Clinical update

Pulmonary embolism: risk assessment and management

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Acute pulmonary embolism (PE) poses a significant burden on health and survival. Its severity ranges from asymptomatic, incidentally discovered subsegmental thrombi to massive, pressor-dependent PE complicated by cardiogenic shock and multisystem organ failure. Rapid and accurate risk stratification is therefore of paramount importance to ensure the highest quality of care. This article critically reviews currently available and emerging tools for risk-stratifying acute PE, and particularly for distinguishing between elevated (intermediate) and low risk among normotensive patients. We focus on the potential value of risk assessment strategies for optimizing severity-adjusted management. Apart from reviewing the current evidence on advanced early therapy of acute PE (thrombolysis, surgery, catheter interventions, vena cava filters), we discuss recent advances in oral anticoagulation with vitamin K antagonists, and with new direct inhibitors of factor Xa and thrombin, which may contribute to profound changes in the treatment and secondary prophylaxis of venous thrombo-embolism in the near future.

Keywords Pulmonary embolism • Prognosis • Risk assessment • Imaging • Biomarkers • Prediction rules • Anticoagulants • Thrombolysis • Embolectomy • Intervention

Clinical cases in pulmonary embolism

Case 1
A 75-year-old man who underwent left nephrectomy for renal cell carcinoma 6 months ago is admitted to the emergency department with acute severe dyspnoea and cyanosis. His blood pressure is 100 over 60 mmHg; his heart rate, 120 b.p.m. Arterial oxygen saturation is 75% while breathing room air and fails to rise under supplemental oxygen. The patient undergoes endotracheal intubation and is mechanically ventilated with 100% oxygen, which results in further drop of the arterial saturation to 65% despite correct positioning of the tube. Chest X-ray shows clear lungs without infiltrates. Transthoracic echocardiography reveals a large right ventricle with a hypokinetic free wall. What are the next diagnostic and therapeutic steps?

Case 2
A 50-year-old woman is re-admitted to the hospital with mild-to-moderate dyspnoea 10 days after surgical cholecystectomy. Physical examination reveals a swollen right calf and no further pathological findings. Acute pulmonary embolism (PE) and deep vein thrombosis are confirmed by computed tomography (CT) and ultrasonography, respectively. The patient strongly desires to be discharged immediately and receive treatment at home. Is this acceptable?

Case 3
A 60-year-old woman presents for clinical follow-up 6 months after acute PE. The event was unprovoked, i.e. no reversible predisposing factors were found, but thrombophilia screening revealed heterozygous factor V Leiden mutation; the patient is obese (body mass index, 34 kg/m2). She had an uneventful in-hospital course and was treated with vitamin K antagonists over the past 6 months without recurrence; there were a few minor bleeding episodes under warfarin. Can anticoagulation be safely discontinued now, or is the patient a candidate for indefinite secondary prophylaxis? Is regular echocardiographic follow-up necessary for early detection of chronic thrombo-embolic pulmonary hypertension (CTEPH)?

Introduction

Pulmonary embolism spans a broad spectrum of illness, ranging from asymptomatic, incidentally discovered subsegmental...
thrombus detected on chest CT scan to pressor-dependent PE complicated by cardiogenic shock and multisystem organ failure. Between these two extremes are patients with symptomatic low-risk or intermediate-risk disease.

As clinicians specializing in cardiovascular medicine, we are likely to be consulted on patients at the sicker end of the risk continuum. Our toolbox of options is rapidly expanding. For the patient without haemodynamic compromise, we can offer conventional unfractionated heparin, low-molecular-weight heparin (LMWH), or fondaparinux as a ‘bridge’ to vitamin K antagonists. More recently, oral monotherapy anticoagulation (without any injectable or intravenous anticoagulant) was reported to be safe and effective. On the other hand, some normotensive and most unstable patients will require specific advanced therapy, in addition to parenteral anticoagulation. Options for advanced therapy include placement of an inferior vena cava filter, systemic thrombolysis, open surgical embolectomy, or pharmacomechanical therapy.

This article critically reviews currently available and emerging tools for risk-stratifying acute PE as well as severity-adjusted management strategies. We also discuss the recent advances in oral anticoagulation with vitamin K antagonists, and with new direct inhibitors of factor Xa and thrombin which are being introduced into the market and may contribute to profound changes in the treatment strategy for acute venous thromboembolism in the near future.

Risk assessment in pulmonary embolism

Initial risk stratification

The key to an effective treatment of PE in the acute phase lies in the assessment of the patient’s early death risk. A crucial determinant is the presence and severity of right ventricular (RV) dysfunction resulting from acute pressure overload. The definition of high-risk (European classification) or massive (North American classification) PE is usually straightforward and relies on the presence of clinically overt RV failure which results in haemodynamic compromise. This condition, which is encountered in <5% of all patients presenting with acute PE, constitutes a medical emergency, since it is associated with at least a 15% risk of in-hospital death, particularly during the first hours after admission.

