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Acute Pulmonary Embolism. Part 2:
Treatment CME



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Abstract and Introduction

Abstract

The clinical presentation of pulmonary embolism (PE) varies widely, ranging from only limited symptoms to severe cardiogenic shock. Treatment of PE comprises initial therapy—with low-molecular-weight heparin (LMWH), fondaparinux, or unfractionated heparin—and long-term treatment, most commonly with vitamin-K antagonists (VKAs). Methods of risk stratification, to determine whether a patient will benefit from thrombolysis, are currently under investigation. However, at present, insufficient evidence exists that hemodynamically stable patients who demonstrate echocardiographic right ventricular strain (submassive PE) benefit from thrombolysis. By contrast, thrombolysis is a widely accepted treatment strategy for patients with hemodynamic shock (massive PE). The duration of VKA treatment is commonly 3-12 months and depends on the type of PE and on the balance between the risks of recurrent PE, major bleeding, and the patient's preference. In patients with a malignancy, treatment with LMWH during the first 6 months after diagnosis of PE is recommended. Several new oral anticoagulants, such as factor IIa and factor Xa inhibitors, are now being investigated. For prevention of recurrent PE in situations where anticoagulation is contraindicated, a temporary inferior vena cava filter might be useful. Some patients with PE can be safely treated at home, but few outcome studies in this setting have been published.

Introduction

Despite the long history of research on the diagnosis and prognosis of pulmonary embolism (PE), the disease remains a cause of high mortality with a case-fatality rate without treatment of up to 15% in normotensive patients, rising to 58% in patients with cardiogenic shock, which exceeds mortality for acute myocardial infarction.^[1] The incidence of venous thromboembolism (VTE)—comprising PE and deep-vein thrombosis (DVT)—is high, particularly among elderly individuals (>75 years) and is, therefore, a major health problem.^[2-4] The clinical presentation of PE varies widely. Some patients are asymptomatic or have only limited symptoms caused by small, and often peripheral, emboli. Others experience the more severe complaints of dyspnea, tachycardia, pain on exertion, syncope, or cardiogenic shock, which are caused by multiple, larger, or more-centrally located emboli. Patients with a high thromboembolic load, low cardiac reserve, or both often experience rapid hemodynamic deterioration. The patient's risk of death mainly depends on the presence or absence of hemodynamic instability and the severity of underlying diseases.^[1,5] The epidemiology and diagnosis of PE are discussed in detail in Part 1 of this Review.^[4]

The landmark randomized trial by Barritt and Jordan, published in 1960, was the first to demonstrate that patients with PE benefit from anticoagulant therapy.^[6] This treatment can be administered intravenously as unfractionated heparin (UFH), subcutaneously as low-molecular-weight heparin (LMWH), fondaparinux, or UFH, or orally as vitamin-K antagonists (VKAs). Furthermore, novel oral anticoagulants, such as selective factor IIa or Xa inhibitors, are currently under investigation and could potentially facilitate and improve the treatment of VTE. Although PE can be effectively treated, short-term and long-term sequelae characterize its clinical course. In Part 2 of this Review, we discuss the initial and long-term treatment of PE, including the use of established and novel anticoagulants. We also consider the treatment of PE in patients with comorbid conditions, such as cancer and the antiphospholipid syndrome, and in pregnant women.

Initial Therapy for PE

The choice of initial therapy for patients with PE depends on their risk of severe hemodynamic complications or mortality during the first weeks after diagnosis. Risk stratification is necessary to identify patients who would benefit from a more aggressive approach to treatment than is usually taken.

Risk Stratification

When an embolus occludes one or more of the pulmonary arteries, impaired blood flow and increased right ventricular (RV) afterload can lead to RV dysfunction, which, in combination with hypotension, carries a high mortality risk. Depending on the hemodynamic situation, patients with PE and subsequent RV dysfunction can roughly be divided in two categories: high-risk individuals with 'massive' PE, who have a systolic blood pressure ≤ 90 mmHg or a pressure drop of ≥ 40 mmHg for at least 15 min; and lower-risk patients with 'submassive' PE, whose blood pressure is preserved, but whose RV function is impaired.^[7] Of note, the term 'massive' in this context denotes hemodynamic instability caused by the thrombi, rather than the degree of obstruction. For example, patients can develop a large saddle embolus (that is, a clot that occupies the arterial bifurcation and blocks both branches) without becoming hypotensive. Conversely, patients with several diffusely located peripheral emboli can be hemodynamically unstable.

Although massive PE is rare, representing less than 5% of cases, mortality is higher in patients with massive PE than in normotensive patients with PE.^[1,8] In the MAPPET registry,^[9] PE-related mortality in patients with cardiac arrest, cardiogenic shock, and arterial hypotension was 60%, 23%, and 14%, respectively.

Several tools have been investigated to identify RV dysfunction in normotensive patients with acute PE. The prevalence of RV dysfunction among patients with PE has been reported as 27-40% as assessed by echocardiography and 22-70% as assessed by CT scans.^[8,10]

The presence of RV dysfunction as demonstrated with these imaging tools, however, has a limited positive predictive value (PPV) for mortality (5-12%^[10,11] and 10%^[12] for echocardiography and CT, respectively). The use of these techniques is also restricted by the lack of standardized criteria for the diagnosis of RV dysfunction and the often limited use of echocardiography in this setting.

