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Anticoagulant treatment for acute pulmonary embolism: a pathophysiology-based clinical approach

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ABSTRACT The management of patients with acute pulmonary embolism is made challenging by its wide spectrum of clinical presentation and outcome, which is mainly related to patient haemodynamic status and right ventricular overload. Mechanical embolic obstruction and neurohumorally mediated pulmonary vasoconstriction are responsible for right ventricular overload. The pathophysiology of acute pulmonary embolism is the basis for risk stratification of patients as being at high, intermediate and low risk of adverse outcomes. This risk stratification has been advocated to tailor clinical management according to the severity of pulmonary embolism.

Anticoagulation is the mainstay of the treatment of acute pulmonary embolism. New direct oral anticoagulants, which are easier to use than conventional anticoagulants, have been compared with conventional anticoagulation in five randomised clinical trials including >11 000 patients with pulmonary embolism. Patients at high risk of pulmonary embolism (those with haemodynamic compromise) were excluded from these studies. Direct oral anticoagulants have been shown to be as effective and at least as safe as conventional anticoagulation in patients with pulmonary embolism without haemodynamic compromise, who are the majority of patients with this disease. Whether these agents are appropriate for the acute-phase treatment of patients at intermediate-high risk pulmonary embolism (those with both right ventricle dysfunction and injury) regardless of any risk stratification remains undefined.

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Introduction

Pulmonary embolism is a common disease with an estimated incidence of 1–2 per 1000 annually in the general population [1]. Anticoagulation is the mainstay for the treatment of acute pulmonary embolism [2]. For several decades, low-molecular-weight heparin or unfractionated heparin followed by oral vitamin K antagonists have been the conventional treatment for pulmonary embolism.

Direct oral anticoagulants have recently been evaluated as an alternative to conventional anticoagulation for the treatment of venous thromboembolism [3]. All but one of the phase III studies with the new oral agents included both patients with deep vein thrombosis and patients with pulmonary embolism. The risk of early in-hospital death in patients with pulmonary embolism ranges from 1% to >30%, depending on clinical presentation, and is higher than in patients with deep vein thrombosis [4–6]. This requires the availability of efficacy and safety data for the new oral agents across the spectrum of severity of pulmonary embolism.

This article focuses on currently available evidence for the potential use of new anticoagulants in patients with acute pulmonary embolism, taking into account the pathophysiology of this disease and its link to the risk of in-hospital death.

Pathophysiology of acute pulmonary embolism

The arrival of emboli into the pulmonary circulation can induce acute pulmonary hypertension and acute right heart overload, which could potentially result in right ventricular failure and, in some patients, right ventricular infarction [7]. This condition is diagnosed at autopsy in ~60% of patients who die of a pulmonary embolism [8]. Landmark angiographic studies showed that pulmonary artery pressure increases when thromboemboli occlude more than 30–50% of the total cross-sectional area of the pulmonary arterial bed [9]. Several studies have suggested that the correlation between the extent of mechanical embolic obstruction and the degree of pulmonary hypertension is relatively modest [10]. Indeed, pulmonary embolism with obstruction of only 25% of the pulmonary vascular tree can cause marked pulmonary hypertension, while wider obstructions can cause only slight increases in pulmonary arterial pressure [11]. This is consistent with more recent data on the assessment of the burden of emboli by computed tomography (CT) angiography. By using this imaging technique, a moderate correlation was found between the burden of embolic obstruction and right ventricular dilation or other indirect signs of pulmonary hypertension [12, 13] but no correlation was found between the extent of embolic obstruction and all-cause death or clinical deterioration [14]. A correlation has been claimed between the localisation of emboli and all-cause death or clinical deterioration in haemodynamically stable patients (localisation in the main pulmonary arteries: hazard ratio 8.3, 95% CI 1.0–67; localisation in segmental or subsegmental branches: hazard ratio 0.12, 95% CI 0.015–0.97) [14]. The prominent prognostic value of proximal location of emboli for the overall burden of embolic obstruction is intriguing, as the cross-sectional size of the pulmonary vasculature increases exponentially from the main pulmonary artery to the subsegmental level. Whether the apparent discordance between the burden of obstruction and the degree of pulmonary hypertension can be partially explained by pre-existing cardiopulmonary diseases is unclear.