Advanced risk stratification: clinical scores

The absence of haemodynamic collapse or persistent hypotension at presentation is generally thought to predict a favourable early outcome, provided that the disease is diagnosed correctly and anticoagulation is started without delay. However, some of the (initially) normotensive patients with acute PE may have an elevated risk of death or major complications (intermediate-risk PE in Europe; submassive PE in North America) which warrants further risk stratification and possibly specific advanced therapy.

Prediction rules based on clinical findings at diagnosis can help with the prognostic assessment of patients with acute PE. These scores account both for the clinical severity of the acute event and the patient’s comorbidity. The Pulmonary Embolism Severity Index (PESI) is the most extensively validated prognostic clinical score to date. Its major strength lies in excluding (ruling out) an adverse outcome as indicated by the high negative predictive value (NPV) of the lowest PESI classes I and II. In fact, a recently published randomized trial successfully employed a low PESI score as the main inclusion criterion for home treatment of acute PE. The main limitation of the index is that it requires numerous variables and is relatively complex to calculate, which may reduce its practicability in high-volume centres. Reliable prognostic information can also be obtained with a simplified version of the score (sPESI) which focuses on six equally weighted variables: age >80 years; history of cancer; history of heart failure or chronic lung disease; systolic blood pressure <100 mmHg; pulse rate >110 b.p.m.; and arterial oxygen saturation <90%. In an external validation study, the sPESI was at least as accurate as imaging and biomarker criteria for excluding an elevated risk. The implications of this latter score for patient management remain to be shown.

Advanced risk stratification: imaging findings

Imaging of the right ventricle with echocardiography detects the changes occurring in the morphology and function of the right ventricle as a result of acute pressure overload in PE. Registries and cohort studies demonstrate an association between echocardiographic parameters of RV dysfunction and a poor in-hospital outcome. Nevertheless, the prognostic value of cardiac ultrasound in haemodynamically stable patients appears moderate at best, mostly due to the poor standardization of echocardiographic criteria. In a prospective randomized trial, normotensive patients with intermediate-risk PE (mostly) defined by echocardiography appeared to have a low early mortality risk, regardless of whether they received thrombolysis plus heparin or heparin alone. It thus appears that an abnormal echocardiogram needs to be accompanied by clinical signs indicating severe PE, or by a positive biomarker test indicating the presence of heart failure or myocardial injury (as explained below), to justify advanced therapy in normotensive patients with acute PE.

Four-chamber views of the heart on multidetector-row CT may, besides visualizing the thrombi in the pulmonary vasculature (Figure 1A and B), also detect RV enlargement and (indirectly) dysfunction (Figure 1C). The prognostic value of an enlarged right ventricle on CT was recently confirmed by an international prospective cohort study, but data from therapeutic trials are needed before it can be safely concluded that this modality can replace the echocardiogram in guiding risk-adjusted management of acute PE.

Advanced risk stratification: laboratory markers

Circulating biochemical markers have been proposed as an alternative (or additional) tool for risk stratification of normotensive patients with PE. Among these, circulating natriuretic peptides are highly sensitive indicators of neurohormonal activation due to acute and chronic heart failure. A meta-analysis of 13 studies found...
that 51% of 1132 patients with acute PE had elevated brain natriuretic peptide (BNP) or N-terminal (NT)-proBNP concentrations; these were associated with an increased risk of early death and a complicated in-hospital course. Nevertheless, their positive predictive value for an elevated risk has been consistently low. Elevated cardiac troponin I or T levels are also found in up to 50% of the patients with acute PE. A meta-analysis of studies published between 1998 and 2007, with a total of 1985 patients, showed that cardiac troponin elevation was associated with an increased risk of death and major adverse events in the acute phase. However, another meta-analysis which excluded hypotensive patients did not confirm the prognostic value of circulating troponin levels. Recently developed high-sensitivity assays may improve the prognostic performance of this biomarker, at least at the low-risk end of the severity spectrum. More specifically, a derivation study showed that high-sensitivity troponin T (hsTnT) was useful for excluding an adverse outcome in the acute phase of PE. In a multicentre, multinational cohort of 526 normotensive patients with acute PE, hsTnT exhibited a high NPV (98%) which was comparable with that of the sPESI (99%).

Heart-type fatty acid-binding protein (H-FABP) is a small cytoplasmic protein which diffuses rapidly into the circulation following myocardial cell damage. It may provide relevant prognostic information in non-high-risk PE. Cardiac expression of growth-differentiation factor-15 (GDF-15), a distant member of the transforming growth factor-β cytokine family, also increases sharply after pressure overload or myocardial ischaemia. Growth-differentiation factor-15 might be capable of integrating information on RV dysfunction, myocardial injury, and possibly co-morbidity in patients with acute PE. Both biomarkers appear promising and deserve further evaluation in external patient cohorts.

