Review

Steps toward simplifying the treatment of pulmonary embolism

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Practice Points

- Prognostic stratification to identify patients with pulmonary embolism (PE) at high versus low risk of short-term mortality is fundamental.
- Current standard treatment (low-molecular-weight heparin plus vitamin K antagonist) for acute, nonmassive PE is challenged by the new oral anticoagulants (NOACs).
- NOACs are as effective as, simpler and possibly safer than vitamin K agonists, and are likely to drastically change the short- and long-term treatment of PE.
- The issues of best management of major bleeding in patients on NOACs and of the availability of standardized tests to measure NOAC activity in specific clinical settings needs to be addressed.
- Home treatment is feasible for PE patients at very low risk of mortality and may be facilitated by NOACs whenever a dedicated adequate outpatient program is available.

SUMMARY: Therapeutic strategies for most patients with pulmonary embolism (PE) include the administration of low-molecular-weight heparin, fondaparinux or unfractionated heparin, followed by vitamin K antagonists. Over the last few years, research has focused on the development of new oral anticoagulant drugs that could overcome some of the main limitations of available parenteral anticoagulants or vitamin K antagonists. These drugs (e.g., dabigatran, rivaroxaban, apixaban or edoxaban) have been compared with standard treatment in a number of Phase III clinical trials in different clinical settings, including the treatment of acute deep-vein thrombosis and PE. The results of the completed trials with dabigatran and rivaroxaban suggest that both compounds can at least be as effective and safe as the standard treatment in these patients. Thus, there is now the possibility of greatly simplifying the treatment of PE

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patients with drugs that are administered orally and do not require laboratory monitoring. This treatment could be particularly interesting for those PE patients who are deemed eligible for home treatment, based on well-validated scores. However, well-organized outpatient programs need to be implemented before this strategy becomes widely applied.

Current treatment strategies for patients with pulmonary embolism

Current guidelines emphasize the need for immediate anticoagulation in patients with acute pulmonary embolism (PE) or high-clinical suspicion of PE while awaiting definitive diagnostic confirmation, in order to reduce mortality rate and prevent recurrent thrombotic events [1,2]. Until now, parenteral administration of unfractionated heparin (UFH), low-molecular-weight heparin (LMWH) or fondaparinux has been the only available approach to achieving rapid anticoagulation.

UFH was the first drug to be studied and became the standard treatment of PE; however, it requires continuous intravenous infusion with frequent laboratory monitoring and dose titration. In the 1990s, several randomized controlled trials (RCTs) evaluated the use of LMWH as the initial treatment of venous thromboembolism (VTE) [3–5]. Strong evidence that subcutaneous LMWH is more effective and safe than intravenous UFH came from the results of a recently updated Cochrane review [6], thus endorsing the current predominant role of LMWH. Fondaparinux, a selective, indirect inhibitor of factor Xa, was subsequently shown to be noninferior to UFH in a RCT conducted in patients with acute symptomatic PE [7]. As a result, LMWH and fondaparinux currently represent the recommended therapeutic strategies for the acute-phase treatment of hemodynamically stable PE, whereas UFH remains the preferred choice in patients with severe renal insufficiency [1,2]. Parenteral anticoagulation is usually followed by early initiation of oral vitamin K antagonists (VKAs), which should be continued for at least 3 months [2].

Only limited evidence is available on the benefit of thrombolysis in patients with acute PE [8]. Thrombolytic therapy may actively promote the lysis of thromboembolic obstruction, resulting in rapid resolution of symptoms, stabilization of respiratory and cardiovascular function and reduction in mortality; however, it is associated with a considerable increase in major bleeding, mainly fatal and intracranial. A previous meta-analysis showed a benefit of thrombolysis compared with heparin only in the subgroup of patients with hemodynamically unstable PE, with a significant reduction in the composite outcome of death and recurrent PE [9]. In addition, a recent retrospective evaluation of patients receiving thrombolysis for PE showed that, among the single-risk factors, shock was associated with the highest in-hospital mortality from PE [10]. Therefore, current guidelines recommend thrombolysis only for patients with hypotension and low-bleeding risk [1,2]. Although evidence suggests that thrombolytic therapy may reduce all-cause case-fatality rate from 47 to 15% and PE-related case-fatality rate from 42 to 8.4%, only 30% of unstable patients received thrombolytic therapy in a Nationwide Inpatient Sample [11].