In addition to mechanical obstruction, vasoconstriction of the pulmonary arterial bed secondary to hypoxia seems to contribute to pulmonary hypertension in acute pulmonary embolism [15]. Thromboxane A₂ and serotonin have been reported to be among the principal mediators of pulmonary artery vasoconstriction [16]. Limited data on the role of neurohumorally mediated vasoconstriction and on the clinical benefit of its reversal are available in humans [17–20].

As a non-preconditioned, thin-walled right ventricle is unable to overcome a mean pulmonary artery pressure >40 mmHg, the rapid rise in afterload results in right ventricular dilation (fig. 1). Dilation alters the contractile properties of the right ventricle, and leads to an increase in wall tension and myocyte stretch. As a consequence of dilation, right ventricular contraction time is prolonged and this could result in paradoxical interventricular septal motion [21] and, eventually, in a marked reduction of left ventricular filling. The consequent reduction of the cardiac output further contributes to the onset of systemic hypotension and haemodynamic instability [22]. The stretching of the right ventricle due to the pressure overload is associated with an elevation in circulating levels of biomarkers of myocardial injury. The imbalance between oxygen supply and demand can damage cardiomyocytes and further reduce right ventricular function.

Relationship between pathophysiology and risk of in-hospital death

Acute pulmonary embolism has a wide spectrum of clinical presentation, severity and outcome, and advocates risk stratification to assess the severity of the event and to tailor clinical management [2, 23]. Several studies have been conducted in order to correlate the pathophysiology of the pulmonary circulation to the clinical course of acute pulmonary embolism.

FIGURE 1 Pathophysiology of pulmonary embolism. NT-proBNP: N-terminal pro-brain natriuretic peptide.

Severe right heart failure with low-output syndrome inducing shock or sustained hypotension identifies patients with severe pulmonary embolism who are regarded as being at “high risk” or affected by “massive” pulmonary embolism; in these patients in-hospital mortality can be as high as 15–30% [2, 23].

In haemodynamically stable patients, risk stratification can be initially performed through the use of clinical models [24]. An association between pre-existing chronic pulmonary diseases (e.g. chronic obstructive pulmonary disease) or chronic heart failure and mortality has been described in patients with acute pulmonary embolism [5]. These conditions have been included in clinical models for the assessment of short-term mortality [25]. As suggested by the recent guidelines of the European Society of Cardiology (ESC), the assessment of right ventricle dysfunction and injury could be avoided in haemodynamically stable patients at low risk of death according to these clinical models (fig. 2) [24].

In patients with acute pulmonary embolism, right ventricular dilation can be sought by echocardiography but can also be found by CT performed for diagnostic purposes [26]. Right ventricular dilation, as assessed by either echocardiography (OR 2.4, 95% CI 1.3–4.3) or CT (OR 2.08, 95% CI 1.63–2.66), is associated with an increased risk of death [27, 28]. Patients with pulmonary embolism and increased levels of biomarkers of myocardial injury, mainly troponin (OR 5.24, 95% CI 3.28–8.38), also have an increased risk for death even in the absence of haemodynamic impairment (OR 5.90, 95% CI 2.68–12.95) [29]. The risk of death or clinical deterioration in haemodynamically stable patients with evidence of both right ventricular dysfunction and injury is further increased (hazard ratio 14.2, 95% CI 1.94–104.16) [30]. Thus, in the recent ESC guidelines, haemodynamically stable patients with evidence of both right ventricular dysfunction and injury are indicated as patients at intermediate–high risk of death, while those with none or only one of these are at intermediate–low risk [24].

Despite remarkable evidence, translating the correlation between pathophysiology and clinical outcome to clinical management of patients with acute pulmonary embolism is challenging. The potential for home treatment or short hospitalisation for patients with a low risk of pulmonary embolism needs to be confirmed in further randomised clinical trials. The need for treatment upgrading for patients at intermediate–high risk of death has been only partially shown by randomised clinical trials, as thrombolytic therapy reduces the rate of in-hospital clinical deterioration but not mortality [24–31].

Anticoagulant treatment for acute pulmonary embolism

The anticoagulant treatment of pulmonary embolism includes three phases: initial, long-term and extended treatments [24, 32]. The goals of treatment are to reduce mortality and early recurrence for initial anticoagulation (first 5–10 days), and to reduce late recurrences for the long term (mostly 3–6 months) and extended anticoagulation (beyond the first 3–6 months).

FIGURE 2 Expected prevalence (blue) of and short-term mortality (red) in different risk categories of pulmonary embolism according to the European Society of Cardiology risk stratification scheme. HD: haemodynamically; RVD: right ventricular dysfunction.