In addition to these imaging techniques, biomarkers, such as troponins (I or T) and N-terminal pro-brain natriuretic peptide (NT-proBNP), have been evaluated for their sensitivity and predictive value, either alone or in combination, for risk stratification of patients with PE.^[13,14] In a meta-analysis assessing normotensive patients with PE, 21% had elevated troponin levels and mortality among these patients was 18% (odds ratio [OR] 5.9, 95% CI 2.68-12.95).^[14] In addition, Ten Wolde *et al.* reported that the PPV of BNP level >21.7 pmol/l for PE-related death was 17% (95% CI 6-33%).^[15] The negative predictive value for an uneventful outcome of a BNP level of <21.7 pmol/l was 99% (95% CI 93-100%). Combining the tests for NT-proBNP and troponin T increases the PPV to 33%.^[16]

Despite the increased risk of adverse outcomes in patients with RV dysfunction or elevated levels of cardiac biomarkers, the use of these risk stratification tools is limited by the many different cut-off values that have been reported in the literature and the high prevalence of these clinical features among normotensive patients with PE (low specificity for adverse outcomes). Selecting patients for thrombolysis on the basis of elevated biomarker levels or RV dysfunction seen on echocardiograms or CT scans can, therefore, lead to misclassification and expose a substantial proportion of patients to a high risk of major bleeding.^[17] We advocate treating these patients in a similar way to low-risk patients, until further research has demonstrated that risk stratification is effective and without the disadvantages that currently limit its use.

Low-risk Patients

Patients with PE who do not have signs of hemodynamic instability or RV dysfunction have the lowest short-term mortality risk among those with the disease.^[16] Initial therapy for these individuals comprises either subcutaneous LMWH or fondaparinux,^[18] or UFH given intravenously or, very rarely, subcutaneously (Table 1).^[19,20] However, LMWH or fondaparinux are usually preferred because, when compared with intravenous UFH, they rarely require monitoring and are both associated with fewer recurrent thrombotic events (3-month recurrence rate: LMWH 3.0% versus UFH 4.4%, OR 0.68, 95% CI 0.42-1.09;^[20] fondaparinux 3.8% versus UFH 5.0%, absolute difference 1.2%, 95% CI 3.0-0.5%),^[21] and because LMWH results in a lower incidence of major bleeding (LMWH 1.3% versus UFH 2.1%, OR 0.67, 95% CI 0.36-1.27).^[20] UFH is preferred in patients with an increased risk of bleeding or those for whom thrombolysis is being considered, because its short-acting effect can be directly reversed with protamine sulfate. UFH is also indicated in patients with severe renal impairment (creatinine clearance <30 ml/min) because most LMWHs, with the exception of tinzaparin sodium, undergo renal clearance.^[22,23] UFH could also be indicated in patients with extreme obesity, for whom the correct dose of LMWH is unpredictable and necessitates laboratory monitoring (activated partial thromboplastin time can only be used for UFH, not for LMWH). Although monitoring of LMWH or fondaparinux is possible with an anti-factor-Xa assay, this test is not available in the majority of hospitals.

Table 1. Drugs and Dosages for the Initial Treatment of PE⁸⁹

Fondaparinux	Body weight <50 kg: 5.0 mg Body weight 50–100 kg: 7.5 mg Body weight >100 kg: 10.0 mg Administered subcutaneously daily
Unfractionated heparin	Bolus of 5,000 U followed by intravenous infusion adjusted to the aPTT
Low-molecular-weight heparin	0.6–1.0 IU/ml (depending on the patients' body weight) for once-daily or twice-daily administration
Abbreviations: aPTT, activated partial thromboplastin time; PE, pulmonary embolism.	
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Patients with a history of surgery, trauma, or a gastrointestinal bleed or ulcer in the previous 4 weeks, or those with a predisposing factor, such as thrombocytopenia, are at increased risk of major bleeding when receiving anticoagulant medication. In general, the risk of major bleeding during initial anticoagulant therapy is 1.4% for LMWH and 2.3% for UFH.^[24]

Heparin-induced thrombocytopenia (HIT, reduced platelet count) is a rare, but serious, complication of UFH therapy, (2.7%, 95% CI 1.3–5.1%) and, to a lesser extent, of LMWH (0%, 95% CI 0–1.1%).^[25] HIT is extremely rare when fondaparinux is used and this agent has a very low cross-reactivity with HIT-antibodies *in vitro*.^[26] The risk of this prothrombotic condition is higher in women than in men (OR 2.37, 95% CI 1.37–4.09, $P = 0.0015$)^[27] and in surgical patients compared with those receiving medical (nonsurgical) treatment (OR 1.61, 95% CI 1.24–2.08, $P = 0.0003$), with ORs for the orthopedic and cardiac subgroups of 1.51 ($P = 0.009$) and 1.92 ($P = 0.006$), respectively.^[28] For patients with strongly suspected or confirmed HIT, whether or not complicated by thrombosis, an alternative anticoagulant, such as lepirudin, argatroban, bivalirudin or danaparoid, can be given. VKA therapy should be avoided until after the platelet count has substantially recovered.^[29]

Patients with Submassive PE

For normotensive patients with PE who have right ventricular (RV) dysfunction—so-called 'submassive' PE—the benefit of thrombolysis is undefined.^[1] These patients are, therefore, initially treated in the same way as low-risk patients with 'nonmassive' PE (that is, those who are hemodynamically stable with no RV dysfunction). However, risk stratification to investigate if thrombolytic therapy might be useful in patients with submassive PE is currently under investigation. Thrombolytic therapy accelerates clot lysis, when compared with non-thrombolytic therapy, resulting in faster restoration of lung perfusion and a decrease in RV overload. The short-term mortality in patients with submassive PE who do not undergo thrombolysis but receive regular therapy varies from 0% to 5%, which is significantly lower than in patients with massive PE.^[30,31]

