overview of the therapeutic management of established PE, discussing conventional medical therapy, the recently introduced non-vitamin K-dependent oral anticoagulants (NOACs), outpatient treatment, thrombolytic therapy and the duration of treatment. In particular, we will focus on recent advances as a follow-up to a review of a similar topic published in this journal in 2010 [8].

## DIAGNOSTIC MANAGEMENT OF CLINICALLY SUSPECTED ACUTE PE

Symptoms that may suggest the presence of acute PE are the sudden onset of dyspnoea, pleuritic chest pain, haemoptysis, extremity swelling suggestive of deep vein thrombosis (DVT) and syncope [3]. Of note, these symptoms are nonspecific for PE and may also be present in many other acute cardiopulmonary conditions. In large diagnostic management studies, the PE prevalence amongst patients with a clinical suspicion of PE ranged from 10% to 30% [4, 5, 9]. PE can only be diagnosed using an imaging test, at present usually computed tomography pulmonary angiography (CTPA), which is associated with high healthcare costs, radiation exposure and a risk of complications such as contrast-induced nephropathy and allergic reactions [10-12]. Therefore, diagnostic management algorithms have been developed to exclude PE without the need for imaging tests in a proportion of patients. These algorithms start with a clinical decision rule (CDR), which predicts the clinical pretest probability of PE, followed by a D-dimer blood test and/or a CTPA.

## CDRs and D-dimer testing

Various CDRs have been standardized and validated for use in clinical practice, of these, the Wells rule and revised Geneva score are the most widely validated for PE **(Table 1)** [13, 14]. Originally, different items were awarded different scores, but for practical reasons, both rules have been simplified by assigning only one point to each item, without lowering their diagnostic accuracy [15, 16]. The CDRs are used to categorize patients into either 'PE unlikely' or 'PE likely' groups, with PE prevalences of 12–17% and 37–43%, respectively, in European cohorts [4, 5]. The accuracy of the original and simplified versions of the Wells rule and revised Geneva score were shown to be similar, and the choice of a specific rule may therefore depend on local preference [4].

**Table 1.** Clinical decision rules.

| Item | Original version | Simplified version |
|---|---|---|
| **Wells rule** | | |
| Previous PE or DVT | 1.5 | 1 |
| Heart rate >100 beats/min | 1.5 | 1 |
| Surgery or immobilization within 4 weeks | 1.5 | 1 |
| Haemoptysis | 1 | 1 |
| Active malignancy | 1 | 1 |
| Clinical signs of DVT | 3 | 1 |
| Alternative diagnosis less likely than PE | 3 | 1 |
| **Clinical probability categories** | | |
| PE unlikely | ≤4 | ≤1 |
| PE likely | >4 | >1 |
| **Revised Geneva score** | | |
| Previous DVT or PE | 3 | 1 |
| Heart rate 75–94 beats/min | 3 | 1 |
| Heart rate ≥95 beats/min | 5 | 2 |
| Surgery or fracture within 1 month | 2 | 1 |
| Haemoptysis | 2 | 1 |
| Active malignancy | 2 | 1 |
| Unilateral lower limb pain | 3 | 1 |
| Pain on lower limb deep vein palpation and unilateral oedema | 4 | 1 |
| Age >65 years | 1 | 1 |
| **Clinical probability categories** | | |
| PE unlikely | ≤ 5 | ≤2 |
| PE likely | > 5 | >2 |

**Note:** DVT, deep vein thrombosis; PE, pulmonary embolism.

The D-dimer level in plasma is a marker of fibrinolysis and is elevated in the presence of acute VTE as well as in many other clinical conditions. The sensitivity of D-dimer testing for the latest generation of assays is very high (95–100%), whereas the specificity is moderate (43–93%) [17]. Accordingly, using the standard threshold of <500 µg/L, the negative predictive value of D-dimer testing allows for the exclusion of PE in patients with a PE unlikely clinical probability [4, 5, 9]. By applying this strategy, PE can be ruled out in 25–46% of patients without performing an imaging test, with a 3-month VTE incidence of 0.04–0.96% after anticoagulant therapy is withheld [18].

Recently, attempts have been made to increase the number of patients in whom PE can be ruled out without imaging tests. As D-dimer levels increase with age, an age-dependent D-dimer cut-off level was proposed: age × 10 µg/L in patients over 50 years of age [19]. The safety of applying this age-dependent D-dimer cut-off was recently confirmed in a large prospective outcome trial [9]. The 3-month VTE incidence in patients in the PE unlikely category and with a D-dimer level >500 µg/L but below the age-adjusted threshold was only 0.3% (95% confidence interval (CI) 0.1–1.7). The absolute increase in the proportion of patients above 50 years old that could be managed without CTPA was 11.6%. In particular, patients aged 75 years and older could be more frequently managed safely without CTPA.

### Imaging tests

The historical gold standard imaging test for diagnosing PE is pulmonary angiography, which is associated with a 3-month VTE incidence after a negative result of 1.7% (95% CI 1.0–2.7) [20]. Because pulmonary angiography is an invasive procedure, this test was first replaced by ventilation-perfusion lung scanning (V/Q scanning) and later by CTPA. Although it has been demonstrated that V/Q scanning is safe for excluding PE, with a 3-month VTE incidence of only 0.9% (upper limit of 95% CI 2.3) after a normal result, its major disadvantage is an inconclusive result in 28–46% of patients, in whom the PE prevalence is still 10–30% and who thus require an additional imaging test [21, 22]. CTPA results in an inconclusive test result in only 0.9–4.6% of patients [23]. Furthermore, CTPA is more widely available with faster acquisition and the possibility of establishing an alternative diagnosis, although the value of the latter has recently been questioned [24]. A possible advantage of V/Q scanning is the lower radiation exposure compared to CTPA (1.1 vs. 2–6 mSv), which may be relevant for specific patient groups, particularly young (particularly female) patients and pregnant women. V/Q scanning may also be considered for patients with a known allergy to contrast medium [11, 12].