### Emerging concepts: combined parameters and scores

A critical overview of currently available and emerging prognostic tools for patients with acute PE is shown in Table 1. For the time being, no individual laboratory marker or imaging parameter has been shown to justify advanced therapy in haemodynamically stable patients with PE. Therefore, attention is shifting to prognostic models combining clinical, imaging, and biochemical parameters. Some registries and cohort studies did suggest that biomarkers may possess prognostic value additive to that of clinical parameters and echocardiography, and various combinations of the three modalities were reported to possess satisfactory predictive performance. An external validation of these scores has not yet been undertaken. At present, one large randomized trial is testing the possible implications of a combination prognostic model for the management of intermediate-risk or submassive PE. The Pulmonary Embolism Thrombolysis Study (PEITHO) is randomizing 1000 normotensive patients with acute PE, an echocardiogram (or CT scan) indicating RV dysfunction, and a positive cardiac troponin test, to receive thrombolysis with tenecteplase as opposed to heparin alone. Recruitment is completed, and the results will be available in 2013.

### Initial treatment of pulmonary embolism

**Heparin anticoagulation**

Anticoagulant treatment should be administered to all patients with high or intermediate clinical probability of acute PE, without awaiting definitive confirmation by imaging procedures. Intravenous unfractionated heparin is the preferred mode of initial anticoagulation for patients with severe renal impairment (creatinine clearance <20–30 mL/min); for those at high risk of bleeding; for high-risk, hypotensive patients; and, as a rule, for extremely overweight, underweight, or old patients. With the exception of these circumstances, LMWH or fondaparinux is given subcutaneously at weight-adjusted doses (Figure 2); routine anticoagulation monitoring, i.e. measurement of anti-factor Xa levels, is not necessary. Though controversial, obtaining these levels may be
### Table 1  Risk assessment tools in acute pulmonary embolism

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| Laboratory markers  |                                                                            |                                                                           |
|---------------------|                                                                            |                                                                           |
| Cardiac troponin I, T | Troponin elevation correlated with PE prognosis                           | Non-specific test, positive predictive value low (positive test does not justify advanced therapy) |
|                     | Sensitive test, high NPV                                                   |                                                                           |
|                     | Widely used test                                                           |                                                                           |
| Natriuretic peptides (BNP, NT-proBNP) | BNP/NT-proBNP elevation correlated with PE prognosis                      | Non-specific test, positive predictive value very low (positive test does not justify advanced therapy) |
|                     | High NPV                                                                  | Appropriate cut-off value(s) unclear                                      |
|                     | Widely used test                                                           |                                                                           |
| H-FABP              | Early marker of adverse outcome                                           | Not available for routine use at present                                 |
| GDF-15              | ‘Global’ marker of myocardial injury, heart failure, comorbidity           | Not available for routine use at present                                 |

PESI, Pulmonary Embolism Severity Index; CT, computed tomography; PE, pulmonary embolism; BNP, brain natriuretic peptide; GDF-15, growth differentiation factor-15; H-FABP, heart-type fatty acid-binding protein; NT-proBNP, N-terminal pro-brain natriuretic peptide; PA, pulmonary artery; RV, right ventricular; NPV, negative predictive value.

### Figure 2  Current and evolving anticoagulation regimens for acute pulmonary embolism.

**Overlapping**

Current standard of care

- LMWH or Fondaparinux (s.c.)
- VKA

**Switching**

- LMWH s.c. dabigatran b.i.d. / edoxaban o.d.

**Single oral drug**

- Rivaroxaban 15 mg b.i.d. for 3 weeks, then 20 b.i.d.
- Apixaban 10 mg b.i.d. for 1 week, then 5 b.i.d.

**RE-COVER** (published)

**HOKUSAI-VTE** (NCT00965154—ongoing)

**EINSTEIN-DVT/PE** (published)

**AMPLIFY** (NCT006432901—ongoing)

LMWH, low-molecular-weight heparin; o.d., once daily; s.c., subcutaneously; VKA, vitamin K antagonist. *Unfractionated heparin (continuous intravenous infusion) can be given as an alternative to LMWH; †see text and reference 90 for details of dosing regimen; ‡see text and references 6 and 85 for details of dosing regimen.
considered in patients with (moderate) impairment of renal function, and intermittently during pregnancy. In these cases, anti-Xa levels should be determined 4 h after the morning injection; the proposed target range is 0.6–1.0 IU/mL for twice-daily and 1.0–2.0 IU/mL once-daily administration. The anti-Xa assay must be calibrated separately by the laboratory for each anticoagulant that is assayed.

