Effective diagnosis and treatment of pulmonary embolism: Improving patient outcomes

Des changements dans le diagnostic et la thérapeutique pour améliorer le pronostic de l’embolie pulmonaire

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Summary  Pulmonary embolism can be life threatening and difficult to diagnose as signs and symptoms are not specific. European guidelines recommend stratification of pulmonary embolism by risk of early mortality. Patients with suspected pulmonary embolism should be assessed for clinical probability of pulmonary embolism using a validated risk score. A low or intermediate clinical probability plus a negative high-sensitivity D-dimer test excludes pulmonary embolism. Anticoagulation is indicated in patients with a positive multidetector computed tomography or high-probability lung scan. An important part of the management of patients with pulmonary embolism has traditionally been anticoagulant treatment with parenteral heparins and oral vitamin K antagonists. Although effective, this dual-drug approach is associated with limitations. Direct oral anticoagulants that may overcome some of these problems have been tested in phase III clinical trials for the treatment of venous thromboembolism. Of these, rivaroxaban and apixaban have demonstrated non-inferiority to standard therapy when given as single-drug approaches for venous thromboembolism treatment, and provided

Abbreviations: CI, Confidence interval; CrCl, Creatinine clearance; CT, Computed tomography; DVT, Deep vein thrombosis; GARFIELD, Global Anticoagulant Registry in the FIELD; HR, Hazard ratio; LMWH, Low-molecular-weight heparin; OAC, Oral anticoagulant; PE, Pulmonary embolism; RIETE, Registro Informatizado de Pacientes con Enfermedad TromboEmbólica; VKA, Vitamin K antagonist; VTE, Venous thromboembolism.

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Introduction

Pulmonary embolism (PE) is a relatively common disease, with an incidence ranging from 60 to 112 per 100,000 inhabitants of the United States [1], and is the third most common cause of death among patients with cardiovascular diseases [2]. Patients are at particular risk in the acute stage of the disease, with 30-day mortality rates in excess of 15% for PE associated with shock and/or hypotension [3]. PE is difficult to diagnose because of the wide range of presentations of the disease. Among those patients who die of PE, 94% do so before diagnosis [4]. The mainstay of treatment for most patients with PE is anticoagulation, and the risk of death is much reduced in optimally anticoagulated patients. The recurrence rate of venous thromboembolism (VTE) after stopping anticoagulant treatment varies with the cause of the disease and is much higher in patients with unprovoked VTE than in patients with VTE provoked by a major transient risk factor [5]. Duration of anticoagulant treatment is tailored to the risks of VTE recurrence and bleeding for each individual patient [3,6].

Treatment of PE has predominantly involved the use of low-molecular-weight heparins (LMWHs), unfractionated heparin or fondaparinux in combination with vitamin K antagonists (VKAs) [3,6]. However, this dual-drug approach is associated with some limitations, including the need to co-administer the parenteral agent and VKA concurrently for several days at the start of treatment, and the subsequent need for regular coagulation monitoring and dose adjustments during VKA monotherapy. The recently developed direct oral anticoagulants circumvent some of these limitations, and several have completed large phase III clinical trials in the treatment of acute VTE. In Europe, only rivaroxaban is currently approved for the treatment and secondary prevention of deep vein thrombosis (DVT) and PE. In the USA, rivaroxaban and, more recently, dabigatran have been approved for VTE treatment.

This review covers the diagnosis and treatment of PE, focusing on data for direct oral anticoagulants.

Clinical presentations of PE

Most patients with suspected PE present with some degree of chest pain and dyspnoea, a frequent cause of referral to the emergency department. These symptoms are non-specific and can be confused with other differential diagnoses, such as acute coronary syndromes, exacerbation of chronic obstructive pulmonary disease or pneumonia [7]. The most specific symptoms of PE—haemoptysis and calf
pain—are encountered in only up to 10% and 42% of patients with PE, respectively [8,9]. In the most severe cases of PE, patients may present with shock and/or haemodynamic instability [3]. The lack of specific symptoms and the presence of underlying disease in a significant proportion of patients with PE probably explain the significant diagnostic delay observed in some cases.