To date, two randomized, placebo-controlled trials have evaluated the efficacy of thrombolytic therapy in patients with submassive PE. Konstantinides and colleagues showed that early treatment with heparin plus alteplase (recombinant tissue plasminogen activator) could improve the clinical course of patients with acute submassive PE ($n = 256$) when compared with heparin alone, and particularly reduced the need for emergency escalation of treatment.^[32] However, the latter finding has been debated owing to its subjectivity; physicians were permitted to break the randomization code before the decision to escalate treatment, and patients undergoing thrombolysis with alteplase might then have been treated differently to those receiving heparin alone. In this study, no difference in mortality between the treatment groups was reported.^[32] This trial was included in a meta-analysis, together with five other studies focusing on hemodynamically stable patients ($n = 494$).^[33] Again, no difference in mortality between patients treated with thrombolysis and patients treated with heparin alone was found (3.3% versus 2.4%, OR 1.16, 95% CI 0.44–3.05).^[33] A more-recent exploratory analysis of 58 hemo-dynamically stable patients showed that treatment with heparin plus a single bolus of tenecteplase was feasible and was associated with a significant reduction in right to left end-diastolic dimension ratio during the 7-day follow-up ($P = 0.043$) when compared with treatment with heparin plus placebo.^[34] Moreover, the use of the combined anticoagulant and thrombolytic therapy raised no safety concerns.^[34] However, clinical benefit was not an end point in this study and needs to be further investigated. To this end, the clinical benefit of thrombolysis in normotensive patients with PE, RV overload, and elevated troponin levels is being investigated in

the ongoing PEITHO trial.^[35] In the absence of clear benefit of thrombolysis in patients with submassive PE, these patients should still be treated in the same way as low-risk patients.^[36]

Patients with Massive PE

Patients with massive PE are at high risk of adverse events, such as hypotension, hypoxia, and RV dysfunction, as well as cardiac morbidity and mortality. Given the short-term resolution of emboli and the suggested beneficial hemodynamic effect of thrombolysis, together with the often critical clinical status of the patient, systemic thrombolysis is currently widely accepted as the first-line treatment in hemodynamically unstable patients with PE.^[1,18,37,38] The thrombolytic drug (urokinase, streptokinase, or tissue-type plasminogen activator) is usually administered systemically (Table 2). However, the available evidence on the benefit of thrombolytic therapy in patients with massive PE is modest and ambiguous, particularly with regard to long-term benefit during the months following presentation.

Table 2. Thrombolytic Regimens for PE*

Thrombolytic agent	Regimen
Tissue plasminogen activator	100mg intravenously for 2 h
Streptokinase	250,000 U intravenously during the initial 30 min, then 100,000 U/h for 24 h [‡]
Urokinase	4,400 U/kg intravenously during the initial 10 min, then 4,400 U/kg/h for 12 h
<p>*aPTT should be measured when infusion of the thrombolytic therapy is complete. Heparin should be resumed without a loading dose when the aPTT is less than twice its upper limit of normal.⁸ Regimens with short infusion times (2 h) are recommended over those with a prolonged infusion time (24 h).^{18,90} Thrombolytic therapy should be administered intravenously instead of placing a pulmonary catheter.⁸</p> <p>[‡]Monitor closely for hypotension, anaphylaxis, asthma, and allergic reactions. Abbreviations: aPTT, activated partial thromboplastin time; PE, pulmonary embolism.</p>	

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To date, only one randomized controlled trial of thrombolysis in patients with massive PE ($n = 8$) has been published.^[39] This trial was stopped prematurely by the ethics committee, because survival was significantly greater among patients who received thrombolysis than in those allocated to heparin. The evidence on the effect of thrombolytic therapy in massive PE is further called into question by the fact that, in most studies of this intervention, no distinction is made between patients with hemodynamic instability and those who were normotensive. Wan *et al.* conducted a meta-analysis of five studies focusing on patients with massive PE and cardiac shock ($n = 254$).^[40] The investigators found that thrombolysis was associated with a significant reduction in recurrent PE and death compared with heparin (OR 0.45, 95% CI 0.22-0.92).^[40] By contrast, data from 108 patients with massive PE who were enrolled in ICOPER^[41] showed no difference in mortality or recurrence of PE at 90 days between those receiving thrombolytic therapy and those receiving heparin. 90-day mortality was 46.3% (95% CI 31.0-64.8%) in patients receiving thrombolytic therapy and 55.1% (95% CI 44.3-66.7%) among those who did not undergo thrombolysis.^[41]

The drawback of thrombolysis is the risk of bleeding. According to the most recent meta-analysis and Cochrane collaboration review, which were published in 2004 and 2006, respectively, the risk of major bleeding with thrombolytic therapy is nonsignificantly increased compared with treatment with heparin alone.^[40,42] The incidence of intracranial hemorrhage associated with thrombolytic therapy has been reported to be around 3%.^[1] Catheter-directed thrombolytic therapy is another available strategy, but evidence is lacking for the efficacy of this treatment in patients with acute PE.^[43,44]