Anticoagulation with unfractionated heparin or LMWH/fondaparinux should be continued for at least 5 days. Oral anticoagulants (vitamin K antagonists) should be initiated as soon as possible in haemodynamically stable patients, preferably on the same day as heparin (Figure 2). Parenteral anticoagulation can be stopped as soon as the international normalized ratio (INR) has been in the therapeutic range (between 2.0 and 3.0) on 2 consecutive days.

**Thrombolysis**

Randomized trials have consistently shown that thrombolytic therapy of PE effectively resolves thrombo-embolic obstruction and promptly reduces pulmonary artery pressure and resistance with a concomitant increase in cardiac output. One trial also demonstrated a significant improvement in RV function as assessed by echocardiography. In the only randomized thrombolysis trial with clinical endpoints, early thrombolytic treatment given to normotensive patients with evidence of RV dysfunction significantly reduced the need for emergency escalation of therapy during the hospital stay.

Currently approved thrombolytic regimens for PE, and the contraindications to thrombolysis, are shown in Table 2. Overall, >90% of patients with PE appear to respond favourably to thrombolysis as indicated by clinical and echocardiographic improvement within the first 36 h. The greatest benefit is observed when treatment is initiated within 48 h of symptom onset, but thrombolysis can still be useful in patients who have had symptoms for 6–14 days.

Two recent epidemiological reports, derived from the Nationwide Inpatient Sample (representing ~20% of non-federal, short-term hospitals in the USA) and including more than 2,000,000 patients discharged between 1998 and 2008 with the diagnosis of PE, support the efficacy and safety of thrombolysis in haemodynamically unstable patients with acute PE. In the first report, case fatality rates attributable to PE were drastically lower among unstable patients who received (compared with those...
who did not receive) thrombolytic treatment [relative risk, 0.20; 95% confidence interval (CI), 0.19–0.22]. Unfortunately, only 21,390 out of 72,230 unstable (30%) patients received thrombolytic agents as recommended. In the second report,\(^5\) the overall prevalence of intracerebral haemorrhage after thrombolytic therapy was low (0.9%), although it did appear to increase in the elderly and in patients with kidney disease.

**Surgical or interventional treatment**

Pulmonary embolectomy is a recommended therapeutic option in patients with high-risk PE in whom there are absolute contraindications to thrombolysis, or if thrombolysis has failed.\(^5,53\) Recent technical advances in transportable extracorporeal assist systems, and particularly the timely early involvement of the cardiac surgeon as part of an interdisciplinary approach to high-risk PE before haemodynamic collapse, have contributed to improved postoperative outcomes and case fatality rates as low as 23%.\(^58\)

As an alternative to surgical procedures, catheter-based reperfusion is an option for patients with high-risk PE, and possibly also for selected patients with intermediate-risk PE. In case of absolute contraindications to thrombolysis, thrombus fragmentation, rheolytic thrombectomy, suction thrombectomy, or rotational thrombectomy have been performed. If no absolute contraindications are present, conventional catheter-directed thrombolysis and, more recently, pharmacomechanical thrombolysis have become available. The methods and techniques of catheter-based interventions were reviewed recently.\(^59\) Although the evidence is thus far mostly based on uncontrolled data and single-centre experience, a review of 29 retrospective and 6 prospective series yielded promising success rates.\(^60\) Two multicentre clinical trials, a randomized study in Europe and a single-arm study in the USA (NCT01166997 and NCT01513759, respectively), are currently underway to determine the efficacy and safety of ultrasound-enhanced low-dose catheter-delivered thrombolysis in intermediate-risk PE.

**Inferior vena cava filters**

Caval filters may be used as a means of primary or secondary PE prevention. However, the data on their safety and efficacy remain inconclusive. Moreover, therapeutic anticoagulation is generally very effective in preventing recurrent thrombo-embolism.\(^61\) In a meta-analysis, fatal PE occurred in 0.3–1.3% of patients during the first 3 months of treatment with heparin or warfarin.\(^62\)

On the other hand, recent epidemiological data suggest that the combination of thrombolytic therapy with the placement of a vena cava filter may be particularly effective in lowering case fatality rates in unstable patients.\(^63\) At present, retrievable inferior vena cava filters have a place mostly when anticoagulation is absolutely contraindicated, or in cases of recurrence despite therapeutic dosing of anticoagulants.\(^53\) Their widespread use in clinical practice, as recently recorded in the USA,\(^64\) may not be justified.

**Risk-adjusted management strategy**

In view of the high early mortality and complication risk associated with high-risk PE, patients who present with persistent arterial hypotension or shock are in need of immediate pharmacological or mechanical recanalization of the occluded pulmonary arteries.\(^5,7,53\) Patients with suspected high-risk PE should immediately receive a weight-adjusted bolus of unfractionated heparin; if PE is confirmed, thrombolysis should be administered without delay. If thrombolysis is contraindicated or has failed, surgical embolectomy or catheter-based reperfusion treatment are valuable alternatives.