15%	HD unstable patients		>15%
55%	HD stable	RVD and troponin	3–10%
		RVD or troponin	2–5%
		No RVD/troponin	~1%
~30%	Low risk as for clinical scores (20–30%)		~1%
Prevalence	Risk category		Expected short-term mortality

Anticoagulant treatment with unfractionated heparin reduces 2-week mortality by ~70% compared with no treatment [33]. In patients with pulmonary embolism, weight-adjusted low-molecular-weight heparin is associated with a statistically nonsignificant decrease in recurrent symptomatic venous thromboembolism (1.4% *versus* 2.4%; OR 0.63, 95% CI 0.33–1.18) and major bleeding (1.4% *versus* 2.3%; OR 0.67, 95% CI 0.36–1.27) in comparison to activated partial thromboplastin time-adjusted unfractionated heparin [34]. No difference in all-cause mortality (1.4% *versus* 1.2%; OR 1.20, 95% CI 0.59–2.45) has been reported between the two treatment strategies [34].

Fondaparinux, the pentasaccharide sequence responsible for the anti-factor Xa activity of heparin, given subcutaneously once daily, has been shown to be as effective (absolute difference of –1.2%, 95% CI –3.0–0.5%) and safe as unfractionated heparin for the initial treatment of patients with symptomatic, objectively confirmed pulmonary embolism [35]. Idraparinux, a long-acting inhibitor of activated factor X given subcutaneously once weekly, was compared with heparin followed by vitamin K antagonists in a randomised, open-label, noninferiority trial in 2215 patients with pulmonary embolism [36]. Idraparinux did not meet the noninferiority requirement for efficacy as the incidence of recurrence was 3.4 and 1.6% in the idraparinux and in the conventional treatment group, respectively (OR 2.14, 95% CI 1.21–3.78). Although the higher risk of recurrence observed in patients randomised to treatment with idraparinux persisted up to the end of the study (180 days), it was deemed to be mainly related to a potential under-anticoagulation in the acute phase. The renewed attention to intensity of anticoagulation in the acute phase mainly influenced the clinical development of newer anticoagulants, leading to the design of regimens with high intensities of anticoagulation or with heparin pre-treatment in the acute phase.

Thrombolytic therapy given on the top of anticoagulation achieves faster pulmonary reperfusion, as detected by both conventional pulmonary angiography and lung scintigraphy. A meta-analysis of studies including haemodynamically unstable patients showed a 50% reduction in recurrent pulmonary embolism or death compared with heparin alone (9.4% *versus* 19.0%; OR 0.45, 95% CI 0.22–0.92; number needed to treat, 10) [37]. In a more recent meta-analysis, thrombolytic therapy was associated with a significant reduction in overall mortality compared with heparin (OR 0.59, 95% CI 0.36–0.96) [38]. This reduction was not statistically significant after exclusion of studies including high-risk pulmonary embolism (OR 0.64, 95% CI 0.35–1.17).

Long-term treatment up to ≥ 3 months after the acute pulmonary embolism is required in all patients to stabilise the results obtained in the initial phase of treatment and should be regarded as a continuum of the acute-phase treatment [39]. Oral vitamin K antagonists have been the drugs of choice for this phase of treatment for their efficacy and for the potential of oral administration. In patients with cancer-associated venous thromboembolism, long-term treatment with low-molecular-weight heparin should be preferred over vitamin K antagonists.

Direct oral anticoagulants

Two classes of new oral anticoagulants have been developed to overcome the limits of conventional anticoagulation: anti-Xa (rivaroxaban, apixaban and edoxaban) and antithrombin (dabigatran) agents [40]. All these agents are synthetic low-molecular-weight compounds that act as direct, selective and reversible inhibitors of a specific step in the coagulation cascade [41–47]. The anticoagulant effect of these agents is more predictable compared to that of heparin or vitamin K antagonists, allowing their administration in fixed doses without the need for laboratory monitoring or dose adjustment. The short half-lives of the new agents could make clinical management of situations requiring reversal of anticoagulation (need for invasive procedures and bleeding) easier.

Direct oral anticoagulants for acute pulmonary embolism

New oral anticoagulants have been compared to conventional anticoagulation for the initial and long-term treatment of venous thromboembolism, and to placebo or warfarin for the extended treatment of this

disease. Patients with pulmonary embolism with haemodynamic instability or requiring thrombolytic therapy were excluded from these studies.