Risk stratification for suspected PE

Risk stratification is a relatively new concept in the field of PE. The size of the emboli and degree of vessel occlusion do not accurately describe the risk of death of a patient with suspected PE, and the terms 'massive' and 'sub-massive' are misleading [3]. Therefore, other methods are required to assess mortality risk and inform management decisions. Accordingly, the guidelines of the European Society of Cardiology categorize patients presenting with suspected PE by their predicted risk of early mortality. Patients are divided into high-risk or non-high-risk (which is further divided into intermediate- and low-risk) categories based on the presence of shock, myocardial injury and right ventricular dysfunction detected by echocardiography and cardiac biomarkers [3]. The risk category to which a patient is assigned informs the approach, whether it be emergency thrombolysis or embolectomy (high-risk: >15% early mortality risk) or further confirmatory diagnostic steps and, if PE is confirmed, management with anticoagulants (non-high-risk: 1—15% early mortality risk) [3]. Risk stratification also allows for the selection of patients who may be suitable for outpatient anticoagulant treatment [10].

The Pulmonary Embolism Severity Index is a clinical tool designed to assess the risk of death in patients with PE. According to this, patients with PE can be divided into five groups with different outcomes. The 30-day risk of death in patients belonging to the low-risk categories I and II is usually <3%, whereas that in patients belonging to the high-risk category V varies between 10% and 25% [11,12]. A simplified version of the rule, based on six variables that all carry the same weight (one of which is a composite of two original variables), has been shown to have the same sensitivity and specificity as the original [13]. Right ventricular dilatation on echocardiography or computed tomography (CT) pulmonary angiography, and right ventricular dysfunction or injury detected by brain natriuretic peptide and troponin testing, allow further risk stratification of clinically stable patients with PE [14].

Confirmatory diagnosis in suspected high-risk PE

In patients with suspected high-risk PE, CT pulmonary angiography is the preferred technique to confirm the diagnosis (Fig. 1) [3]. Echocardiography is an alternative if CT pulmonary angiography is unavailable or the patient is too unstable. In haemodynamically unstable patients, acute pulmonary hypertension and right ventricular overload seen on echocardiography may justify a decision for thrombolysis or embolectomy, particularly when other tests cannot be performed (Fig. 1) [3].

Confirmatory diagnosis in suspected non-high-risk PE

If a diagnosis of non-high-risk PE is suspected, the first step is to assess the clinical probability of PE using a standardized clinical prediction rule (Fig. 1) [3]. According to the result, patients can be divided into three (low, intermediate or high probability of PE) or two (‘PE unlikely’ and ‘PE likely’) groups, each with different probabilities of PE. A negative result from a high-sensitivity D-dimer test in patients with either low—intermediate probability or ‘PE unlikely’ safely excluded PE in about 30% of outpatients presenting to seven Dutch hospitals with suspected PE [15]. In patients with either a high clinical probability or an elevated D-dimer plasma concentration, three options for confirmatory diagnosis are available: CT pulmonary angiography, ventilation—perfusion lung scanning or venous compression ultrasound [3].

Nowadays, multidetector spiral CT pulmonary angiography is considered the standard option for confirming non-high-risk PE (Fig. 1). Using multidetector spiral CT pulmonary angiography, the rate of recurrent VTE within 3 months after a negative examination has been reported to be as low as 0.3% with or without additional ultrasound, confirming a high sensitivity [16]. Compared with single-detector CT pulmonary angiography and the first generation of multidetector devices, the recent 64-detector systems detect a higher rate of isolated subsegmental PEs, the clinical significance of which has been questioned [17].

Ventilation—perfusion lung scanning has been used to diagnose PE for many years. A normal ventilation—perfusion lung scan virtually eliminates the diagnosis of PE, but about 50% of examinations are non-diagnostic and do not by themselves allow exclusion or confirmation of the diagnosis of PE [18]. On the other hand, a high-probability scan is strongly correlated with a diagnosis of PE, but further tests may be considered in patients with a low clinical probability risk score [3].

Compression ultrasound allows diagnosis of DVT in patients with clinically suspected PE, and the finding of a proximal DVT in a patient with clinically suspected PE is accepted as a surrogate for the diagnosis of PE and does not need to be confirmed by an examination of the chest [3]. However, a normal proximal compression ultrasound does not exclude the diagnosis of PE [19], and only 10% of examinations are positive in patients with suspected PE [20]. Thus, compression ultrasound cannot be considered an efficient diagnostic method for most patients with suspected PE.

Current treatment options for PE

In the relatively few patients with high-risk PE (presence of shock and/or hypotension), thrombolytic therapy is recommended. In cases where thrombolytic therapy fails or is contraindicated, cather-assisted thrombus removal or surgical embolectomy provides a back-up option [3,6]. Such patients should also receive immediate anticoagulation with
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unfractionated heparin with haemodynamic and respiratory support as required. Anticoagulation is the mainstay treatment option for haemodynamically stable patients with non-high-risk PE and should be started as soon as the diagnosis is suspected, at least in patients with a high clinical probability of PE and no contraindication to anticoagulant therapy [3,6].

