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REVIEW

Frontiers in cardiovascular medicine

Management of venous thrombo-embolism: an update

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Venous thrombo-embolism is the third most frequent acute cardiovascular syndrome after myocardial infarction and stroke. Recently published landmark trials paved the way for significant progress in the management of the disease and provided the evidence for the ESC Pulmonary Embolism (PE) Guidelines 2014 update. Risk stratification strategies for non-high-risk PE continue to evolve, with an increasing emphasis on clinical prediction rules and right ventricular (RV) assessment on computed tomographic pulmonary angiography. In the field of anticoagulation treatment, pharmacogenetic testing for vitamin K antagonists on top of clinical parameters was not found to offer a significant benefit during the initiation phase; on the other hand, dosing based on the patient's clinical data seems superior to fixed loading regimens. The phase 3 trial programme of new oral anticoagulants in the treatment of venous thrombo-embolism has been completed, and the results indicate that these agents are at least as effective and probably cause less major bleeding than currently standard treatment. A multicentre prospective phase 4 trial will determine whether early discharge and out-of-hospital treatment of low-risk PE with the oral factor Xa inhibitor rivaroxaban is feasible, effective, and safe. For intermediate-risk PE defined on the basis of imaging tests and laboratory biomarkers, the bleeding risks of full-dose thrombolytic treatment appear too high to justify its use, unless clinical signs of haemodynamic decompensation appear. Patients in whom PE has resulted in chronic thrombo-embolic pulmonary hypertension and who are not suitable for pulmonary endarterectomy, may be expected to benefit from emerging pharmaceutical and interventional treatment options.

Keywords Venous thrombo-embolism • Pulmonary embolism • Prognosis • Management • Risk assessment • Anticoagulants • Thrombolysis • Chronic thrombo-embolic pulmonary hypertension

Clinical case

An 84-year-old woman suddenly complained of chest pain at home; a few moments later she collapsed and became unconscious. Her relatives called the emergency physician who diagnosed pulseless electrical activity and started chest compressions. The patient's blood pressure returned promptly and she regained consciousness. She was admitted to the chest pain unit of a University hospital, where she remained oriented but continued to complain of chest pain and dyspnoea. The ECG was non-diagnostic. Troponin I levels measured by a high-sensitivity assay were abnormally high. She was taken to the catheterization laboratory after receiving aspirin and a loading dose of ticagrelor. A 90% stenosis of the right coronary artery was found and dilated. A bare metal stent was successfully implanted into the lesion and the patient was transferred to the coronary care unit saying that she felt better. Laboratory findings included anaemia (haemoglobin 9.5 g/dL) and reduced renal function (calculated ceratinine clearance 40 mL/min).

Twelve hours later, the patient collapsed again after standing up to go to the bathroom. She was cyanotic and orthopnoeic; her blood pressure was 80 over 40 mmHg, her heart rate 125 b.p.m. Bedside echocardiography was performed (*Figure 1*, left) followed by computed tomographic pulmonary angiography (*Figure 1*, middle and right).

How would you manage this patient?

Introduction

Venous thrombo-embolism (VTE) is the third most frequent cardiovascular disease after myocardial infarction and stroke,[1,2] affecting almost all medical disciplines including paediatrics.[3,4] Its most serious clinical presentation, acute pulmonary embolism (PE), is a major cause of mortality, morbidity, and hospitalization in Europe;[2]

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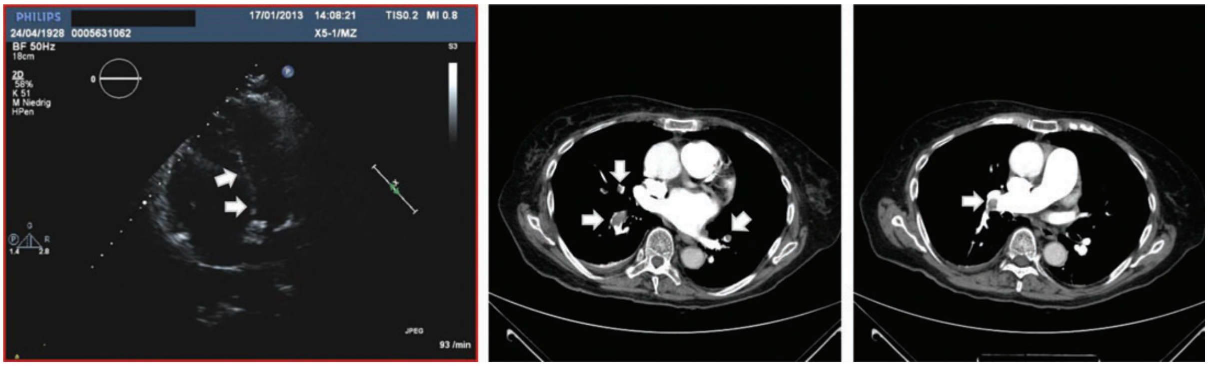