Embolectomy is indicated in patients with arterial hypotension in whom thrombolysis has failed or is contraindicated owing to a high risk of bleeding.^[18] Embolectomy can either be performed surgically or by using percutaneous catheters.^[45,46] Surgical removal of the embolus is performed by a median sternotomy and opening of the pulmonary artery, with extracorporeal support of the circulation, followed by either aspiration or mechanical removal of the clot(s).^[47] Catheter-based embolectomy can be either rheolytic or rotational. Rheolytic embolectomy involves

maceration of the embolus with pressurized saline, whereas in rotational embolectomy a rotating device on the catheter is used to fragment the embolus. Both catheters subsequently aspirate the embolus. Balloon angioplasty is an alternative to rheolytic and rotational embolectomy; the balloon compresses the embolus against the vessel wall and fragments the thrombus with distal embolization.^[46]

The choice between surgical or catheter-based embolectomy depends on the availability of resources and expertise of the physician, since surgical embolectomy can only be performed in large, specialized centers. A comparison between the surgical and the catheter based techniques has not been performed and, more importantly, neither has a randomized clinical trial to investigate the comparative efficacy of these approaches. Catheter-based embolectomy should, therefore, be restricted to patients in whom thrombolysis is indicated, but is not feasible, except in centers where adequate expertise is available.^[18]

Patients with a High Risk of Bleeding

PE can be treated by interrupting the vena caval flow using an inferior vena cava (IVC) filter if anticoagulant or thrombolytic therapy is contraindicated or the patient has a high risk of bleeding. IVCs allow blood to flow while preventing large emboli from travelling from the pelvis or lower extremities to the lung.^[48] Absolute contraindications to thrombolysis include hemorrhagic stroke, closed head trauma, and ischemic stroke within the previous 3 months.^[49]

IVC filters can be permanent or retrievable. Retrievable filters can be removed through the jugular vein; however, those that have been in place for a few weeks can be overgrown by cells from the IVC wall, with a risk of IVC injury if the filter is dislodged.^[50] Retrievable IVC filters can be removed up to 1 year after placement. However, removal of the filter becomes more complicated as the duration of placement increases.^[51,52] Patients with an IVC filter are recommended to receive a conventional course of anticoagulant therapy when the risk of bleeding is diminished, for example when a surgical procedure was uncomplicated or with increasing postoperative duration.^[18,53] Currently, insufficient data exist to allow a comparison between the safety and efficacy of various types of IVC filters. In the randomized PREPIC trial,^[54] the incidence of PE in patients with DVT who received a permanent IVC filter in addition to anticoagulant treatment was reduced after 12 days, and after 2 and 8 years when compared with anticoagulant therapy alone. However, combined therapy led to an increase in the incidence of recurrent DVT. Total mortality and the incidence of post-thrombotic syndrome were the same in both groups.^[54] No randomized trials or prospective cohort studies have been performed to evaluate IVC filters as monotherapy, without concurrent anticoagulation, in patients with PE. Consequently, the use of IVC filters is restricted to patients with PE who have a temporary contraindication to anticoagulant treatment. If a permanent IVC filter is inserted and the patient's bleeding risk is acceptable, long-term anticoagulant treatment is indicated.^[18]

Long-term Treatment

In all patients with PE, long-term anticoagulant treatment is required to prevent (symptomatic) extension of the thrombus and recurrence of the disease. Treatment with an orally administered VKA is still the mainstay of long-term anticoagulation therapy. VKA administration can usually be started immediately after diagnosis of PE—together with LMWH, UFH, or fondaparinux—and the effective range of anticoagulation (International Normalized Ratio [INR] 2-3) is reached after 5-10 days. Initial treatment with LMWH, UFH, or fondaparinux can only be stopped after the INR remains above 2.0 for at least 24 h.^[18]

The risk of recurrent PE after stopping long-term anticoagulant therapy is approximately 10% in the first 2 years after treatment has begun.^[38,55] Recurrence risk is primarily determined by the patient's intrinsic risk.^[18] If the thrombotic episode was provoked by a reversible risk factor, such as surgery or trauma, the incidence of recurrent VTE after stopping VKA therapy is lower at 2 years than if VTE was unprovoked (0% versus 19%; Figure 1).^[56] In 1995, Schulman and colleagues showed that 6 weeks of treatment with a VKA resulted in a higher recurrence rate of VTE compared with treatment for 6 months.^[57] Subsequently, two studies of patients with VTE showed that the rates of recurrence and major bleeding were comparable after 3 months and 6 months of therapy (Table 3).^[58,59] In addition, Agnelli and colleagues found that 12 months of treatment with a VKA resulted in similar rates of recurrence (~16%) to those of 3 months of treatment (Table 3).^[60] Rates of major bleeding were 1.5% and 3% for patients who received 3 months and 12 months of therapy, respectively.^[60] Most major bleeding episodes occur in the first 3 months of treatment.^[56] In addition, the risk of a major bleeding rises with patient age.^[61] Consequently, the decision to continue treatment beyond 12 months should be individually determined, taking the patient's preferences into consideration,

and should be reassessed periodically.^[18]