The sensitivity of multidetector row high-resolution CTPA is excellent and several outcome studies have consistently demonstrated the safety of withholding anticoagulant therapy in patients with a negative CTPA alone [23]. In a meta-analysis, the pooled 3-month VTE incidence after a negative CTPA alone in patients in whom CTPA was

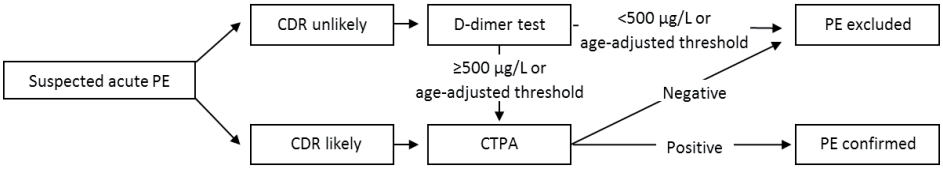
indicated based on a validated CDR and/or D-dimer test was 1.2% (95% CI 0.8–1.8), compared to 1.1% (95% CI 0.6–2.0) after negative CTPA and subsequently negative lower limb compression ultrasonography, indicating that the safety could not be further improved by excluding asymptomatic DVT after a negative CTPA [23]. In addition to ionizing radiation, other potential concerns related to the easily available CTPA as the first-line imaging test are an increased incidence of contrast-induced nephropathy, a risk of unsuspected findings requiring additional medical attention and an increased incidence of isolated subsegmental PE, of which the clinical relevance has become increasingly under debate [10, 25-27].

## Integrated approach

The first step in the diagnostic management of patients with clinically suspected acute PE is to determine whether the patient has signs and symptoms of haemodynamic shock. If so, patients should be immediately referred for additional imaging tests and thrombolytic therapy should be started without waiting for a CDR result or D-dimer level.

In patients who are haemodynamically stable, diagnostic management starts with the assessment of the clinical probability of PE using one of the validated CDRs (**Table 1**). In patients with a PE unlikely clinical probability, a D-dimer test is indicated and PE can be ruled out without further imaging tests if the level is <500 µg/L or below the age-adjusted threshold for patients over the age of 50 years. In the remaining patients with either a PE unlikely CDR score in combination with an elevated D-dimer level or a PE likely CDR score, CTPA is indicated to determine the presence of PE (**Figure 1**).

**Figure 1.** Integrated approach for clinically suspected acute pulmonary embolism in haemodynamically stable patients.




**Note:** CDR, clinical decision rule; CTPA, computed tomography pulmonary angiography; PE, pulmonary embolism.

Correct use of a validated diagnostic algorithm is required to ensure its safety; this is highlighted by several recent studies showing that a validated diagnostic algorithm is frequently not or incorrectly applied. This leads to the unnecessary use of CTPA and, even more relevant, to a higher 3-month VTE incidence in patients in whom anticoagulant therapy is withheld [28]. A promising intervention to improve adherence may be the implementation of computerized clinical decision support for clinicians [29]. Future studies should focus on further simplification of the diagnostic algorithms to improve

the compliance and consequently the safety and efficiency of diagnostic management in daily clinical practice. Future studies should also investigate whether increasing the D-dimer threshold, for instance with variable D-dimer thresholds depending on the pretest probability, may further improve the efficiency without reducing the safety of the diagnostic algorithm [30].

## TREATMENT OF ACUTE PE

### Risk stratification of acute PE

Patients with acute PE should be stratified according to the short-term PE-related mortality risk. Risk stratification starts with identifying patients in haemodynamic shock, who are classified as having high-risk or massive PE with an estimated 30-day PE-related mortality risk of >15% [7].

For the remaining haemodynamically stable patients, the ability of clinical prediction rules and several tests to distinguish patients with a low risk (<1%) from those with an intermediate risk (3–15%) of an adverse outcome has been investigated [7].

The Hestia decision rule consists of a set of criteria that can be used to select patients with low-risk PE who are candidates for early discharge or outpatient treatment (**Table 2**) [31]. The major strength of the Hestia decision rule is its clinician friendliness, as it consists of only 11 easy-to-use bedside criteria that should all be negative before early discharge or outpatient treatment can be considered. The Pulmonary Embolism Severity Index (PESI), which combines several clinical signs, symptoms and comorbidities (**Table 3**), is also available and is able to identify patients at low risk of short-term PE-related mortality [6]. To overcome its complexity, a simplified version (sPESI) has been proposed [32].

In addition to the Hestia decision rule and the PESI, several laboratory biomarkers have been shown to predict adverse outcome in haemodynamically stable patients. High concentrations of brain-type natriuretic peptides (BNPs) or the N-terminal of the prohormone of BNP (NT-proBNP) that are elevated during PE-associated right ventricular (RV) overload are strongly associated with mortality in acute PE with an OR of 7.6 (95% CI 3.4–17), whereas normal levels identify patients with a low risk of short-term PE-related mortality (17% vs. 1.7%) [33]. In addition, elevated plasma troponin I or (high-sensitivity) troponin T levels are associated with a high risk of short-term mortality (18% vs. 2.3%) in haemodynamically stable patients with an OR of 5.90 (95% CI 2.7–13) [34].