Systemic infusion of the thrombolytic agent is the suggested method, since direct local infusion in the pulmonary artery did not show any advantage. Thrombolysis can still be effective in patients with symptoms for up to 14 days, but the greatest benefit is observed when treatment is started within 48 h after the onset of symptoms [1]. Large clinical trials are ongoing in order to assess whether thrombolysis may also be beneficial for selected patients with right ventricular (RV) dysfunction, but without hemodynamic instability [12].

Can we simplify the treatment of PE with the new anticoagulant drugs?

Long-term treatment with VKAs, the only available oral anticoagulants in the past 60 years, requires frequent laboratory monitoring because of the inter- and intra-individual variability in dose response, as well as the narrow therapeutic window.

In the last decade, several novel oral anticoagulants (NOACs) have been developed and evaluated in Phase III RCTs for the prevention and treatment of VTE, along with the treatment of atrial fibrillation, including the direct, selective inhibitors of thrombin (e.g., dabigatran)

and factor Xa (e.g., rivaroxaban, apixaban and edoxaban) [13]. These new compounds may potentially overcome some of the limitations of VKAs, since they have a predictable anticoagulant effect that allows fixed dosing regimens without the need for routine laboratory monitoring.

Dabigatran has been evaluated in two large RCTs on the treatment of acute VTE [14,15]. After the initial administration of the approved parenteral anticoagulants, patients were randomized to 150-mg dabigatran twice-daily (b.i.d.) or warfarin titrated to an international normalized ratio range of 2.0–3.0, in a double-blind, double-dummy manner, for 6 months. The choice of initial parenteral treatment was made in order to ensure the immediate anticoagulant effect and to reduce the risk of early recurrences, which were observed in the trial with the precursor ximelagatran administered as a standalone treatment from the beginning [16].

The RE-COVER trial enrolled 2564 patients with acute symptomatic VTE, of whom 31% had PE. Dabigatran was demonstrated to be noninferior to warfarin in the primary efficacy outcome of recurrent symptomatic VTE and VTE-related deaths (2.4 vs 2.1%; HR [hazard ratio]: 1.10; 95% CI: 0.65–1.84) and in the rate of major bleeding events (1.6 vs 1.9%; HR: 0.82; 95% CI: 0.45–1.48) [14]. These results were confirmed in a second study: the RE-COVER II trial [15]. The most common side effect of dabigatran was dyspepsia, reported in 3% of patients [14], which was probably due to the formulation of dabigatran, containing a tartaric acid core.

Dabigatran was later assessed in two RCTs for the long-term, secondary prevention of VTE [16,17]. The RE-SONATE trial confirmed the efficacy of extended treatment with dabigatran. After 6–18 months of anticoagulant therapy, 1343 patients with VTE were randomized to 150-mg dabigatran b.i.d. or placebo for an additional 6 months, in a double-blind manner. Dabigatran obtained a 92% relative risk reduction of recurrent VTE (0.4 vs 5.6%; HR: 0.08; 95% CI: 0.020–0.25; $p < 0.0001$) with a low risk of major bleeding (0.3 vs 0%; $p = 0.5$) [17].

In the RE-MEDY trial, dabigatran was compared with warfarin in 2856 patients with VTE for 6–36 months after the initial treatment of the disease. Dabigatran was as effective as warfarin, showed a trend toward less major bleeding events (0.9 vs 1.8%; HR: 0.52; 95% CI: 0.27–1.01), but an increased incidence of acute coronary syndromes (0.9 vs 0.2%; $p = 0.02$) [18].

An increased risk of myocardial infarction has been noted with the use of dabigatran. A recent meta-analysis reported an estimated 27–33% relative risk increase for acute coronary events, with the use of dabigatran for primary and secondary prevention of cardiovascular diseases [19]. However, it is not clear whether this can be due to an intrinsic property of dabigatran or a protective effect of the comparator antithrombotic drugs [20].

Rivaroxaban was compared with standard treatment of VTE in two RCTs, one carried out in patients with acute deep-vein thrombosis (DVT) [21] and the second in patients with PE [22]. In this second study with an open-label design, 4832 patients with acute symptomatic PE, with or without DVT, were randomized to rivaroxaban alone (15-mg b.i.d. for 3 weeks, then 20-mg daily) or to standard treatment with enoxaparin followed within 48 h by adjusted-dose VKA for 3, 6 or 12 months. Rivaroxaban was found to be noninferior to standard treatment in the primary efficacy outcome of symptomatic recurrent VTE (2.1 vs 1.8%; HR: 1.12; 95% CI: 0.75–1.68). Of note, this similar efficacy was confirmed in the early phase, with a similar rate of recurrent events at the end of the twice-daily administration period. Moreover, fewer episodes of major bleeding were reported with rivaroxaban compared with standard therapy (1.1 vs 2.2%; HR: 0.49; 95% CI: 0.31–0.79; $p = 0.003$), thus confirming the favorable benefit–risk profile of this new drug [22].