Table 3. Outcomes of Short-term and Long-term Treatment in Patients with PE

Study	n	Major hemorrhage (%)			Recurrence of VTE (%)		
		3 months	6 months	12 months	3 months	6 months	12 months
Campbell <i>et al.</i> ⁵⁸	749	0	2	NR	8	7	NR
Pinede <i>et al.</i> ⁵⁹	736	2	3	NR	8	9	NR
Agnelli <i>et al.</i> ⁶⁰	267	1.5	NR	3	16	NR	16
Abbreviations: NR, not reported; PE, pulmonary embolism; VTE, venous thromboembolism.							
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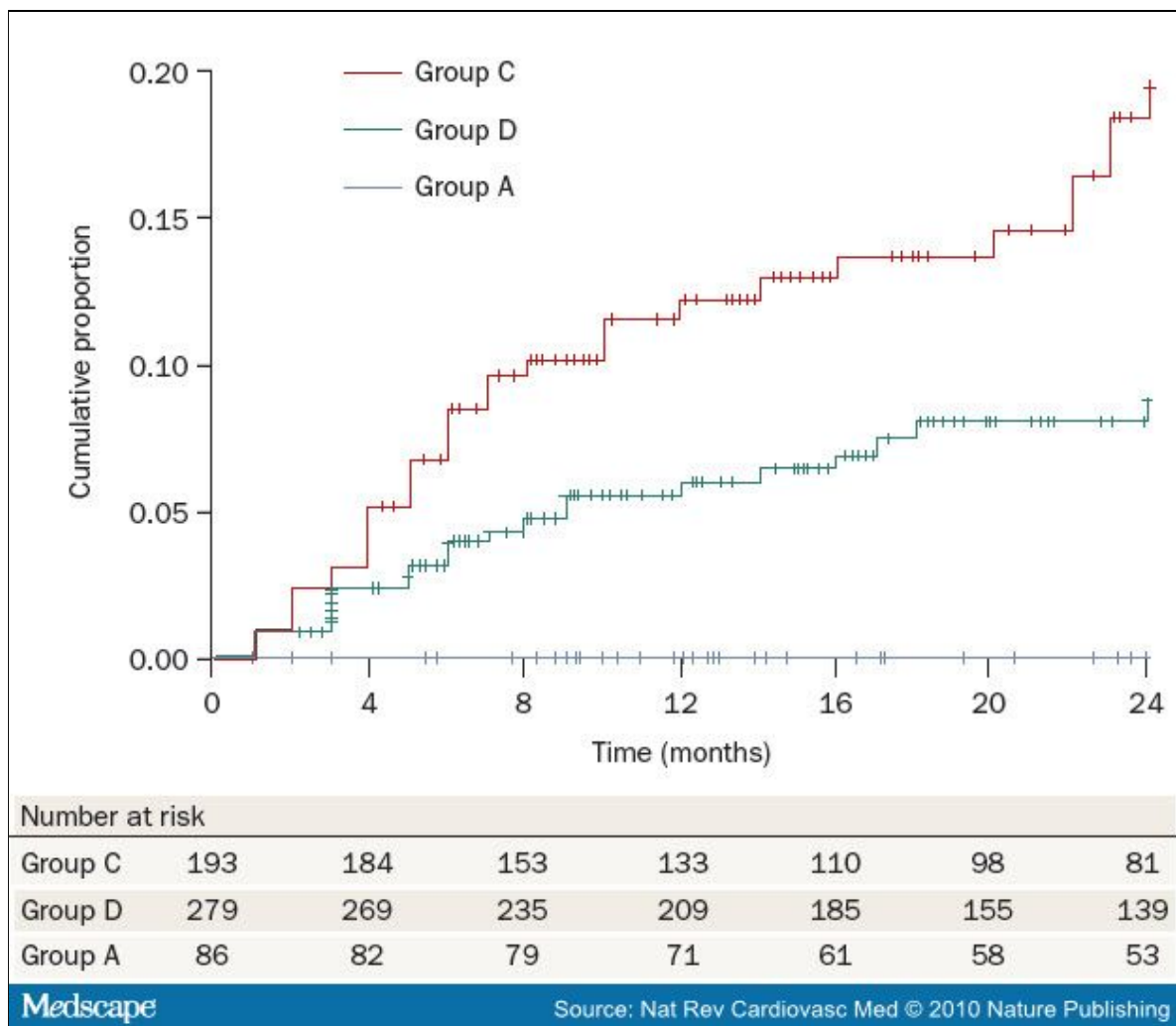


Figure 1. Cumulative Proportions of Recurrent Thrombosis after Cessation of Anticoagulant Therapy. Group A: patients with surgery in the previous 6 weeks. Group C: patients with no identifiable clinical risk factor. Group D: patients with non-surgical risk factors for venous thromboembolism. Data for group B are not included because it was a small group with no recurrences. reprinted from *The Lancet*, Vol. **362**, Baglin, T., Luddington, R., Brown, K. & Baglin, C. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. Pages 523–526, Copyright 2003, with permission from Elsevier.

On the basis of the frequency, as well as on the consequences, of recurrent VTE and anticoagulant-related major bleeding, duration of treatment for provoked PE is recommended to be 3 months. For patients with unprovoked PE, in whom risk factors for bleeding are absent and for whom good anticoagulant monitoring is achievable, long-term treatment is recommended for a period between 3 and 12 months. In clinical practice, therefore, most patients with unprovoked PE will be treated for 6-12 months. In case of recurrent PE, treatment with VKA should have an indefinite duration (Figure 2).^[18]