Both echocardiography and CTPA images can be used to detect RV dysfunction, which is also associated with an elevated risk of short-term PE-related mortality in patients who are haemodynamically stable. At least 25% of patients with PE have signs of RV dysfunction on echocardiography, such as RV dilatation, an increased RV/left ventricular (LV) diameter ratio, hypokinesia of the free RV wall, increased tricuspid regurgitation

**Table 2.** Hestia decision rule.

| |
|---|
| Haemodynamically unstable?[a] |
| Thrombolysis or embolectomy necessary? |
| High risk of bleeding?[b] |
| Oxygen supply to maintain oxygen saturation >90% for more than 24 h? |
| Pulmonary embolism diagnosed during anticoagulant treatment? |
| Intravenous pain medication for more 24 h? |
| Medical or social reason for treatment in hospital for more than 24 h? |
| Creatinine clearance <30 mL/min?[c] |
| Severe liver impairment?[d] |
| Pregnant? |
| Documented history of heparin-induced thrombocytopenia? |
| **Interpretation** |
| If the answer to at least one of the above questions is 'YES', the patient cannot be treated as an outpatient |

**Note:** [a]Includes, at the discretion of the physician, systolic blood pressure <100 mmHg with heart rate >100 beats/min; condition requiring admission to an intensive care unit; [b]gastrointestinal bleeding in the preceding 14 days, recent stroke (within 4 weeks), recent operation (within 2 weeks), bleeding disorder or thrombocytopenia (platelet count <75 x $10^9$/L) and/or uncontrolled hypertension (systolic blood pressure >180 mmHg or diastolic blood pressure > 110 mmHg); [c]creatinine clearance calculated according to the Cockroft–Gault formula; [d]at the discretion of the treating physician.

jet velocity or decreased tricuspid annulus plane systolic excursion. Echocardiographic signs of RV dysfunction in haemodynamically stable patients with PE are associated with an OR of 2.4 (95% CI 1.3–4.3) for short-term mortality [35]. The RV/LV dimensional ratio can also be assessed on axial or reconstructed four-chamber CTPA views, for which thresholds of ≥0.9 or ≥1.0 are generally used. CTPA-assessed RV dysfunction in haemodynamically stable patients is associated with an increased risk of short-term mortality (7.8% vs. 5.1%) as well as with short-term PE-related mortality (2.2% vs. 0.2%) with ORs of 1.8 (95% CI 1.3–2.6) and 7.4 (95% CI 1.4–40), respectively [36]. Interestingly, several studies have shown that models combining prediction rules, biomarkers and imaging tests improve the predictive accuracy compared with the individual tests, although at present, none of these combinations can be recommended to guide management in daily clinical practice [37, 38].

## Management of high-risk patients

Thrombolytic therapy is able to rapidly resolve thromboembolic obstruction enabling prompt reduction in pulmonary artery pressure and improvement in RV function. The results of one study suggested that a clinical and echocardiographic improvement can be observed in more than 90% of patients who receive thrombolysis [39]. Thrombolytic therapy is generally recommended for high-risk patients with PE with overt haemodynamic instability without a high risk of bleeding complications, although there is a lack

**Table 3.** PESI score.

| Parameter | Original version | Simplified version |
|---|---|---|
| Age | Age in years | *1 point (if age >80 years)* |
| Male sex | +10 points | |
| Cancer | +30 points | 1 point |
| Chronic heart failure | +10 points | 1 point |
| Chronic pulmonary disease | +10 points | |
| Heart rate ≥110 beats/min | +20 points | 1 point |
| Systolic blood pressure <100 mmHg | +30 points | 1 point |
| Respiratory rate >30 breaths/min | +20 points | |
| Temperature <36 °C | +20 points | |
| Altered mental status[a] | +60 points | |
| Arterial oxygen saturation <90%[b] | +20 points | 1 point |
| **Risk strata** | | |
| | Class I: ≤65 points<br>very low 30-day mortality risk<br>0–1.6% | 0 points = 30-day mortality risk 1.0%<br>(95% CI 0–2.1) |
| | Class II: 66–85 points<br>low mortality risk<br>1.7–3.5% | ≥1 point(s) = 30-day mortality risk 10.9%<br>(95% CI 8.5–13.2) |
| | Class III: 86–105 points<br>moderate mortality risk<br>3.2–7.1% | |
| | Class IV: 106–125 points<br>high mortality risk<br>4.0–11.4% | |
| | Class V: >125 points<br>very high mortality risk<br>10.0–24.5% | |

**Note:** PESI, Pulmonary Embolism Severity Index. [a]Defined as disorientation, lethargy, stupor or coma. [b]With and without the administration of supplemental oxygen.

of convincing supporting evidence from large randomized controlled trials. A meta-analysis of randomized trials including haemodynamically unstable patients with PE demonstrated an OR of 0.53 (2.2% vs. 3.9%; 95% CI 0.32–0.88) for recurrent PE and death in patients who received thrombolytic therapy [40]. In addition, in an epidemiological study, haemodynamically unstable patients with PE who received thrombolytic therapy had a relative risk of 0.2 (95% CI 0.19–0.22) for PE-related in-hospital death compared to those who had not received thrombolytic therapy [41]. Of major concern, it was shown in a recent meta-analysis that thrombolytic therapy substantially increased the risk of major bleeding complications with an OR of 2.73 (9.2% vs. 3.4%; 95% CI 1.91–3.91) compared to standard anticoagulant treatment [40]. Percutaneous catheter-directed therapy and surgical embolectomy are alternatives to thrombolytic therapy, for example

in the case of a contraindication to thrombolysis or after thrombolytic therapy has failed or is deemed inadequate as first-line treatment, although these interventions have not been investigated in clinical outcome studies [42].