Low-molecular-weight heparin or fondaparinux is considered adequate initial treatment for most normotensive patients. Thrombolysis may be considered in selected cases,\(^7\) such as in patients with evidence of RV dysfunction or myocardial injury, particularly if they also present with acute respiratory failure and/or are at high risk of death (due, for example, to diminished cardiopulmonary reserves and severe comorbidity), provided they have no contraindications to thrombolytic agents. A recently presented small pilot study in patients with ‘moderate’ PE suggested that a lower dose of a thrombolytic (half the standard dose of alteplase) might reduce the rate of PE recurrence and persistent pulmonary hypertension without causing excess bleeding (ACC 2012 Late-Breaking Trials; session 308). These results may be hypothesis-generating, but do not justify a change in our practice regarding the management of the intermediate-risk group or the dosing of alteplase.

A large multinational randomized trial has set out to determine whether normotensive patients with RV dysfunction, detected by echocardiography or CT, plus evidence of myocardial injury indicated by a positive troponin test, may benefit from early thrombolytic treatment.\(^52\) The primary efficacy endpoint is a clinical composite endpoint of all-cause mortality or haemodynamic collapse within the first 7 days. Six-month and 2-year follow-up is also being conducted.

Normotensive patients without serious comorbidity or signs of (right) heart failure belong to a low-risk group which could be treated out of hospital.\(^65–67\) Recently, a randomized study reported that low-risk patients as defined by the PE severity index can safely be discharged within 24 h and treated as outpatients.\(^23\) Early discharge of patients with low-risk PE is mentioned as an option in updated guidelines,\(^53\) but the appropriate criteria for identifying the patients to benefit from such treatment remain to be defined.

**Established and new oral anticoagulants in treatment and secondary prophylaxis**

**Vitamin K antagonists**

Worldwide, vitamin K antagonists such as warfarin, acenocoumarol, or phenprocoumon remain the predominant anticoagulant prescribed for PE. In 2010, for example, more than 25 million prescriptions were written for warfarin in the USA.\(^68\) Nevertheless, this is a difficult medication to utilize properly, being responsible for one-third of emergency hospitalizations due to adverse drug events in patients 65 years of age or older.\(^69\) Not surprisingly, in view of its actual and perceived bleeding risks, warfarin continues to be largely underused in clinical practice.\(^70\)

Although warfarin is an ‘old drug’, several developments have improved its profile and the quality of anticoagulation. Centralized
anticoagulation services appear to reduce the risks of warfarin compared with usual care. Certain ‘tricks of the trade’ have emerged. If the INR is out of range, it is preferable to make small and subtle changes in warfarin dosing rather than large dosing adjustments. And, counterintuitively, vitamin K supplementation can improve the stability of anticoagulation for patients with unexplained variability in response to warfarin. Some patients may have stable INRs from month to month, and thus their INR testing can be reduced in frequency to once every 12 weeks. Trials of self-testing INR at home with ‘point of care’ devices have generally been favourable, but the results are not conclusive. A recent meta-analysis of 11 trials with 6417 participants and 12,800 person-years of follow-up demonstrated a halving of thrombo-embolic events in the self-monitoring group, but no difference in major bleeding.

Rapid turnaround pharmacogenetic testing may increase the precision of warfarin dosing. In particular, variations in two genes may account for more than one-third of the dosing variability of warfarin. One gene determines the activity of cytochrome CYP2C9, the hepatic isoenzyme that metabolizes the S-enantiomer of warfarin into its inactive form, whereas the other determines the activity of vitamin K epoxide reductase (VKORC1), the enzyme that produces the active form of vitamin K. Pharmacogenetic algorithms, such as the one available at www.warfarindosing.org, incorporate genotype and clinical information and recommend warfarin doses according to the integration of these data. A randomized trial undertook a clinical effectiveness comparison of pharmacogenetic vs. standard care warfarin dosing in 1866 patients who were starting warfarin therapy. The pharmacogenetic cohort had a 10% absolute reduction in out-of-range INRs at 1 month, primarily due to fewer INR values <1.5, which coincided with a 66% lower rate of deep vein thrombosis. The pharmacogenetic cohort also had higher times in therapeutic ranges than the usual care group: 69 vs. 58% at 1 month, and 71 vs. 59% at 3 months. There are at least four ongoing large randomized, controlled trials testing pharmacogenetic testing to guide warfarin dosing: two in the USA, one in Europe, and one in Asia.