Traditional anticoagulants for the treatment of PE

The traditional parenteral anticoagulants employed in the initial treatment of non-high-risk PE include LMWH, intravenous or subcutaneous unfractionated heparin or fondaparinux. Except for patients with VTE and cancer, LMWH is normally given for the first 5–7 days of treatment and is overlapped with and followed by treatment with an oral VKA until the international normalized ratio reaches between 2.0 and 3.0 [3,6]. Owing to their slow onset of action, VKAs must initially be used in conjunction with the faster-acting parenteral anticoagulants. During treatment with a VKA, patients require frequent coagulation monitoring to maintain treatment within a therapeutic range (international normalized ratio 2.0–3.0). The initial dosage varies greatly between patients and, because of drug and food interactions, the subsequent dosage may vary according to changes in associated treatment and diet. Even under controlled conditions, the time in the therapeutic range usually does not exceed 65% [21–24]. VKAs represent one of the most frequent causes of referral to emergency departments because of adverse drug reactions, especially in the elderly [25]. These limitations underscore the need for simpler anticoagulant drugs for the initial and long-term treatment of PE.

Figure 1. Recommended diagnostic pathway for patients with suspected PE—European Society of Cardiology guidelines 2008 [3]. Notes: CT is defined as not immediately available if the patient’s critical condition allows only bedside diagnostic tests. Confirmation of DVT via compression venous ultrasound may also assist with clinical decisions. CT is considered diagnostic of PE if the most proximal thrombus is at least segmental. If single-detector CT is negative, a negative proximal lower limb venous ultrasound is required to safely exclude PE. If MDCT is negative in patients with a high clinical probability of PE, further investigations may be considered. CT: computed tomography; CTPA: computed tomography pulmonary angiography; DVT: deep vein thrombosis; echoCG: echocardiography; MDCT: multidetector spiral computed tomography; PE: pulmonary embolism; RV: right ventricular.
Direct oral thrombin and Factor Xa inhibitors for the treatment of PE

A series of novel anticoagulant drugs have recently been developed. These drugs are direct inhibitors of Factor IIa (thrombin) or Factor Xa, are not subject to food interactions and have minimal drug interactions compared with VKAs. They can be administered orally at a fixed dosage without the need for routine coagulation monitoring [26]. Among these drugs, rivaroxaban, dabigatran, apixaban and edoxaban have been tested for the initial and/or secondary prevention of VTE in large phase III studies [21–24,27–30]. In 2012, rivaroxaban became the first direct oral anticoagulant to be approved for the treatment of DVT and PE and the prevention of recurrent VTE [31,32]. In contrast to the combination of LMWH and VKA, rivaroxaban provides a fixed-dose, single-drug approach to the initial and continued treatment of PE in patients who are haemodynamically stable and do not require thrombolysis or embolectomy.

Phase III studies of the direct oral anticoagulants in the treatment of acute VTE

The EINSTEIN PE study was an open-label, randomized, non-inferiority study that compared oral rivaroxaban with standard therapy in patients with acute, symptomatic PE with or without DVT [23]. Among other criteria, patients were excluded if they had haemodynamic instability, creatinine clearance (CrCl) < 30 mL/min, clinically significant liver disease, had received therapeutic parenteral anticoagulation for > 48 hours, or more than a single dose of a VKA before randomization. Rivaroxaban was given at a dose of 15 mg twice daily for the first 3 weeks followed by 20 mg once daily. Standard therapy was subcutaneous enoxaparin 1.0 mg/kg twice daily followed by either warfarin or acenocoumarol for 3, 6 or 12 months. A total of 2419 patients were assigned to rivaroxaban and 2413 to standard therapy. Recurrent VTE occurred in 2.1% of patients who were given rivaroxaban compared with 1.8% who received standard therapy (P = 0.003 for non-inferiority; Fig. 2). Major or non-major clinically relevant bleeding occurred in 10.3% and 11.4% of patients, respectively (hazard ratio [HR] 0.90, 95% confidence interval [CI] 0.76–1.07; P = 0.23; Fig. 2). Major bleeding occurred in 1.1% and 2.2% of patients, respectively (HR 0.49, 95% CI 0.31–0.79; P = 0.003), representing a 51% relative risk reduction (Fig. 2) [23]. Subgroup analysis demonstrated that rates of recurrent VTE and bleeding were similar in both treatment groups regardless of age, weight, sex, renal function or extent of PE.