### Management of nonhigh-risk patients

Amongst the nonhigh-risk haemodynamically stable patients, two key questions with regard to therapeutic management remain to be answered: (i) Do patients with intermediate-risk PE benefit from thrombolytic therapy? (ii) Which patients with low risk of adverse outcome are suitable candidates for outpatient treatment or early discharge?

The benefit of administering thrombolytic drugs to haemodynamically stable patients with intermediate-risk PE has been debated for many years. Individual small randomized trials have consistently demonstrated that thrombolytic therapy reduces the risk of haemodynamic deterioration and recurrent PE, at the cost of a higher risk of major haemorrhage without an effect on overall mortality [40, 43]. In 2014, the results of the randomized double-blind PEITHO trial were published. This study investigated the effects of a single dose of tenecteplase (varying from 30 to 50 mg depending on body weight) versus placebo in 1006 patients with an intermediate risk of PE [44]. Intermediate-risk PE was defined as a PESI score of III–V, elevated biomarkers of cardiac injury and signs of RV dysfunction on echocardiography or CTPA. The study demonstrated a significant reduction in the primary efficacy outcome (a composite of all-cause death or haemodynamic deterioration within 7 days of randomization), with an OR of 0.44 (2.6% vs. 5.6%; 95% CI 0.23–0.88). However, 7-day mortality was not different between the two groups: 1.2% of patients who received tenecteplase and 1.8% of patients who received placebo (OR 0.65; 95% CI 0.23–1.85). Of interest, patients who were randomly assigned to receive tenecteplase had a significantly higher risk of major extracranial bleeding and (predominantly haemorrhagic) stroke within 7 days with ORs of 5.6 (6.3% vs. 1.2%; 95% CI 2.3–13.4) and 12 (2.4% vs. 0.2%; 95% CI 1.6–93.4), respectively. It should be noted that only 23 patients (4.6%) from the placebo cohort eventually received rescue thrombolysis during follow-up because of in-hospital haemodynamic deterioration, and two of these patients died within 7 days.

In conclusion, thrombolytic therapy in haemodynamically stable intermediate-risk patients with PE reduces the risk of the composite endpoint consisting of haemodynamic deterioration and death at the cost of an increase in the incidence of major haemorrhage. Therefore, thrombolytic therapy cannot be recommended for haemodynamically stable intermediate-risk patients with PE. These patients should receive standard anticoagulant therapy and close monitoring, whilst thrombolytic therapy should be reserved for patients with haemodynamic deterioration during the first days of treatment.

One randomized trial and two cohort studies evaluating outpatient treatment or early discharge for patients with PE have been completed and the results published. In the

largest study reported to date, there were initially 14 exclusion criteria (**Table 4**) and thereafter patients with a PESI class I or II were selected [45]. Patients were randomly assigned to either conventional in-hospital treatment or outpatient treatment (discharge after a mean of 0.5 days). Of the 1557 patients screened, 470 (30%) were potentially eligible for early discharge (<24 h) of whom 344 were eventually enrolled in the study. Only one of the 171 (0.6%) evaluable patients receiving outpatient treatment developed a nonfatal recurrent VTE during the 3-month follow-up, and two patients (1.2%) had a major haemorrhage within 14 days. Amongst the 168 evaluable patients treated in hospital, neither recurrent VTE nor major haemorrhage occurred within 14 days. Based on these results, the authors concluded that outpatient treatment was noninferior to in-hospital treatment [45]. A major limitation of this strategy is the complexity of scoring the 11 (items) of the PESI score combined with the many other exclusion criteria that were used in the study. Although this limitation may be partly overcome using the sPESI, it should be noted that the simplified score has not been validated in a prospective management study.

**Table 4.** Exclusion criteria in a randomized trial investigating outpatient treatment amongst PE patients with a PESI class I or II (from Aujesky et al. [45]).

| |
|---|
| Arterial hypoxaemia (oxygen saturation on room air <90% measured by pulse oximetry or a partial pressure of oxygen <60 mmHg on arterial blood gas analysis) |
| Systolic blood pressure <100 mmHg |
| Chest pain necessitating parenteral administration of opioids |
| Active bleeding or high risk of bleeding (defined as stroke during the preceding 10 days) |
| Gastrointestinal bleeding during the preceding 14 days or platelet count <75 x $10^9$/L |
| Severe renal failure (creatinine clearance <30 mL/min based on the Cockcroft–Gault equation) |
| Extreme obesity (body mass >150 kg), history of heparin-induced thrombocytopenia or allergy to heparins |
| Therapeutic oral anticoagulation at the time of diagnosis of PE (INR ≥2·0) |
| Any barriers to treatment adherence or follow-up (e.g. current alcohol abuse, illicit drug use, psychosis, dementia or homelessness) |
| Pregnancy |
| Imprisonment |
| Diagnosis of pulmonary embolism >23 h before the time of screening (to avoid enrolling already stabilized patients) |
| Previous enrolment in the trial |

**Note:** INR, international normalized ratio; PE, pulmonary embolism; PESI, Pulmonary Embolism Severity Index.

The Hestia decision rule has also been evaluated a. a selection tool for outpatient treatment (**Table 2**) [31]. In a prospective cohort study, 297 (51%) of the 581 consecutive patients with acute PE were selected for outpatient treatment of whom six (2.0%) experienced a nonfatal recurrent VTE. Two patients (0.7%) experienced a major haemor-

rhage, one (0.3%) of whom suffered fatal intracranial bleeding. The major advantages of this strategy are the clinician friendliness and the high degree of simplicity.