Finally, the EINSTEIN-EXTENSION trial confirmed the efficacy of rivaroxaban in the secondary prevention of VTE [21]. In a double-blind RCT, 1196 patients with DVT or PE who were treated with either rivaroxaban or VKAs for 61–62 months were randomized to 20-mg rivaroxaban daily or placebo for an additional 6 or 12 months. Rivaroxaban showed superior efficacy in the primary efficacy outcome of symptomatic recurrent VTE (1.3 vs 7.1%; HR: 0.18; 95% CI: 0.09–0.39; $p < 0.001$) with an acceptable rate of major bleeding (0.7 vs 0%; $p = 0.11$) [21].

Two other factor Xa inhibitors are currently being evaluated for the treatment of VTE: edoxaban, in the ongoing HOKUSAI-VTE trial and apixaban, in the ongoing AMPLIFY and AMPLIFY-EXTENSION trials.

The NOACs have the potential to simplify the management of PE. These new molecules have remarkable pharmacologic properties (rapid

onset of action, short half-life and predictable anticoagulant effect), which make routine laboratory monitoring unnecessary and may reduce overdosage or bleeding events [23]. In several RCTs focusing on VTE treatment, dabigatran and rivaroxaban appeared to be at least as safe and effective as conventional anticoagulant therapy, with the advantage of lower rates of intracranial bleeding [14,22]. Notably, rivaroxaban administered as monotherapy seemed to have a better net clinical benefit than standard therapy [18], thus appearing as an attractive treatment strategy for the outpatient management of selected patients with acute, stable PE.

In the abovementioned RCTs, the NOACs were compared with a high-quality management of warfarin dosing, expressed by a time within therapeutic range of 60% in the RECOVER trial [14] and 63% in the EINSTEIN-PE trial [22], thus suggesting that their benefit might be even higher in the setting of less optimal quality of VKA management, especially in patients with unstable international normalized ratios.

There remain a number of issues that need to be carefully addressed while NOACs (rivaroxaban) are introduced into clinical practice for the treatment of DVT in Europe, Canada and other countries, and while waiting for their approval in the setting of PE. First, unlike warfarin, which can be reversed by the administration of vitamin K, fresh-frozen plasma or prothrombin complex concentrates (PCCs), no specific antidote is currently available for NOACs in case of major bleeding events. Rivaroxaban could be partially antagonized by PCCs [24,25], while for direct thrombin inhibitors, hemodialysis is a reasonable option [25,26]. The role of fresh-frozen plasma, PCCs and recombinant activated factor VIIa in the reversal of NOACs still needs to be better established.

Second, although routine laboratory monitoring is not necessary, reliable laboratory tests to measure a drugs' activity in specific clinical settings (e.g., in the case of thromboembolic or bleeding complications, drug interactions, or renal or liver failure) are necessary and need to be standardized.

Third, careful patient education is essential in order to ensure treatment adherence.

Can we tailor treatment strategies based on the individual risk profile?

The risk of adverse outcomes varies among different groups of patients with PE. Indeed, PE is associated with a wide prognostic spectrum, ranging from prompt and complete resolution of symptoms after a few hours of treatment to sudden death.

In recent years, research has focused on stratifying the risk of adverse outcomes associated with PE in order to tailor treatment and management strategies. Recent clinical practice guidelines on the management of PE, both from Europe and North America, identify at least two categories of patients: those at high risk of early mortality (>15%), that is, massive PE and those not at high risk of early mortality, that is, submassive and low-risk PE, based on the presence or absence of shock, or sustained arterial hypotension, respectively [1,27].

Patients with acute, hemodynamically unstable PE, which is presenting with sustained hypotension (systolic blood pressure of <90 mmHg for at least 15 min) or requiring inotropic support, pulselessness or persistent profound bradycardia, have the highest risk of short-term mortality (>50%) [28].