Figure 1 A patient with recurrent syncope and an initial diagnosis of acute coronary syndrome. Left panel: bedside transthoracic echocardiography (apical four-chamber view) showed an enlarged right ventricle with end-diastolic bowing of the interventricular septum towards the left ventricle (arrows). Middle and right panels: Computed tomographic angiography of the chest revealed multiple filling defects in the branches of both pulmonary arteries (arrows).

its exponential increase with ageing of the population[5] is expected to result in an ever larger number of patients diagnosed with (and dying of) the disease in the years to come. The present update focuses primarily on the management of acute PE, taking into account that several aspects related to the treatment and secondary prophylaxis of the disease equally apply to patients with acute deep-vein thrombosis (DVT). We discuss the recent advances in the management of VTE, focusing on the results of major studies published over the past 12 months. Topics covered by our review include the evolution of risk stratification tools and strategies for managing normotensive patients with acute PE; the shift from efficacy to safety of the thrombolysis debate in non-high-risk PE; the use of new oral anticoagulants in treatment and secondary prophylaxis; and the potential transition of acute VTE to chronic thrombo-embolic pulmonary hypertension (CTEPH).

Progress in diagnosis and risk assessment of pulmonary embolism

Clinical, imaging, and laboratory parameters

Risk-adjusted diagnostic algorithms for patients with clinically suspected acute PE have remained largely unchanged since the last (2008) update of the ESC Guidelines.[6] More recently, the Wells and revised Geneva clinical prediction rules for the assessment of pre-test probability were simplified[7,8] and the simplified versions externally validated.[9,10] Independently from the (original or simplified) rule used, the proportion of patients with confirmed PE (after diagnostic workup) is ~10% in the low-probability category, 30% in the moderate-probability category, and 65% in the high-probability category.

A multicentre prospective management study evaluated age-adjusted cut-offs (age × 10 µg/L >50 years) to improve the performance of D-dimer testing in the elderly.[11] Patients with a normal age-adjusted D-dimer value did not undergo computed tomographic pulmonary angiography (CT), but were left untreated and followed over a 3-month period. Of 3346 patients included in the study, 766 were 75 years or older, and 673 of those had a non-high clinical (pre-test) probability. In this elderly group, use of the age-adjusted cut-off (instead of 500 µg/L) increased the number of patients in whom PE could be excluded on the basis of D-dimer testing from 43 to 200, without additional false-negative findings.[11]

Computed tomographic angiography has been established as the imaging gold standard for confirmation or exclusion of the disease. However, a number of uncertainties remain. For example, the clinical significance and particularly the therapeutic implications of isolated subsegmental PE on CT angiography are questionable. A meta-analysis reported that this finding was present in 4.7% (2.5–7.6%) of patients with PE imaged by single detector CT angiography and 9.4% (5.5–14.2%) of those submitted to multidetector CT.[12] The positive-predictive value was low, and the inter-observer agreement was poor at this level.[13] Another relevant issue is the incidental discovery of clinically unsuspected PE on CT angiography, which is becoming increasingly frequent (1–2% of all thoracic CT examinations at present); it concerns primarily patients with cancer, but also those with heart failure or atrial fibrillation.[14–17] There are no robust data to guide the decision on how to manage unsuspected ('incidental') PE, particularly, if it is limited to segmental or subsegmental branches.

The definition of high-risk[6] (or massive, based on the North American classification[18]) PE relies on the presence of clinically overt RV failure that results in haemodynamic compromise. Currently, research on the usefulness of (further) risk stratification focuses on patients with 'non-high-risk' PE, i.e. those without haemodynamic instability at presentation. Prediction rules based on clinical parameters were shown to be helpful in the prognostic assessment of patients with acute PE. Of those, the Pulmonary Embolism Severity Index (PESI) is the best known and most extensively validated score to date.[19] The principal strength of the PESI lies in the reliable identification of patients at low risk for 30-day mortality (PESI classes I and II). One randomized trial employed a low PESI as the inclusion criterion for home treatment of acute PE.[20] A simplified version of the original PESI has also been developed and validated.[21,22] As with the original index, the clinical value lies primarily in ruling out (rather than indicating) an elevated risk.[23]

Echocardiographic findings indicating RV dysfunction have been reported in at least 25% of patients with PE.[24] Frequently used parameters include RV dilatation, an increased right-to-left ventricular diameter ratio (with the cut-off value usually set at 0.9 or 1.0), hypokinesia of the free RV wall, increased velocity of the jet of tricuspid regurgitation, decreased tricuspid annulus plane systolic excursion, or combinations of the above. Meta-analyses have shown that RV dysfunction detected by echocardiography is associated with an elevated risk of short-term mortality in patients without haemodynamic instability, but its overall positive-predictive value is low.[25,26] Notwithstanding its limitations, echocardiographic assessment of the morphology and function of the RV remains a valuable bedside tool in the prognostic stratification of non-high-risk patients with acute PE, particularly when used in combination with clinical and/or laboratory parameters (see below).