NT-proBNP has also been evaluated in a cohort study as a tool for selecting patients for outpatient treatment [46]. Haemodynamically stable patients with a low NT-proBNP concentration (threshold <500 pg/mL) were discharged within 24 h of diagnosis. Of the 351 patients in this cohort, 152 (43%) were treated as outpatients and none developed a recurrent VTE or major haemorrhage or died during 3 months of follow-up [46]. In the Vesta study, the results of which will be presented at the congress of the International Society of Thrombosis and Haemostasis in June 2015, a total of 550 patients were randomly assigned to the Hestia decision rule combined with an NT-proBNP test or the Hestia decision rule alone (NTR2603). Of the 275 patients managed according to the Hestia decision rule in combination with an NT-proBNP test, 34 (12%) had a concentration of NT-proBNP >500 ng/L and were managed as inpatients. None of these patients suffered from the primary outcome (30-day adverse outcome defined as PE or bleeding-related mortality, cardiopulmonary resuscitation or admission to the intensive care unit). Of the 275 patients managed according to the Hestia decision rule alone, three (1.1%; 95% CI 0.2–3.2) experienced the primary outcome, all of whom had a normal NT-proBNP level, which were determined in a post hoc analysis. Therefore, the findings of this study confirm the safety of selecting patients who can be treated as outpatients and suggest that NT-proBNP measurements are of limited additional value.

In conclusion, it has been shown that outpatient treatment of patients with PE based on the Hestia decision rule or a combination of several exclusion criteria and the PESI score is safe. Of note, neither the PESI nor the sPESI rule has been evaluated as a sole test to select patients for outpatient treatment. The combination of a clinical prediction rule, laboratory biomarkers and/or findings on imaging tests to further optimize the identification of patients who can be safely managed in the outpatient setting remains to be evaluated.

### Initial anticoagulant therapy (first 3 months)

Acute PE requires initial treatment with a direct-onset anticoagulant drug to prevent the extension of thrombosis or fatal recurrent VTE [7, 47]. Weight-adjusted subcutaneous low molecular weight heparin (LMWH) is the treatment of choice for the large majority of patients. Intravenous unfractionated heparin is reserved for patients with severe renal impairment (creatinine clearance <20–30 mL/min), patients with a high risk of haemorrhage including those receiving thrombolytic therapy, haemodynamically unstable patients and individuals who are extremely overweight or underweight. Fondaparinux is an alternative to LMWH and unfractionated heparin in patients with (a history of) heparin-induced thrombocytopenia [7, 48]. Monitoring of the anticoagulant effect of LMWH by determining the antifactor Xa activity is not generally recommended, although it can

be considered in specific circumstances (i.e. in patients with moderate renal impairment or during pregnancy). The target range measured 4 hours after administration is 1.0–2.0 IU/mL for once-daily administration and 0.6–1.0 IU/mL for twice-daily administration of LMWH [7].

Patients with acute PE should be treated for at least 3 months. For decades, vitamin K antagonists (VKAs) have been the long-term treatment of choice and must be started in parallel with one of the parenterally administered direct-onset anticoagulant drugs for at least 5 days and until the international normalized ratio (INR) has reached a therapeutic range (between 2.0 and 3.0) on 2 consecutive days. VKA therapy is highly effective with a rate of recurrent VTE of 3–4% during the initial 3 months of therapy [49]. It has been estimated that the rate of major haemorrhage during the initial 3 months of VKA therapy is 1–2% [49]. A major disadvantage of VKA therapy is the need for frequent laboratory monitoring of the INR with tailored dosing, as a result of the variable pharmacokinetic and pharmacodynamic parameters, and interactions with food and drugs [50].

In recent years, several NOACs have become available for anticoagulant therapy (**Table 5**). These drugs directly and specifically inhibit either thrombin (factor II) or factor Xa. The major advantage of this new drug class is the simplification of PE treatment, due to the rapid onset of action, the predictable anticoagulant effect and a low potential for drug and food interactions [50]. Rivaroxaban and apixaban were investigated with an initial higher dose for 3 weeks and 7 days, respectively, without the need for preceding LMWH therapy, whereas dabigatran and edoxaban were administered after a mean period of 10 days of treatment with LMWH. These drugs can be prescribed in fixed doses and routine laboratory monitoring is not required. A noninferior efficacy compared to standard treatment with VKA has been demonstrated for all NOACs individually in phase III trials [51-55] and confirmed in a meta-analysis: the risk ratio for recurrent VTE was 0.9 (95% CI 0.7–1.1) [56]. Moreover, this meta-analysis demonstrated a beneficial safety profile of NOACs in terms of bleeding complications with a risk ratio for major haemorrhage of 0.6 (95% CI 0.4–0.9); however, it should be noted that the absolute risk of major haemorrhage in real-world daily care may be higher than reported in the randomized controlled trials which applied strict patient selection criteria [57]. Based on these results and the practical advantages of NOACs, these drugs are likely to replace VKAs as the treatment of choice for the majority of patients with PE in the future.