EINSTEIN-PE is the only trial that exclusively included patients presenting with acute pulmonary embolism. In this trial, rivaroxaban was compared with conventional anticoagulant treatment (enoxaparin or fondaparinux followed by vitamin K antagonists). Both treatments were given for 3, 6 or 12 months at discretion of the attending physician [48]. This randomised, open-label, noninferiority trial included 4832 patients with acute pulmonary embolism. Rivaroxaban was given at the dose of 15 mg twice daily for 3 weeks followed by 20 mg once daily thereafter without heparin pre-treatment. The regimen of rivaroxaban was derived from evidence obtained from phase II studies in patients with acute deep vein thrombosis [49]. Recurrent venous thromboembolism occurred in 2.1% and 1.8% of the patients with rivaroxaban and conventional therapy, respectively (hazard ratio 1.12, 95% CI 0.75–1.68; non-inferiority $p=0.003$). The primary safety outcome of major or clinically relevant non-major bleeding occurred in 10.3% and 11.4% of patients in the rivaroxaban or conventional therapy group, respectively, but major bleeding was significantly lower in patients receiving rivaroxaban than in patients receiving enoxaparin/vitamin K antagonists (1.1% *versus* 2.2%, respectively; hazard ratio 0.49, 95% CI 0.31–0.79; $p=0.003$).

Patients with acute pulmonary embolism constituted about one-third of the patients included in phase III trials with dabigatran, apixaban and edoxaban for the treatment of venous thromboembolism.

RE-COVER I and II were double-blind, double-dummy trials in which patients with acute deep vein thrombosis and/or pulmonary embolism were randomised to 6 months treatment with dabigatran (150 mg twice daily) or warfarin after an initial heparin treatment given for a median of 9 days [50, 51]. In the pooled analysis of the RE-COVER I and II studies, 1602 patients had pulmonary embolism at time of inclusion in the studies [51]. In these patients, recurrent nonfatal or fatal venous thromboembolism occurred in 2.2% *versus* 2.6% of those randomised to dabigatran or warfarin, respectively, confirming similar treatment effects of dabigatran compared with warfarin in this subgroup of patients and in the overall study population (hazard ratio 1.08, 95% CI 0.64–1.80 in the overall study population; p -value for interaction 0.36 for index pulmonary embolism).

In the Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy (AMPLIFY) study, 5395 patients with acute symptomatic proximal deep vein thrombosis or acute symptomatic pulmonary embolism were randomised to either initial treatment with apixaban (10 mg twice daily for 7 days followed by 5 mg twice daily) or standard treatment with enoxaparin followed by vitamin K antagonists for 6 months in a double-blind fashion [52]. On inclusion in the study, 1836 patients had symptomatic, objectively confirmed pulmonary embolism. Among these patients, recurrent symptomatic venous thromboembolism or death related to venous thromboembolism occurred in 2.3% and in 2.6% of those randomised to apixaban or conventional therapy (relative risk 0.90, 95% CI 0.50–1.61).

Edoxaban 60 mg once daily (30 mg daily in patients with risk of overdose) was compared with dose-adjusted warfarin in patients with symptomatic deep vein thrombosis (4921 patients) or pulmonary embolism (3319 patients) in a double-blind, double-dummy clinical trial after all patients received an initial 5-day treatment with heparin [53]. Treatment duration was pre-specified based on patients' individual risk as 3, 6 or 12 months. Among patients with index pulmonary embolism randomised to edoxaban or warfarin, recurrent venous thromboembolism and related deaths occurred in 2.8% *versus* 3.9%, respectively (OR 0.73, 95% CI 0.50–1.06).

Direct oral anticoagulants and risk stratification in acute pulmonary embolism

Whether the results obtained with direct oral anticoagulants in the treatment of acute pulmonary embolism apply to all patients with intermediate pulmonary embolism is unclear. These patients, identified through the presence of right ventricle dysfunction and increase in serum troponin, represents from 30% to >50% of the entire population with pulmonary embolism [26, 30, 54]. Data on right ventricle dysfunction and injury are not available in patients included in most of phase III trials. In these studies, the severity assessment of pulmonary embolism was mainly based on the thrombotic burden at CT (table 1).