New oral anticoagulants

New oral anticoagulants are characterized by a rapid onset of action, a predictable anticoagulant effect, a specific coagulation enzyme target, and a low potential for drug or food interactions. They can be prescribed in fixed doses because of predictable pharmacokinetics, and routine laboratory coagulation monitoring is not required. Of the drugs that have completed phase 3 trials in venous thrombo-embolism, rivaroxaban competitively binds activated factor X, whereas dabigatran is a direct inhibitor of thrombin. To date, neither drug has a specific antidote. In a randomized crossover study performed in 12 male healthy volunteers, prothrombin complex concentrate rapidly reversed the effect of rivaroxaban on the prothrombin time, although it could not reverse the prolongation of coagulation parameters (activated partial thromboplastin time, ecarin clotting time, and thrombin time) caused by dabigatran. Of note, however, this study did not address clinical endpoints such as the reversibility of drug-related bleeding. If emergent bleeding must be reversed, dialysis appears to be an option for dabigatran but not for rivaroxaban, which is 95% protein bound.

The ‘Oral Rivaroxaban for Symptomatic Venous Thromboembolism’ (EINSTEIN) programme tested the efficacy and safety of oral monotherapy (replacing both parenteral anticoagulation and warfarin) with rivaroxaban to treat venous thromboembolism. EINSTEIN comprised three trials: (i) the Acute Deep Vein Thrombosis (DVT) Study; (ii) the Continued Treatment Study of DVT; and (iii) the Acute PE Study. In both the acute DVT and PE studies, the dosing regimen of rivaroxaban was 15 mg twice daily for the first 3 weeks, followed by 20 mg once daily thereafter. A higher dose was administered for 3 weeks because PE and DVT patients are considered especially hypercoagulable during this period, when the highest rate of treatment failures occur. Patients with a creatinine clearance <30 mL/min were excluded from the EINSTEIN programme. This approach differed from the dosing regimen of rivaroxaban in the atrial fibrillation trial, in which patients with a creatinine clearance between 30 and 49 mL/min received a reduced dose (15 mg rather than 20 mg once daily).

In the EINSTEIN-PE study, 4832 patients were enrolled. Recurrent venous thrombo-embolism occurred in 2.1% of patients receiving rivaroxaban compared with 1.8% of those on standard enoxaparin/warfarin therapy. Rivaroxaban was non-inferior to standard therapy ($P = 0.003$). Major or clinically relevant non-major bleeding occurred in 10.3% of rivaroxaban patients compared with 11.4% standard therapy patients ($P = 0.32$); however, major bleeding was observed in only 1.1% of patients taking rivaroxaban compared with 2.2% of those on enoxaparin/warfarin ($P = 0.003$). In particular, intracranial bleeding occurred in one rivaroxaban patient compared with 10 patients receiving standard therapy. Thus, the results of the EINSTEIN trial support the use of rivaroxaban as monotherapy for the management of acute PE. The single oral drug approach is also being evaluated in an ongoing trial testing the factor Xa inhibitor, apixaban (AMPLIFY; NCT00643201). In this latter trial, the dosing regimen of apixaban is 10 mg twice daily for the first week, followed by 5 mg twice daily thereafter (Figure 2).

Dabigatran also showed non-inferiority for the prevention of recurrent venous thrombo-embolism in patients presenting with acute PE or DVT. In the RE-COVER trial, dabigatran 150 mg twice daily was compared with warfarin for the treatment of acute venous thrombo-embolism. Patients with a creatinine clearance <30 mL/min were excluded. All patients, regardless of randomization assignment, received at least 5 days of parenteral anticoagulation, usually enoxaparin. The primary outcome was the 6-month incidence of recurrent symptomatic and objectively confirmed venous thrombo-embolism. Overall, 2564 patients were enrolled, 21% with PE only and the rest with DVT with/without PE. Parenteral anticoagulation was administered for a mean of 10 days in both groups. For the efficacy endpoint, dabigatran was non-inferior to warfarin (2.4% vs. 2.1%, respectively). The rates of major bleeding in the two groups were similar: 1.6% for dabigatran and 1.9% for warfarin. There were no intracranial bleeds with dabigatran compared with three intracranial bleeds with warfarin. There were also fewer episodes of any bleeding with dabigatran (16%) compared with warfarin (22%). The RE-COVER study supports the use of dabigatran as a fixed dose.
oral treatment for acute DVT and PE, after an initial period of par-
tenteral anticoagulation. The switch to a new oral anticoagulant (com-
pared with warfarin) following at least 5 days of parenteral anticoag-
lation is also being evaluated in an ongoing trial testing the fact 
Xa inhibitor edoxaban (Hokusai, NCT00986154) (Figure 2).