A potential concern with regard to the NOACs is the current unavailability of specific antidotes, although the relevance of this in clinical practice may be limited due to the lower incidence of major haemorrhage as well as the shorter half-life of these drugs compared to VKAs [50]. Moreover, specific antidotes are currently under clinical investigation and are likely to become available in the coming years. The humanized monoclonal antibody idarucizumab, which is specifically designed as an antidote for dabigatran, directly binds to dabigatran with a higher affinity than thrombin and is currently being

**Table 5.** Long-term anticoagulant therapy regimens.

| Drug | Standard dose | Comments |
|---|---|---|
| **VKA** | *Individually based on INR* | - Target range INR: 2.0–3.0 |
| *Oral administration* | | |
| **LMWH**[a] | *Enoxaparin* | - Treatment of choice for cancer-associated PE for at least the first 6 months, evidence for the period beyond the first 6 months is lacking and a switch to a VKA may be considered |
| | *1.0 mg/kg b.i.d.* | |
| *Subcutaneous injection* | *1.5 mg/kg o.d.* | |
| | *Tinzaparin* | - After the first month a dose reduction to 80% of the initial dose can be considered |
| | *175 U/kg o.d.* | - Contraindicated if creatinine clearance <30 mL/min |
| | *Nadroparin* | |
| | *86 IU/kg b.i.d.* | |
| | *171/kg o.d.* | |
| **Dabigatran**[a] | 150 mg b.i.d. | - At least 5 days combined with a direct-action anticoagulant therapy (i.e. LMWH) |
| *Oral administration* | | - Almost completely renal clearance |
| | | - Contraindicated if creatinine clearance <30 mL/min |
| **Rivaroxaban**[a] | 20 mg b.i.d. | - First 3 weeks, a higher dose of 15 mg b.i.d. |
| *Oral administration* | | - Contraindicated if creatinine clearance <30 mL/min |
| **Apixaban**[a] | 5 mg b.i.d. | - First 7 days, a higher dose of 10 mg b.i.d. |
| *Oral administration* | | - Contraindicated if creatinine clearance <25 mL/min |
| **Edoxaban**[a] | 60 mg o.d. | - At least 5 days combined with a direct-action anticoagulant therapy (i.e. LMWH) |
| *Oral administration* | | - Contraindicated if creatinine clearance <30 mL/min |

**Note:** VKA, vitamin K antagonist; LMWH, low molecular weight heparin; b.i.d., twice daily; o.d., once daily; INR, international normalized ratio; PE, pulmonary embolism. [a]Approval may vary between countries.

tested in a phase III trial (NCT02104947). Andexanet alpha is a recombinant modified form of factor Xa that directly binds factor Xa inhibitors without procoagulant activity and is a potential universal antidote for the anti-Xa inhibitors as well as for LMWH. Two phase III trials have recently been initiated to evaluate the effects of andaxanet alpha in healthy volunteers (NCT02220725, NCT02207725) and a study in patients with a major haemorrhage whilst treated with a factor Xa inhibitor is planned (NCT02329327).

For the specific category of patients with cancer-associated PE, long-term LMWHs are the treatment of choice for at least the first 6 months of therapy, based on a higher efficacy [hazard ratio (HR) of recurrent VTE 0.48; 95% CI 0.30–0.77] in combination with a comparable risk of bleeding complications compared to VKA treatment [58]. Although a meta-analysis of patients with cancer included in the NOAC trials suggested a favourable efficacy and similar safety profile compared to VKAs, dedicated clinical trials comparing these drugs to LMWHs in patients with cancer are required [59]. Therefore, at present, NOACs cannot be recommended for the treatment of cancer-associated VTE. Finally, an inferior vena cava filter is a temporary alternative for patients with an absolute contraindication to anticoagulant therapy [7].

### Long-term anticoagulant therapy (after the first 3 months)

To determine the optimal duration of treatment after the initial 3 months, the perceived risk of anticoagulant therapy-associated haemorrhage should be weighed against the risk of recurrent VTE in every patient individually.

It has been estimated that the risk of major haemorrhage after the initial 3 months of therapy is 2.74 per 100 patient-years, but the risk can vary widely depending on patient characteristics [60]. Known risk factors for bleeding complications are older age, previous gastrointestinal bleeding, previous stroke, chronic renal or liver disease, alcohol abuse, concomitant antiplatelet therapy, presence of serious comorbidities and poor control of anticoagulant therapy [7]. Several clinical prediction rules derived in patients with VTE as well as those derived and validated in patients with atrial fibrillation have been investigated. However, none of these prediction rules is currently validated to use in daily clinical practice as a result of low reproducibility, a low c-statistic indicating a limited predictive value and/or the lack of validation studies [61]. Moreover, it should be noted that the case-fatality rate of anticoagulant therapy-associated major haemorrhage (13.4%; 95% CI 9.4–17.4) has been reported to be higher than that of recurrent VTE (3.6%; 95% CI 1.9–5.7), and therefore, the clinical impact of major haemorrhage may be considered to be higher than that of recurrent VTE [49, 60].

Regarding the risk of recurrent VTE, it should be emphasized that extending the duration of anticoagulant therapy only postpones a potential recurrent VTE without diminishing the VTE recurrence risk after anticoagulant therapy is stopped [62]. In patients with PE related to a transient provoking factor (e.g. recent surgery, immobilization, pregnancy or oral contraceptive use), a recurrence risk of approximately 2.5% per year is usually considered low enough to discontinue anticoagulant therapy after 3 months [7, 47]. On the other hand, the recurrence risk in patients with an active malignancy (20.7% during the first 12 months of therapy) [63], the antiphospholipid syndrome [64] or a previous episode of VTE (20.7% after 4 years of follow-up after initial 6 month therapy) [65] is considered to be high enough for guidelines to suggest that these patients should be treated for an extended or indefinite duration [7].