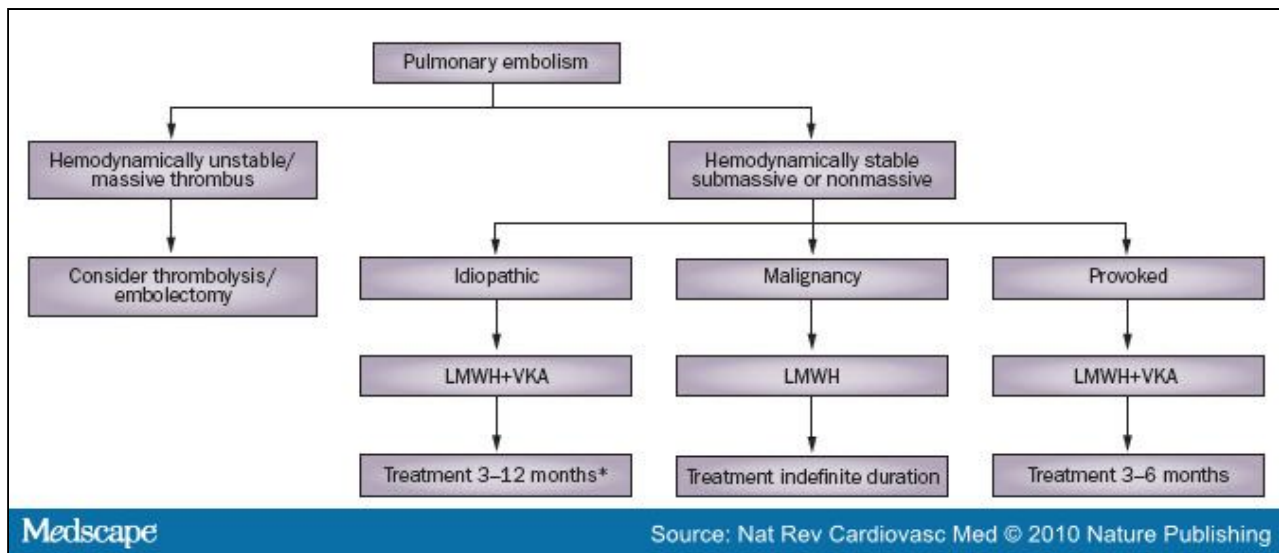


Figure 2. Overview of Treatment Strategies for Patients with Pulmonary Embolism. *Consider prolonged treatment after counseling of the patient. Abbreviations: LMWH, low-molecular-weight heparin; VKA, vitamin-K antagonist.

Although long-term treatment with heparin (>6 months) can induce osteoporosis, the incidence of bone fractures potentially attributable to this complication is extremely low and is comparable with that for treatment with warfarin.^[62]

Biomarkers for Recurrent VTE

Considering the high risk of recurrence associated with PE, and the increased bleeding risk with treatment, tailoring the duration of anticoagulation to the individual patient is important.^[19,63] Several biomarkers have been investigated for this purpose; plasma D-dimer level and presence of residual thrombus are the most-promising candidates.

Elevated D-dimer levels have been associated with an increased risk of recurrence of VTE (relative risk 2.19, 95% CI 1.10-4.35).^[64,65] Eichinger and colleagues found that patients with a D-dimer level below 250 µg/l had a low risk of VTE recurrence and those with levels above 250 µg/l had a high risk of recurrence (cumulative probability of recurrence at 2 years 3.7% [95% CI 0.9-6.5%] and 11.5% [95% CI 8.0-15.0%], respectively), independent of the presence of thrombophilic risk factors.^[65] In the PROLONG study,^[66] D-dimer level was used as a risk stratification tool for determining the duration of anticoagulation therapy. In total, 608 patients with a first unprovoked event underwent D-dimer testing 1 month after discontinuation of anticoagulation therapy. An abnormal D-dimer test result was recorded for 223 patients, who were then randomly assigned to either resume or discontinue VKA treatment. The recurrence rates in the two groups were 2.9% and 15.0%, respectively (adjusted hazard ratio [HR] 4.26, 95% CI 1.23-14.6, $P = 0.02$).^[66] However, thromboembolism also recurred in 6.2% of patients with normal D-dimer levels who discontinued anticoagulation therapy.^[66] Although a clear benefit of continuation of treatment could be observed for patients with an abnormal D-dimer level, the risk-benefit ratio of stopping anticoagulation for patients with a normal D-dimer is uncertain. Therefore, the application of the D-dimer measurement for individual risk stratification is uncertain at the present time.^[66]

Residual thrombus in a leg vein also seems to be associated with an increase in the risk of recurrent VTE,^[67] but this risk disappears after controlling for the influence of the D-dimer level.^[68] In a large study of patients with VTE, women with two or more clinical findings (hyper-pigmentation, edema or redness of either leg, D-dimer level ≥ 250 µg/l while taking warfarin, BMI >30 kg/m², or age ≥ 65 years) had an annual risk of recurrence of 14%, but unfortunately no combination of clinical predictors was useful in men.^[69] Clearly, given the number of unresolved issues, a need exists for a randomized trial comparing various durations of anticoagulation and evaluating a biomarker-based approach to predicting PE recurrence.^[55]

Treatment in Specific Circumstances

Pregnancy

Pregnancy and the postpartum period are associated with an increased risk of PE, which is the leading cause of maternal mortality in the developed world.^[70,71] The increased risk of VTE during pregnancy results from procoagulant changes in the hemostatic and fibrinolytic systems^[72] in combination with venous stasis in the lower extremities.^[73] Pregnant women with acute PE should be treated with LMWH, because this agent does not cross the placenta. Since drug clearance increases during pregnancy, as a result of increased renal perfusion,^[74] the effect of therapy should be monitored each month by measuring anti-factor-Xa levels. VKAs do cross the placenta and are associated with congenital malformations, so they should be avoided during pregnancy. In the postpartum period, therapy can be switched to a VKA, which should be administered for at least 6 weeks. In women receiving adjusted-dose LMWH or UFH, discontinuing heparin therapy for 24 h before elective induction of labor is recommended.^[70,75]

Cancer

Patients with cancer, and particularly those with meta-static disease, have a high risk of VTE because of the prothrombotic effects of the tumor and treatment with chemotherapy and radiotherapy.^[76,77] Patients with malignancy and thrombosis should be treated with long-term LMWH, because the risk of recurrent VTE associated with LMWH is 9%, whereas the recurrence rate associated with VKAs is 17% in the first 6 months after the thrombotic event.^[78] However, the risk of major hemorrhage is similar for LMWH and VKAs in patients with cancer and PE.^[78] Considering the persistently high rate of PE recurrence, these patients should receive anticoagulant treatment for as long as the cancer is active (Figure 2).