According to the anatomical extent of pulmonary embolism, about one-quarter of the patients included in the EINSTEIN-PE had extensive (involvement of multiple lobes and >25% of entire pulmonary vasculature), ~58% had intermediate and ~12% had limited ($\leq 25\%$ of vasculature of a single lobe) pulmonary embolism [48]. The noninferiority of rivaroxaban compared with conventional anticoagulation was consistent in three tertiles of severity of pulmonary embolism in the subgroup analysis. However, the criteria for tertile identification were not reported.

In the AMPLIFY study, about one-third of patients with pulmonary embolism had extensive pulmonary embolism as assessed by the thrombotic burden at CT (multiple lobes and >25% of entire pulmonary

TABLE 1 Noninferiority clinical trials with direct oral anticoagulants for the acute and long-term therapy of pulmonary embolism (PE)

Drug	Trial	Design	Treatments	Duration	Patients	Severity evaluation for PE
Rivaroxaban	EINSTEIN-PE [48]	Open	Rivaroxaban (15 mg twice daily for 3 weeks, then 20 mg once daily)	3, 6 or 12 months	4832 patients with PE	Anatomical extension of PE
Apixaban	AMPLIFY [52]	Double blind	Enoxaparin/warfarin Apixaban (10 mg twice daily for 7 days, then 5 mg twice daily)	6 months	1836 patients with PE	Tertiles of severity Anatomical extension of PE
Edoxaban	HOKUSAI [53]	Double blind	Enoxaparin/warfarin LMWH/edoxaban (60 mg once daily) UFH or LMWH/warfarin	<12 months	3319 patients with PE	NT-proBNP levels (2989 patients) Right ventricle dilation at CT (1002 patients) Not reported
Dabigatran	RE-COVER I and RE-COVER II [50, 51]	Double blind	Enoxaparin/dabigatran (150 mg twice daily) Enoxaparin/warfarin	6 months	1602 patients with PE	

AMPLIFY: Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy; LMWH: low-molecular-weight heparin; UFH: unfractionated heparin; NT-proBNP: N-terminal pro-brain natriuretic peptide.

vasculature at CT) [52]. Efficacy and safety profiles of apixaban were confirmed in patients with different extents of vascular involvement ($p=0.0569$ for interaction on efficacy, not evaluable for safety).

In the HOKUSAI study, 2989 patients had the assessment of N-terminal pro-brain natriuretic peptide levels and 1002 the assessment of right ventricle dysfunction at CT. Increased N-terminal pro-brain natriuretic peptide levels were observed in 938 (31%) patients [53]; the rate of recurrent venous thromboembolism in this subgroup was 3.3% with edoxaban and 6.2% with warfarin (hazard ratio 0.52, 95% CI 0.28–0.98). Right ventricular dysfunction, as assessed by means of CT, was present in ~30% of the 1002 evaluated patients. In patients with right ventricular dysfunction at CT, a nonsignificant reduction in recurrent venous thromboembolism was observed with edoxaban as compared with warfarin (hazard ratio 0.42, 95% CI 0.15–1.20).

No data are available for dabigatran in subgroups of patients with pulmonary embolism of different severity.

None of the phase III studies with the new oral anticoagulants was large enough to have sufficient power for subgrouping according to right ventricular dysfunction. Further studies should assess the efficacy and safety of direct oral anticoagulants in subgroups of patients with different risk for death (*e.g.* those with right ventricle dysfunction and/or injury).

Only preliminary evidence is currently available on the use of rivaroxaban in patients who have been treated with thrombolytic agents [55]. No data in this clinical setting are available with the other agents.

Recurrent venous thromboembolism can be reduced by extending anticoagulant treatment [56, 57].

Phase III studies have been conducted with rivaroxaban, apixaban or dabigatran *versus* placebo in the extended treatment of venous thromboembolism [58–60]. All these agents were shown to be superior to placebo in the prevention of recurrences with a relatively favourable safety profile in terms of major bleeds. Dabigatran was also shown to be as effective and safer than warfarin in this indication [60].

Conclusions

Risk stratification in patients with acute pulmonary embolism is essentially based on the pathophysiology of the disease, which is mainly reflected by haemodynamic status and right ventricular overload. Recent trials with new anticoagulants have demonstrated the efficacy and safety of these agents in haemodynamically stable patients with acute pulmonary embolism. However, data on the severity of pulmonary embolism in the included patients are limited. Further evidence is awaited on the efficacy and safety of direct oral anticoagulants for patients with acute pulmonary embolism based on currently recommended risk stratification models.

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