Because most recurrences occur shortly after cessation of anticoagulant therapy, it has been proposed that patients with a second VTE that occurred after a long interval following the first VTE may have a relatively low recurrence risk and therefore may benefit from a limited duration of treatment. However, in a recent cohort study, the incidence rate of a third VTE after an interval of >1 year following cessation of treatment for the first VTE was 12 per 100 patient-years (95% CI 7.4–19.0) and 5.6 per 100 patient-years (95% CI 2.2–12.0) in patients with an unprovoked and a provoked second VTE, respectively [66]. Therefore, differentiation based on the interval between the first and second VTE cannot be recommended for patients with an unprovoked second VTE, whereas a limited duration of treatment can be considered in patients with a provoked second VTE.

In patients with a first unprovoked PE not associated with cancer or the antiphospholipid syndrome, which is associated with a recurrence risk of at least 4.5% per year, determining the optimal duration of treatment is usually more complicated. Standard screening for inherited and acquired thrombophilia is not recommended as studies have failed to demonstrate a benefit and the predictive value for a recurrent VTE of most thrombophilic factors is relatively low [67]. Measuring the D-dimer level as a general marker of coagulation activity may be valuable for predicting the recurrence risk, although results from prospective studies were inconsistent with incidence rates varying from 3.0% to 6.7% per year after anticoagulant therapy was stopped in patients with repeated negative D-dimer test results [68, 69]. The Vienna prediction model is a recently externally validated nomogram consisting of the variables sex, location of the VTE and the D-dimer concentration and is currently being evaluated in a prospective management study [70, 71]. In this ongoing study, patients with a low-risk score (<180 points; expected 12-month recurrence risk 4.4%; 95% CI 2.7–6.2) receive anticoagulant therapy for 3–7 months, whilst therapy is continued in the remaining patients (NCT01972243). The "men continue and HER DOO2 prediction rule" consists of four variables: post-thrombotic signs, D-dimer concentration of ≥250 µg/L (whilst on anticoagulant therapy), body mass index ≥30 kg/m$^2$ and age ≥60 years. In an observational study, this score differentiated between a low-risk category with an annual risk of 1.6% (≤1 point; 95% CI 0.3–4.6) and a higher-risk group with an annual risk of 14.1% (≥2 points; 95% CI 10.9–17.3) only in women and is currently being investigated in a prospective management study (NCT00967304) [72]. Finally, the DASH score has been derived from a patient-level meta-analysis and consists of four variables: an abnormal postcoagulation D-dimer concentration, age <50 years, male sex and hormonal therapy. This score was able to differentiate between groups with an annual VTE incidence of 3.1% (95% CI 2.4–3.9) and 9.3% (95% CI 8.1–10.8) [73]. However, in the absence of results from prospective management studies, none of these scores can currently be recommended for daily clinical practice.

The major concern with the use of anticoagulant therapy for an indefinite period is the persistent risk of major haemorrhage. Therefore, alternative strategies that may be associated with a lower risk of haemorrhage have been investigated, including low-intensity VKA therapy with a target INR of 1.5–1.9 and aspirin. Low-intensity VKA therapy was less effective compared to conventional-intensity VKA therapy, with a similar risk of major haemorrhage [74]. Therefore, low-intensity VKA therapy cannot be recommended for the secondary prevention of VTE. More recently, two randomized trials have been conducted to investigate the effect of aspirin after standard anticoagulant therapy for long-term secondary VTE prevention. In the WARFASA trial, a significant reduction in VTE recurrence risk was observed from 11.2% per year for placebo to 6.6% for aspirin (OR 0.58; 95% CI 0.36–0.93), whilst the risk of major haemorrhage was similar (1/197 for

placebo vs. 1/205 for aspirin) [75]. The ASPIRE trial demonstrated only a nonsignificant decrease in the risk of VTE recurrence from 6.5% per year for placebo to 4.8% per year for aspirin (HR 0.74; 95% CI 0.52–1.05) together with a nonsignificant increase in the risk of major haemorrhage from 0.6% to 1.1% per year (HR 1.73; 95% CI 0.72–4.11) [76]. Although these results suggest that aspirin may reduce the VTE recurrence risk, it is clear that it does not provide reliable protection against recurrent VTE in comparison with long-term oral anticoagulation. Therefore, long-term secondary prevention with aspirin is not recommended by current treatment guidelines, although it may be considered as an alternative for extended treatment in patients who are unable to tolerate any type of oral anticoagulants [77].

The effects of dabigatran, apixaban and rivaroxaban on long-term secondary prevention after initial management for VTE (either DVT or PE) have also been investigated. Only dabigatran has been compared to warfarin and was shown to be noninferior (HR 1.44; 95% CI 0.78–2.64) for recurrent VTE with a nonsignificantly lower risk of major haemorrhage (HR 0.52; 95% CI 0.52–1.02) [78]. As expected, dabigatran was more effective than placebo (HR 0.08; 95% CI 0.02–0.25), whilst major haemorrhage occurred in only two of 684 patients (0.3%) versus none of 659 patients receiving placebo. Two doses of apixaban (2.5 and 5 mg twice daily) were compared to placebo for a period of 12 months after initial treatment [79]. These doses of apixaban were shown to be similarly effective with a recurrence risk of 1.7% in both groups compared to 8.8% in patients who received placebo. Remarkably, both doses were not associated with a higher risk of major haemorrhage compared to placebo. Finally, rivaroxaban for an additional 6–12 months after initial treatment demonstrated superior efficacy compared to placebo (8/602 vs. 42/594; HR 0.18; 95%CI 0.09-0.39) for recurrent VTE, whilst nonfatal major haemorrhage occurred in only four of 598 patients (0.7%) treated with rivaroxaban [80]. Although all studies were performed in highly selected groups of patients who completed initial therapy without complications and only dabigatran has been compared to VKA therapy, these findings together with the results from initial management studies suggest that NOACs are as effective as VKA therapy and have a lower risk of major haemorrhage than long-term VKA therapy. Therefore, the introduction of NOACs is likely to change the risk–benefit ratio of long-term anticoagulant therapy and may influence clinicians to extend the duration of treatment more often in selected patient groups.