Antiphospholipid Syndrome

Patients with VTE and the antiphospholipid syndrome (APS), which is described in Part 1 of this Review,^[4] have an increased risk of VTE recurrence ranging from 10% to 70%.^[79-81] The optimal duration of anticoagulation for prevention of recurrent thrombosis in patients with antiphospholipid antibodies is unknown. The general consensus is to treat patients with APS and PE in the same way as patients with nonmassive PE, with a target INR of 2-3, but with a duration of anticoagulation therapy of 1 year.^[38]

New Anticoagulants

Oral VKAs, which indirectly inhibit several steps in the coagulation pathway, have been the most commonly used anticoagulants since the 1950s. However, during the past decade, several new oral anticoagulants (Figure 3) have been investigated that more-selectively inhibit coagulation factors, such as factor IIa (thrombin) or factor Xa (activated factor X).^[82,83] Potential advantages of direct factor IIa and factor Xa inhibitors are oral administration and fact that dose titration or monitoring is not required. Also, owing to their specificity, fewer clinical drug interactions are expected. Nevertheless, the absence of an appropriate antidote for these drugs and the need for monitoring their use in specific circumstances (for example, in patients with renal impairment) are problems that still need to be solved.^[36]

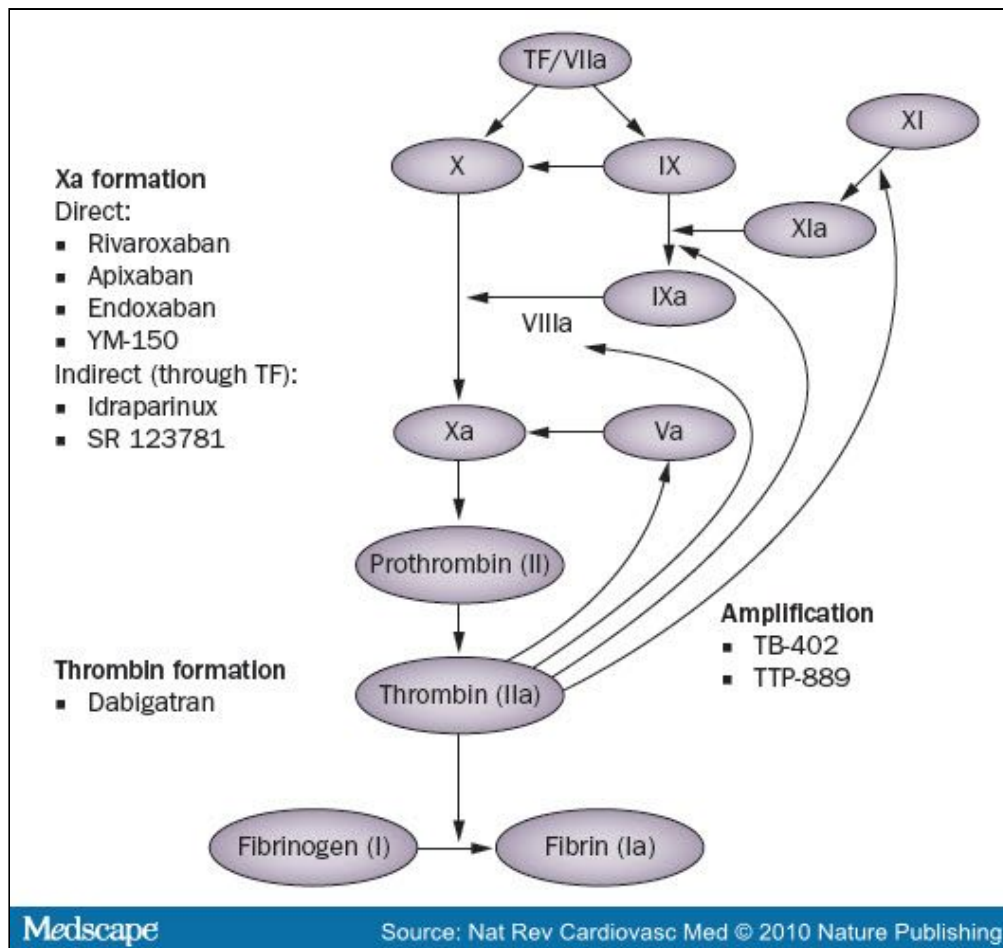


Figure 3. Novel Anticoagulants, such as Factor IIa, Factor Xa, and Amplificationloop Inhibitors, in the Coagulation Cascade. Some drugs are still under investigation for the treatment and prophylaxis of venous thromboembolism. Coagulation factors are represented by their roman numerals. Abbreviation: TF, tissue factor.