The EINSTEIN DVT study enrolled patients with acute, symptomatic proximal DVT without symptomatic PE [22]. General exclusion criteria were similar to those applied in EINSTEIN PE. As in EINSTEIN PE, rivaroxaban was non-inferior to standard therapy (P < 0.001 for non-inferiority) [22]. Major or non-major clinically relevant bleeding and major bleeding alone occurred with similar incidences in both treatment groups [22]. In a pooled analysis of EINSTEIN DVT and EINSTEIN PE, rivaroxaban was non-inferior to standard therapy for efficacy and led to a 46% relative risk reduction in major bleeding (Fig. 3) [33]. Rivaroxaban was associated with a significant improvement in net clinical benefit (defined as the composite incidence of recurrent VTE and major bleeding) in fragile patients (age > 75 years, CrCl < 50 mL/min or weight < 50 kg; HR 0.51, 95% CI 0.34–0.77), primarily as a result of a 63% relative risk reduction in major bleeding in this group compared with standard therapy [33].

AMPLIFY (Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-line Therapy) was a randomized, double-blind study comparing apixaban (10 mg twice daily for 7 days followed by 5 mg twice daily for 6 months) with conventional therapy (subcutaneous enoxaparin followed by warfarin) in 5395 patients with acute VTE [24]. Reasons for ineligibility included contraindications to standard anticoagulant therapy, cancer, provoked thrombosis without a persistent risk factor for recurrence, if < 6 months of treatment was planned, treatment with > 165 mg aspirin daily or CrCl < 25 mL/min. No more than two doses of once-daily LMWH, fondaparinux or VKA; three doses of twice-daily LMWH; or > 36 hours of continuous intravenous heparin were permitted. Apixaban was non-inferior to standard therapy for the primary efficacy outcome of recurrent symptomatic VTE or VTE-related death (P < 0.001 for non-inferiority), with a 69% relative risk reduction in major bleeding (Fig. 3) [24]. Outcomes in subgroups, including elderly patients and those weighing > 100 kg were consistent with the overall population.

RE-COVER was a double-blind, randomized trial that compared 6 months of treatment with dabigatran (fixed dose of 150 mg twice daily) with dose-adjusted warfarin therapy in patients with proximal DVT or PE [21]. Patients were excluded for reasons of haemodynamic instability, symptoms lasting > 14 days, recent unstable cardiovascular disease, high bleeding risk, clinically significant liver disease, CrCl < 30 mL/min, or a requirement for aspirin > 100 mg daily. All patients were initially given an approved parenteral anticoagulant (generally unfractionated heparin or LMWH). Dabigatran was non-inferior to standard therapy for the prevention of recurrent VTE (P < 0.001 for non-inferiority), with a significant reduction in clinically relevant bleeding but not major bleeding (Fig. 3) [21]. Outcomes were consistent regardless of variations in demographic factors. The RE-COVER II study had essentially the same design as RE-COVER and the results, recently published, support the outcomes of RE-COVER [27].

Edoxaban was compared with warfarin in the Hokusai-VTE study, a randomized, double-blind, non-inferiority study of 8292 patients with VTE [30]. Patients were excluded if they had contraindications to standard anticoagulant treatment, had received > 48 hours of heparin treatment or more than one dose of VKA, had cancer with anticipated long-term LMWH treatment, were receiving aspirin > 100 mg/day or dual antiplatelet therapy, or had CrCl < 30 mL/min. As with dabigatran, treatment with edoxaban (60 mg once daily or 30 mg once daily in patients with CrCl 30–50 mL/min or weight ≤ 60 kg or who were receiving treatment with potent P-glycoprotein inhibitors) was initiated after initial parenteral anticoagulation [30]. Edoxaban was non-inferior to standard therapy for the prevention of symptomatic recurrent VTE (P < 0.001 for non-inferiority) [30]. Clinically
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Figure 2. Primary efficacy, safety and net clinical benefit outcomes in patients with PE with or without DVT in the phase III EINSTEIN PE study of single-drug rivaroxaban compared with standard therapy (enoxaparin/VKA). Efficacy endpoints (recurrent VTE and net clinical benefit) were evaluated in the intention-to-treat population. Bleeding outcomes were evaluated in the safety population. Net clinical benefit was defined as the composite incidence of recurrent VTE and major bleeding. Clinically relevant bleeding was defined as the composite of major and non-major clinically relevant bleeding. CI: confidence interval; DVT: deep vein thrombosis; PE: pulmonary embolism; VKA: vitamin K antagonist; VTE: venous thromboembolism.