Risk of recurrence and optimal duration of anticoagulation

One of the most common dilemmas when managing patients with 
PE is to decide upon the optimal duration of anticoagulation. The 
recurrence rate of venous thrombo-embolism after discontinuing 
anticoagulation is surprisingly high. For example, in a cohort of 
1626 patients with proximal DVT or PE, the cumulative incidence 
of recurrence was 11% after 1 year, 20% after 3 years, 29% after 5 
years, and 40% after 10 years; the strongest risk factor predisposing 
to recurrent thrombosis was an initial ‘idiopathic’, unprovoked 
event.91 Another study evaluated the long-term clinical benefit of 
extending a 3-month course of oral anticoagulant therapy to 6 
months (PE associated with temporary risk factors) or to 1 year 
(idiopathic PE); patients with PE had a substantial risk for recur-
rence after discontinuation of oral anticoagulation, regardless of 
treatment duration.92 It thus appears that physicians should try 
to identify patients who are at high risk for recurrence and there-
fore potential candidates for indefinite oral anticoagulant therapy. 
This recommendation is supported by data showing that patients 
who receive extended anticoagulation are effectively protected 
from recurrent thrombo-embolism while on therapy.85,93

What determines recurrence risk after acute PE? In a cohort of 
929 patients, 19% of whom had recurrent venous thrombo-
embolism after a median of 43 months following discontinuation 
of anticoagulation, the most important risk factors for recurrence 
were idiopathic, rather than provoked; PE, male gender; location of 
the thrombotic event (proximal DVT > calf DVT and PE > prox-
imal DVT); and elevated D-dimer levels.94 Other reported risk 
factors include excess body weight95 and persistent RV dysfunc-
tion at hospital discharge after acute PE.96 An association has also been 
reported with immobilization, cancer, chronic obstructive pulmon-
ary disease, low high-density lipoprotein cholesterol, and a positive 
family history.97

A literature review found that >50% of patients with PE had re-
sidual thrombi on CT imaging 11 months after the initial event98; 
this rate was lower, ~30%, when lung scan was used for follow-
up.99 However, the clinical relevance of these findings remains 
unclear and certainly does not support basing the duration of 
anticoagulation therapy on serial imaging tests. Moreover, and 
perhaps counterintuitively, most thrombophlias do not appear to 
be associated with an elevated risk of recurrent venous thrombo-
embolism.100

Current guidelines recommend 3 months of anticoagulation in 
patients with PE provoked by surgery or by a non-surgical transient 
risk factor.5,53 Patients with an unprovoked PE will need evalua-
tion for the risk–benefit ratio of extended anticoagulation therapy after 
the first 3 months of treatment. Nevertheless, many patients reside 
in a ‘grey zone’ where personalized assessment is required to 
decide on the optimal duration of anticoagulation.97

In a recent investigator-initiated, double-blind study, patients 
who had completed 6–18 months of oral anticoagulation after a 
first episode of unprovoked venous thrombo-embolism were ran-
domly assigned to aspirin, 100 mg daily, or placebo for 2 years.101 
Recurrence occurred in 28 of the 205 patients (6.6% per year) on 
aspirin vs. 43 of 197 (11.2% per year) on placebo (hazards ratio, 
0.58; 95% CI, 0.36–0.93). Although the relative proportion of pla-
telets in venous thrombi is low, they participate by releasing poly-
phosphates, microparticles, and proinflammatory mediators, and 
by interacting with neutrophils to generate DNA–histone–
granule constituent complexes.102 Clearly, any protection offered 
by aspirin is inferior to that provided by vitamin K antagonists 
and new oral anticoagulants; however, if these results are con-
firmed by larger trials, aspirin might find a place in long-term sec-
ondary prophylaxis for selected patients with high bleeding risk.

Early discharge and outpatient treatment

The traditional approach to venous thrombo-embolism manage-
ment has been to treat most DVT patients as outpatients and to 
treat virtually all PE patients initially in the hospital. With the devel-
opment of more precise tools for accurate and rapid risk stratifi-
cation, and with the availability of new oral anticoagulants and 
simplified regimens, the decisions about whether to hospitalize 
and the optimal duration of hospital stay may soon warrant 
re-examination.

It is usually straightforward to identify the patients who are not 
candidates for outpatient treatment. Clearly, patients with severe 
comorbidity and a predicted high potential for adverse outcomes 
should be hospitalized. These patients have consistently been 
excluded from prospective management (cohort) studies focusing 
on home treatment4,52 (exclusion criteria reviewed in Lankeit and 
Konstantinides106). Many will require supplemental oxygen, paren-
teral analgesics or antibiotics, or specific treatment for concomi-
tant disease, and they may be considered for advanced therapy 
such as systemic thrombolysis, pharmacomechanical catheter-
directed therapy, surgical embolectomy, or a vena cava filter. 
Another crucial factor besides the patient’s medical prognosis is 
the presence of an adequate social safety net to ensure strict ad-
herence to the prescribed anticoagulation regimen.