Patients not at high risk of early mortality, who actually represent >90% of patients with PE, are highly heterogeneous. Among them, there is a group at low risk of early mortality (defined as ~1%, at 30 days or during hospital stay) and a second group at intermediate risk, with an early mortality rate ranging from more than 1% up to approximately 15% [1,27]. Several parameters have been proposed for the stratification of patients not at high risk of mortality: demographic, anamnestic and objective findings (often combined in clinical prediction rules [CPRs]), as well as imaging tests and laboratory markers of RV dysfunction or injury. These parameters show different prognostic abilities to identify patients at low or intermediate risk of early mortality.

Among several CPRs developed in recent years [29], the Pulmonary Embolism Severity Index (PESI) [30] and its simplified version [31], as well as the Geneva prognostic score [32], are the most rigorously derived and widely validated. PESI takes into account age, gender, presence of cancer, heart failure, chronic lung disease, tachycardia, hypotension, tachypnea, low-body temperature, altered mental status and hypoxia **(Table 1)**. The Geneva prognostic score includes history of DVT, concomitant DVT, presence of cancer, heart failure, hypotension and hypoxia **(Table 2)**.

Table 1. Pulmonary Embolism Severity Index.

Predictors	Points assigned	Class	Risk	Points
Age	Age in years	I	Very low	≤65
Males	+10	II	Low	66–85
Cancer	+30	III	Intermediate	86–105
Heart failure	+10	IV	High	106–125
Chronic lung disease	+10	V	Very high	≥126
Pulse ≥110 beats/min	+20			
Systolic blood pressure <100 mmHg	+30	I–II	Low	≤85
Respiratory rate ≥30 breaths/min	+20	III–V	High	>85
Temperature <36°C	+20			
Altered mental status†	+60			
Arterial blood oxygen saturation <90%‡	+20			

†Defined as disorientation, lethargy, stupor or coma.
‡With and without the administration of supplemental oxygen.

In particular, PESI presents the most solid published data, having been studied in more than 22,000 patients with PE. Its strength relies especially on the ability to detect patients at low risk of PE (high negative predictive power). Indeed, PESI identifies approximately 40% of PE patients (PESI class I and II) with an in-hospital mortality of less than 1% (0.2%; 95% CI: 0.0–0.7%) [30], a threshold that both the European Society of Cardiology [1] and the American Heart Association [28] have adopted to define PE patients at low risk. In addition, CPRs are based on clinical data that are collected routinely, therefore being easy to obtain and widely applicable, even in the absence of specialist physicians.

Findings of RV dysfunction using biomarkers and imaging also show a high negative predictive value, even if they are not as accurate as PESI at identifying patients with early mortality risk ≤1%. Normal levels of BNP, NT-proBNP or troponin were associated with an early mortality rate of 2.2% (95% CI: 0.45–6.2), 1.3% (95% CI: 0.15–4.4) and 3.7% (95% CI: 2.7–4.7), respectively [33,34]. In addition, echocardiographic findings of RV dysfunction had only a 60% negative predictive value (95% CI: 55–65) for the identification of PE patients at low risk [35]. On the other hand, the absence of RV enlargement at computed tomography pulmonary angiography (CTPA; defined as a right-to-left ventricular dimensional ratio of <0.9) has recently been shown to be an independent predictor of early mortality, with a 100% (95% CI: 98–100%) negative predictive power; however, these findings need to be confirmed in other studies [36].

Along with the need to identify PE patients at very low risk of mortality, who may benefit from a short hospital stay or even home treatment, it is equally important to identify those patients who do not present with massive PE (i.e., hemodynamically stable patients), but may need a more aggressive therapeutic strategy. RV dysfunction and/or injury caused by PE has been consistently associated with adverse outcomes in hemodynamically stable patients. RV dysfunction identified by means of imaging tests (echocardiography or CTPA) or elevated biomarkers (BNP) showed a risk ratio for mortality of 2.4 (95% CI: 1.3–4.45) and 9.5 (95% CI: 3.2–28.6), respectively [35]. A large, retrospective evaluation of hemodynamically stable patients confirmed that all-cause mortality was higher in the presence of enlarged RV size as compared with normal RV size (8.0 vs 3.3%; p = 0.003) [37]. In addition to RV dysfunction, RV injury identified by elevated troponins was also associated with increased mortality (odds ratio: 7.03; 95% CI: 2.4–20.4) [34]. In patients with both elevated troponins and enlarged RV, all-cause mortality was 10.2% compared with 1.9% in patients who had neither (p < 0.0001) [37]. The combination of these parameters might indicate a group of patients who would benefit from intense monitoring and aggressive treatment if subsequently indicated. However, despite RV dysfunction and/or injury have been consistently associated with short-term mortality, their prognostic performance in terms of positive predictive value is not accurate enough to routinely recommend more aggressive treatment strategies based only on those markers of RV impairment [1,2,27]. PESI

Table 2. Geneva prognostic score.