## CONCLUSIONS

The standardized diagnostic management of clinically suspected acute PE allows the exclusion of PE without imaging tests in approximately 30% of patients; this proportion can be further increased using the recently validated age-adjusted D-dimer threshold.

Future studies should focus on further limiting the number of required imaging tests as well as improving the implementation of standardized management in daily clinical practice, as nonadherence decreases safety and efficiency.

PE management is becoming increasingly more stratified by developing criteria to select patients who can be safely treated in the outpatient setting, and thrombolytic therapy should be reserved for patients with haemodynamic instability or those with haemodynamic deterioration during the first days after the diagnosis of PE. The introduction of NOACs simplifies anticoagulant therapy and the associated risk of major haemorrhage seems to be lower than that of VKA therapy. Nevertheless, clinical prediction rules to estimate the risk of anticoagulant therapy-associated major haemorrhage as well as clinical prediction rules to estimate the risk of recurrent VTE are required to come to a more tailored long-term management of PE.

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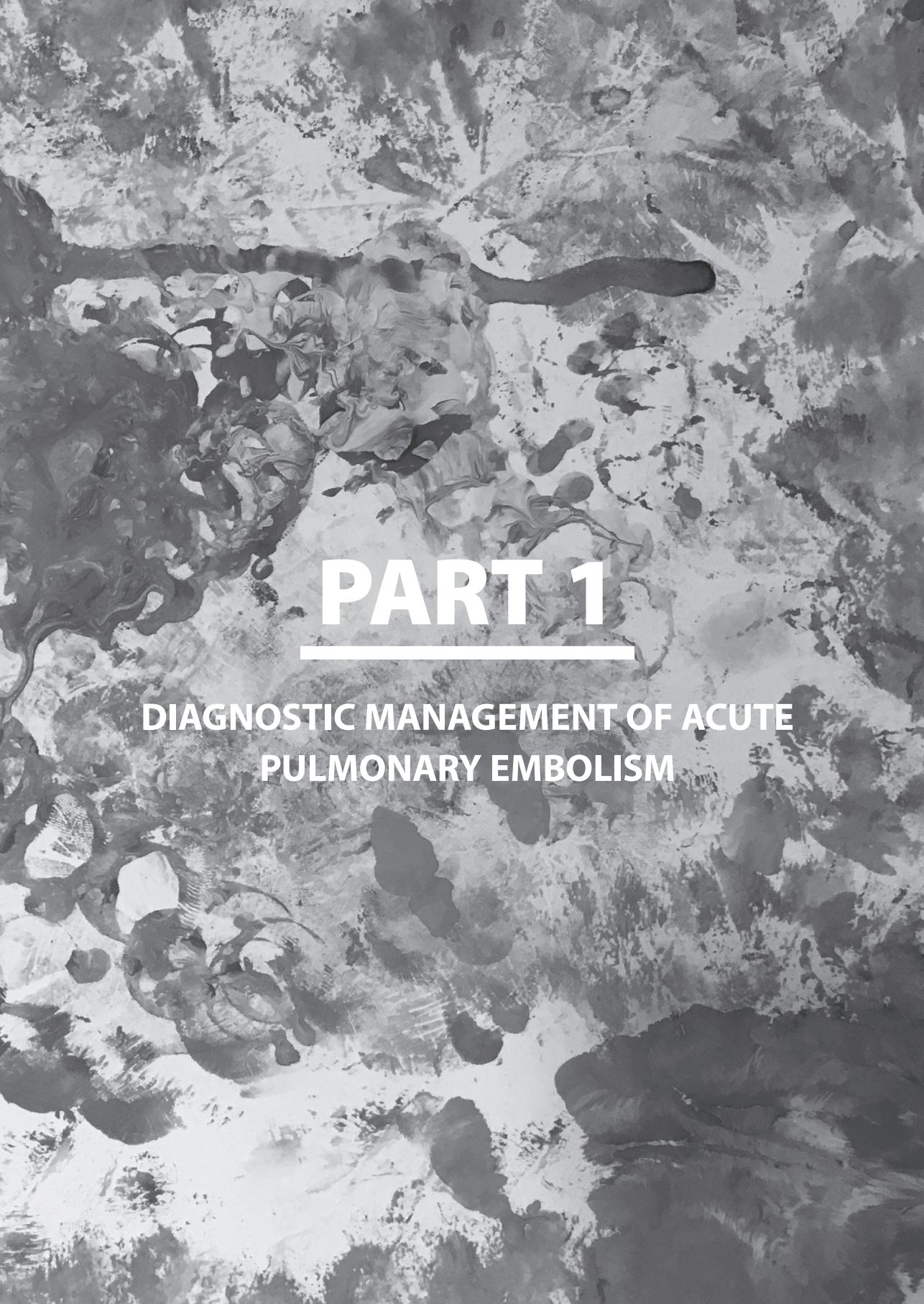

# PART 1

## DIAGNOSTIC MANAGEMENT OF ACUTE PULMONARY EMBOLISM