Figure 3. Published, phase III clinical studies of direct oral anticoagulants for the treatment of acute venous thromboembolism [21,24,30,33]. CI: confidence interval; OAC: oral anticoagulant; VTE: venous thromboembolism.
relevant bleeding was significantly reduced with edoxaban, but major bleeding was not (Fig. 3) [30]. Efficacy with edoxaban was also confirmed in a subset of patients with severe PE (N-terminal prohormone of brain natriuretic peptide level ≥ 500 pg/mL) [30].

**Secondary prevention of VTE with direct oral anticoagulants**

Patients with unprovoked PE (i.e. occurring in the absence of a major risk factor such as trauma, surgery, immobilization or cancer) have a high risk of recurrent VTE after the end of anticoagulant treatment [5]. Approximately 5–10% of these patients will have a recurrent event during the first year after a 3- or 6-month course of anticoagulant therapy, and about 30% of them will have a recurrence within 5 years [34]. Dabigatran, rivaroxaban and apixaban have been investigated for the prevention of these recurrent events. Dabigatran and rivaroxaban were administered using a single-dose regimen (150 mg twice daily for dabigatran and 20 mg once daily for rivaroxaban), whereas apixaban was given at two different doses of 2.5 mg and 5 mg twice daily [22,28,29]. The three drugs achieved a relative risk reduction of recurrent VTE compared with placebo of 64–92% (Fig. 4). This was obtained at the cost of a significant increase in major plus non-major clinically relevant bleeding with rivaroxaban and dabigatran, although not apixaban, but without a significant increase in major bleeding for any agent. The net increase in major bleeding did not exceed 1%, whereas the net decrease in recurrent VTE (plus or minus VTE-related or all-cause mortality, depending on the study) varied from 5.2% to 7.8% [22,28,29]. Only dabigatran has been compared with warfarin for the secondary prevention of VTE [28]. The two treatments were equally efficacious for the prevention of recurrent VTE (P = 0.01 for non-inferiority) and the incidence of major bleeding was similar (HR 0.52, 95% CI 0.27–1.02). Dabigatran was associated with an increase in the rate of acute coronary syndromes (0.9% vs 0.2%; P = 0.02) [28].

**Discussion**

Previous results in patients with VTE explain why, in phase III trials, dabigatran and edoxaban were started only after a standard course of parenteral treatment with LMWH, and why rivaroxaban and apixaban were started immediately after randomization, but at a higher dosage during the acute treatment phase. These treatment schedules were selected to optimize the efficacy of the direct oral anticoagulant regimens during the initial period of treatment where the risk of recurrent VTE is high. Previous experience with ximela-
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The results of clinical studies of direct oral anticoagu-
lants were obtained in selected patients who were relatively
young and had few associated diseases, but at least for
rivaroxaban [22,23] and edoxaban [30], the results also
apply for important subgroups of PE patients. Additionally,
the VKA time in therapeutic range was potentially higher
in these studies than in real life, and so VKAs can be consid-
ered to have been given optimally in these trials. Therefore,
the observed benefits of the direct oral anticoagulants may
be more pronounced in routine clinical practice than in the
study settings. Several registries and real-world studies are
underway or planned to investigate the epidemiology and
treatment outcomes of VTE encountered in daily clinical
practice, including in groups of patients who would nor-
mally be excluded from clinical trials. Established registries
include the Registro Informatizado de Pacientes con Enfer-
medad Tromboembólica (RIETE), which has recruited more
than 39,000 patients since its inception in 2001 and has,
among other important data, provided predictive variables
for major bleeding events in patients who present with acute
VTE [37].

More recently, two registries have been created to look
specifically at patterns of treatment and outcomes in acute
and long-term management of VTE with direct oral anticoag-
ulants. The Dresden Registry aims to recruit 2000 unselected
adult patients in Germany (http://www.noac-register.de/),
and the Global Anticoagulant Registry in the FIELD
(GARFIELD) VTE registry will include patients in more than
20 countries (http://www.trip-london.ac.uk/garfield-vte).

Conclusions

Accurate diagnosis and risk stratification of patients with
PE, together with the simplified treatment that the direct
oral anticoagulants can provide, are likely to improve
patient outcomes and reduce mortality associated with this
disease.

Disclosure of interest

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