Predictors	Points assigned	Risk class	Points
Cancer	+2	Low	≤2
Heart failure†	+1	High	>2
Previous DVT	+1		
Systolic blood pressure <100 mmHg	+2		
PaO_2 <8 kPa (60 mmHg)‡	+1		
DVT shown by ultrasound	+1		

†Defined as history of chronic heart failure or acute pulmonary edema as determined from the admission chest x-ray.
‡While breathing room air.
DVT: Deep vein thrombosis; PaO_2: Arterial partial pressure of oxygen.

or other CPRs do not show high positive predictive value either [29]. The presence of both RV dysfuncion (at echocardiography or CTPA) and injury (elevated troponin) is being used to identify hemodynamically stable PE patients at higher risk of mortality who may benefit from a more aggressive treatment in a large, ongoing RCT comparing pharmacological thrombolysis versus standard treatment [12].

Home treatment & early discharge

Risk stratification of PE patients may assist clinicians in determining both the best treatment and the appropriate setting for the initial therapy [1,27]. PE patients are commonly admitted to hospital for their initial treatment, although some of them may be suitable for a short hospital stay or complete home treatment [38,39]. Emergency physicians are often reluctant to discharge patients for outpatient treatment because PE is a potentially lethal disease [40]. Indeed, safe outpatient management of patients with low-risk PE may theoretically lead to a decrease in unnecessary hospitalizations, reducing the risk of acquired infections and death, and an improvement in health-related quality of life, as well as a reduction in healthcare costs [41]. Moreover, NOAC agents may further simplify PE home therapy, thus avoiding administration of LMWH; many patients are not familiar with subcutaneous injections and a home-care nurse is often needed.

Several published studies have already provided valuable data supporting a safe home treatment for low-risk PE patients [38,39]. Most of these promising data derive from cohorts of PE patients that were prospectively selected for home treatment based on a list of inclusion/exclusion criteria and were recently described in a systematic review by the present authors' group [38]. Until 2009, a total of 25 studies on PE outpatient treatment and early discharge had been published. No RCTs were identified. For only 11 manuscripts, a complete quality assessment and data extraction were possible [38]. A total of 928 and 242 patients were included in these 11 studies and the remaining 14 included studies, respectively [38]. Common patient-related exclusion criteria (i.e., concomitant medical condition, patient's choice) and drug-related reasons for hospital admission (i.e., a body weight of >110 kg and a creatinine clearance of >30 ml/min) were more regularly adopted than disease-related exclusion criteria for patient selection [38].

Only hypoxia was frequently used in eight out of 11 studies [38]. Patients were entirely treated at home in seven of the 11 studies. Conversely, in the remaining four studies, patients were discharged early, between day 1 and 5 of hospitalization [38]. When patients were treated entirely at home, an outpatient treatment program was provided. This usually included home-care nurses for LMWH administration and the availability of a 24-h emergency phone number. No patients died in the first 7–10 days (data available for six of the 11 studies). At a median follow-up of 3 months, mortality rates ranged from 0 to 43.5% in cancer patients [38].

Although available data were not of high quality, promising results from these studies encouraged researchers to design and perform RCTs. From 2009, four additional cohort studies and two RCTs have been published [42–47]. Only two of these four cohort studies were prospective [44,45]. Three of the cohort studies used a classical list of clinical inclusion/exclusion criteria, but the fourth used a blood test – a NT-proBNP level of <500 pg/ml – as the main criterion for out-of-hospital treatment of PE patients [44]. In all four studies, patients were either discharged from the emergency room immediately or within a maximum of 24 h after admission. A total of 1024 patients were finally included. Overall, the

results of these four cohort studies were similar to those previously published [38].