A randomized trial of 344 patients with low-risk PE (PESI risk 
class I or II) was undertaken to determine the safety and effective-
ness of outpatient treatment.13 After randomization to outpatient 
treatment, patients were contacted by the study staff daily for 7 
days, and then on days 14, 30, 60, and 90. Outcomes were excel-
 lent in both groups. Only one patient in the outpatient group and 
none in the inpatient group had recurrent venous thrombo-
embolism within 90 days. Only two outpatients and no inpatients 
had major bleeding. With this model of assiduous outpatient 
care, which may be feasible in the Netherlands106,65 and a few 
other European countries, it appears that low-risk patients with 
PE can be safely and effectively treated without (or with very 
short) hospitalization. Whether the home treatment concept is 
likely to carry over to other, larger parts of the ‘real world’ in 
the future remains to be determined.
Conclusions and outlook

Although case fatality rates appear to have dropped over the past two decades, acute PE continues to pose a serious burden on health and survival. Rapid and accurate risk stratification is of paramount importance to ensure the highest quality of care. We must first classify patients as ‘stable’ or ‘unstable’, i.e. distinguish between high-risk and non-high-risk PE. This dichotomy will help us to optimize patient management. High-risk PE clearly warrants immediate thrombolytic, surgical, or interventional reperfusion therapy. However, the intensive search continues for an intermediate-risk group among normotensive patients who will benefit from advanced therapy in addition to anticoagulation. The large European randomized trial, PEITHO, may yield some answers shortly. Significant progress has been made in the field of anticoagulation with the optimization of treatment with vitamin K antagonists and the encouraging results of trials using new oral anticoagulants. Emerging management strategies may simplify secondary prevention in the future and help to resolve the persistent controversy over the optimal duration of anticoagulation after acute PE.

Resolution of cases

In Case 1, we are dealing with a patient who most likely has high-risk (massive) PE, even if he does not fulfil all formal criteria of haemodynamic instability or cardiogenic shock. This is an emergency situation. The patient’s persistent respiratory insufficiency and ‘paradoxical’ further aggravation of hypoxaemia after endotracheal intubation is a particular reason for concern. We strongly recommend bedside contrast echocardiography, as the most probable explanation is the presence of a patent foramen ovale, which is now wide open due to the increased right atrial pressure and leads to severe right-to-left shunting. In view of the patient’s persistent tachycardia, marginally low blood pressure, and intractable hypoxaemia, we would not demand further confirmation of the diagnosis by CT; instead, we would immediately proceed to systemic thrombolysis with 100 mg of alteplase administered over 2 h.

In Case 2, we need to make clear to the patient that immediate discharge and out-of-hospital anticoagulation is not (yet) a widely accepted treatment option for PE. Even if the calculation of the (simplified) PESI yields a low risk, the patient may still have a residual risk for early complications which needs to be further clarified by future management trials; besides, most studies on home anticoagulation have thus far excluded obese patients. New oral anticoagulants may facilitate home treatment of PE in the future, but they are not yet approved for this indication. Therefore, we would recommend a brief (4–6 days) hospitalization to ensure that parenteral anticoagulants are administered properly and that overlapping administration of a vitamin K antagonist results in a therapeutic INR (2.0–3.0) for 2 consecutive days.

In Case 3, the patient has completed the minimal duration of anticoagulation after a first episode of unprovoked PE. Unequivocal indications for indefinite anticoagulation, such as active cancer or the antiphospholipid antibody syndrome, are not present in this case. The patient is obese and has heterozygous thrombophilia; these conditions increase the risk of recurrence moderately and may not mandate lifelong treatment according to current guidelines. As the patient also reported repeated episodes of minor bleeding during the past 6 months, we would recommend optimization of anticoagulation, perhaps at a lower than standard intensity such as targeting an INR range of 2.0 to 2.5. We would also strongly encourage lifestyle modification and physical activity with weight loss. An alternative approach would be to interrupt treatment for 1 month and then resume anticoagulation (only) if the d-dimer test is positive. Finally, although one study indicated that CTEPH may develop in as many as 3.8% of patients 2 years after acute PE, the true incidence of the disease is probably lower, and the recent data from a large population with idiopathic PE did not provide support for routine echocardiographic follow-up in search of developing CTEPH. We would recommend 6-month echocardiographic follow-up of a patient with elevated pulmonary artery pressure at discharge, but acknowledge that the issue remains unsettled. The randomized PEITHO trial will include a 2-year prospective follow-up to determine whether thrombolysis of intermediate-risk PE may, among others, prevent the development of CTEPH over the long term.

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52. The PEITHO Steering Committee. Single-bolus tenecteplase plus heparin compared with heparin alone for normotensive patients with acute pulmonary embolism who have evidence of right ventricular dysfunction and myocardial injury.