The oral factor IIa inhibitor dabigatran was investigated in the RE-COVER trial,^[84] in which 2,539 patients with acute VTE were treated for 6 months with either dabigatran or warfarin. The results for the 541 patients with PE were similar to those for the total group of patients with VTE. Dabigatran was found to be as effective as warfarin in the prevention of VTE. The rates of recurrent VTE were 2.4% and 2.1%, respectively (HR with dabigatran 1.10, 95% CI 0.65-1.84). Major bleeding occurred in 1.6% and 1.9% of patients in the dabigatran and warfarin groups, respectively (HR with dabigatran 0.82, 95% CI 0.45-1.48).^[84] Therefore, a fixed dose of dabigatran seems to be as effective as warfarin for the treatment and prevention of VTE recurrence and has a safety profile that is similar to that of warfarin.^[84]

Idraparinux, a subcutaneous, long-acting penta-saccharide inhibitor of factor Xa, is being evaluated in the randomized, double-blind CASSIOPEA trial.^[85] 3-month or 6-month treatment with idraparinux (3.0 mg subcutaneously, once-weekly) will be compared with warfarin for the treatment of acute PE. This trial is expected to be completed in October 2010. In addition, the efficacy and safety of the direct factor Xa inhibitors rivaroxaban and apixaban are being evaluated for long-term prevention of recurrent VTE in patients with acute DVT and PE. The results of these investigations will soon be available. Edoxaban, which is also an oral direct factor Xa inhibitor, is currently in phase III investigation for the treatment of VTE. Other oral direct factor Xa inhibitors are in an earlier phase of development. The compound YM-150 is being tested in trials involving patients undergoing surgery and among those with coronary artery disease. In phase II clinical trials of patients undergoing primary hip replacement surgery, a dose-related response to YM-150 was reported, confirming the results of preclinical thrombosis models.^[86] Currently, several other phase II, II/III, and III trials of this compound are ongoing or recruiting patients. The phase III trials will assess the efficacy of YM-150 in the prevention of VTE in a large number of patients.

Home Treatment

Owing to potential hemodynamic instability, the risk of adverse outcome, or the presence of complicating comorbidities, patients with PE are usually admitted to the hospital for administration of initial therapy and monitoring. However, some patients might have only mild symptoms at presentation, with a low expected risk of adverse outcome. In these patients, hospital admission could possibly be avoided, as for many individuals with DVT. Furthermore, with the introduction of LMWH in place of UFH, monitoring of initial anticoagulant treatment is no longer necessary. Home treatment involves patients self-administering anticoagulant therapy under physician guidance, in combination with nurse-led outpatient clinics for those patients who require assistance or monitoring. Risk stratification could be helpful in determining the best treatment setting for each individual patient. Low levels of cardiac biomarkers, such as troponin (>0.07 mg/l) and NT-proBNP (>600 ng/l),^[16] and the absence of ventricular dysfunction may indicate a low risk of morbidity and mortality and identify patients who could safely benefit from being treated at home.

Otero *et al.* performed a randomized clinical trial to compare the efficacy and the safety of early discharge in patients with acute symptomatic PE classified as being at low risk of death (based on a low prediction rule score and the absence of RV dysfunction).^[87] Patients were randomly assigned to early discharge after 3 days in the hospital or to standard hospitalization. During the 3-month follow-up, the incidence of nonfatal recurrences of PE and hemorrhagic complications did not differ significantly between the two groups. However, the study was terminated early, after 132 patients were enrolled, owing to unexpectedly high short-term mortality in the early-discharge group as compared with the standard-hospitalization group (2.8% versus 0%, $P = 0.30$).^[87] Agterof *et al.* investigated the safety of home treatment of hemodynamically stable patients with PE ($n = 152$) with low (<500 ng/l) levels of NT-proBNP, who were discharged from the hospital within 24 h of presentation.^[88] No deaths, occurrence of major bleeding, or recurrences of VTE took place in the first 3 months after hospital discharge. During the first 10 days, seven patients were readmitted; in three cases, readmission was necessitated by complaints that could be related to PE. The patients who were treated at home did not experience anxiety (as assessed by the Hospital Anxiety and Depression scale) and considered home treatment to be convenient.^[88] This study suggests that home treatment in patients with acute PE after risk stratification could be feasible, but more studies are needed to better assess the safety of this strategy.

Conclusions

Untreated PE is associated with high mortality. Initial therapy for PE usually comprises LMWH or fondaparinux. Only hemodynamically unstable patients with PE should receive thrombolysis or thrombectomy. VKAs are still the preferred long-term treatment and should be used for a period of 3-12 months, depending on whether PE was provoked or unprovoked. Longer treatment should be considered after individual counseling of the patient. An IVC filter should only be placed when a contraindication for anticoagulant treatment exists. Pregnant women and patients with cancer should be treated with LMWH instead of VKAs. Several new anticoagulants are currently under investigation, including the factor IIa inhibitor dabigatran and the factor Xa inhibitors rivaroxaban, apixaban, and idraparinux. These agents could potentially replace VKAs and LMWH for the prevention and treatment of VTE. Whether home treatment of patients with PE is safe has not yet been established.

Key Points

- Pulmonary embolism (PE) can be effectively treated with anticoagulant medication
- Initial therapy for PE comprises low-molecular-weight heparin, unfractionated heparin, or fondaparinux, and is followed by long-term treatment with oral vitamin-K antagonists
- Duration of long-term anticoagulation is usually 3-12 months and depends on type of PE, risk of recurrence, risk of major bleeding, and the patient's preference
- Tailoring the duration of treatment using biomarkers, such as D-dimer level or presence of residual vein thrombosis, is not yet recommended
- Patients with PE who are hemodynamically unstable (massive PE) should be treated with thrombolysis
- Currently, insufficient evidence exists that hemodynamically stable patients with right ventricular dysfunction (submassive PE) benefit from thrombolysis

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