In both RCTs, a prognostic CPR (the Uresandi CPR and PESI), was already formally applied to select patients at low risk of mortality [46,47]. The two studies randomized patients with acute PE to receive LMWH either in the hospital for only 3 days versus entirely in the hospital [46], or entirely out of the hospital (discharged within 24 h) versus at least partly in hospital [47]. The former study was stopped prematurely due to an unexpectedly high rate of adverse outcomes in both groups, in particular, overall mortality was 4.2% in the early discharge group and 8.3% in the control group [46]. In the latter, the so-called OPTE study, 344 patients with PESI class I or II were discharged from the emergency department within 24 h after randomization or admitted to the hospital and discharged based on the decision of the treating physician [47]. One (0.6%) out of 171 outpatients developed recurrent VTE within 90 days compared with none out of 168 inpatients (95% upper confidence limit [UCL]: 2.7%). Only one (0.6%) patient in each treatment group died within 90 days (95% UCL: 2.1%) and two (1.2%) out of 171 outpatients and no inpatients had major bleeding within 14 days (95% UCL: 3.6%). By 90 days, three (1.8%) outpatients but no inpatients had developed major bleeding (95% UCL: 4.5%) [47].

Based on this evidence, the latest edition of the American College of Chest Physicians guidelines only suggests "early discharge over standard discharge (e.g., after the first 5 days of treatment) in patients with low-risk PE and whose home circumstances are adequate (grade 2B)" [2].

Conclusion

In patients diagnosed with PE, a correct prognostic stratification is the first step to conveying the best treatment strategy. It is fundamental to identify patients at highest risk of short-term mortality, that is, those with hemodynamically unstable PE (massive PE) who can benefit from pharmacological thrombolysis. Among patients not at high risk of mortality, a group at intermediate risk could be identified by means of imaging and/or laboratory markers of RV impairment; some of these patients are also expected to benefit from a more aggressive treatment strategy; however, specific recommendations cannot be carried out at present, due to a lack of adequate evidence. Finally, a group of patients at low risk of short-term mortality (i.e., <1% at 30 days or in-hospital) can be identified by CPRs (e.g., PESI or Geneva prognostic score) and can be suitable for early discharge or a complete home treatment whenever a dedicated, well-organized, 24-h outpatient program could be provided to each patient, similar to those already existing for DVT patients worldwide. In addition to a correct drug therapy, an outpatient-dedicated program is crucial to rapidly assess and manage any complication and to correctly investigate PE patients for not missing any possible manifest or occult underlying risk factor, such as cancer.

NOACs have the potential to simplify the management of PE, thanks to remarkable pharmacologic properties (rapid onset of action, short half-life and predictable anticoagulant effect), which make them at least as safe and effective as conventional anticoagulant therapy, with the advantage of lower rates of intracranial bleeding and the absence of routine laboratory monitoring. For all these reasons, NOACs also appear an attractive treatment strategy for the outpatient management of selected patients with PE. However, some issues related to NOACs (management of major bleeding and reliable and standardized tests to measure their activity in special situations) still require further research while these drugs are becoming available for the treatment of PE.

Future perspective

In the near future, the clinical scenario of the short-term management of PE is likely to change considerably.

First, high-quality evidence is becoming available on the home treatment of patients with PE who are at very low risk of short-term mortality. On the one hand, this is a very attractive prospect for both patients and clinicians, but on the other hand, it implies that a dedicated, well-organized, adequate outpatient program needs to be implemented for each patient. For this purpose, a pivotal role could be played by the anticoagulation clinics, which are already involved in outpatient programs for DVT and are currently managing anticoagulant therapy and long-term follow-up of patients with PE.

In addition, NOACs are likely to be approved for the treatment of acute PE by the regulatory agencies shortly. This will allow for simpler and possibly safer treatment of acute PE, even on an outpatient basis. However, a number of

issues need to be carefully addressed regarding NOACs, among which the optimal management strategies in case of major bleeding and the development of standardized reliable laboratory tests to measure drug activity in specific clinical settings. Again, a central role is likely to be played by the anticoagulation clinics – they will need to reorganize their activities in order to continue to provide periodic clinical visits (even in the absence of routine laboratory monitoring of NOACs) and immediate availability in case of signs and symptoms of recurrent VTE, bleeding or other clinical problems.

Finally, in the near future, targeted treatment strategies will likely be available for nonhemodynamically unstable patients who are still at intermediate-to-high risk of short-term mortality. Research is focusing on identifying reliable short-term prognostic factors to recognize this group of patients, who may benefit from thrombolysis; a large ongoing RCT is trying to provide an answer to this unmet clinical need [12].

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