Four-chamber views of the heart on CT angiography may detect RV enlargement as an indicator of RV dysfunction. A prospective multicentre cohort study of 457 patients demonstrated the prognostic value of an enlarged RV, defined as a right-to-left ventricular end-diastolic dimensional ratio $\geq$0.9.[27] In that study, in-hospital death or clinical deterioration occurred in 44 patients with and in 8 patients without RV enlargement on CT (14.5 vs. 5.2%, $P <$ 0.004).[27] A recent meta-analysis of 36 studies, eight of which were prospective, confirmed the high-negative-predictive value of the absence of RV enlargement on CT angiography, which reached 99% with regard to PE-related mortality at 30 days.[28] The majority of the included studies used a right-to-left ventricular dimensional ratio of either 0.9 or 1.0 as the cut-off point; cut-off values of 0.9 or 1.0 were also among the inclusion criteria of two recently published multicentre thrombolysis trials.[29,30]

RV pressure overload is associated with increased myocardial stretch, which leads to the release of brain natriuretic peptide (BNP) or N-terminal (NT)-proBNP. In a prospective multicentre cohort study which included 688 patients, NT-proBNP plasma concentrations of 600 pg/mL were identified as the optimal cut-off value for the identification of elevated risk.[31] At the other end of the severity spectrum, low levels of BNP or NT-proBNP can identify patients with a favourable short-term clinical outcome based on their high-negative-predictive value.[25,32] Haemodynamically, stable patients with low NT-proBNP levels may be candidates for early discharge and outpatient treatment.[33]

Elevated plasma troponin concentrations, indicating myocardial injury and necrosis (possibly) in the right ventricle, have repeatedly been reported in PE and associated with a worse prognosis. The negative-predictive value is high and apparently independent from the assays and cut-off values used.[34] Heart-type fatty acid-binding protein (H-FABP), an early marker of myocardial injury, was also found to predict an adverse early outcome in acute PE.[35,36]

Further laboratory parameters reported to be of prognostic value in patients with acute PE are those related to renal dysfunction or acute kidney injury; they include elevated serum creatinine levels and a decreased (calculated) glomerular filtration rate[37] as well as elevated neutrophil gelatinase-associated lipocalin and cystatin C.[38]

The updated (ESC Guidelines 2014 citation) classification of PE severity based on early mortality risk is shown in *Table 1*.

Combined parameters and scores

Various combinations of clinical findings, echocardiography, and laboratory biomarkers have been proposed and tested in registries and cohort studies in an attempt to improve risk stratification of PE.[39–43] Clearly, the ultimate goal is to validate the possible implications of such modalities and scores in therapeutic trials. In this regard, the combination of RV dysfunction on the echocardiogram (or CT angiogram) with a positive cardiac troponin test was used as an inclusion criterion in a randomized thrombolysis trial which enrolled 1006 normotensive patients with acute PE.[30] Patients initially treated with anticoagulation alone had a 5.6% incidence of death or haemodynamic decompensation within the first 7 days following randomization, a rate which supports the ability of this combination to determine intermediate-risk PE.

Treatment in the acute phase of venous thrombo-embolism

Initial parenteral anticoagulation and alternative options

Treatment of VTE with anticoagulants aims at the prevention of early deaths related to the index event as well as of symptomatic or fatal recurrence. With standard anticoagulation regimens, the duration of acute-phase treatment covers the first 5–10 days; during this period, parenteral anticoagulation (usually with low-molecular-weight heparin or fondaparinux) is given in parallel with a vitamin K antagonist (VKA) and is discontinued as soon as the international normalized ratio (INR) reaches therapeutic levels (2.0–3.0) for two consecutive days. In recent trials testing new oral anticoagulants (see below), when dabigatran or edoxaban was compared with a VKA, heparin administration remained unchanged during the acute phase and treatment was switched, without overlap, to the oral agent after the first 5–10 days. Alternatively, when rivaroxaban or apixaban was given from the beginning, initial parenteral heparin treatment was no longer necessary. In this latter case, acute-phase treatment consisted of a higher dose of the oral anticoagulant over the first 3 weeks (for rivaroxaban), or over the first 7 days (for apixaban).

Vitamin k antagonists

Vitamin k antagonists should be initiated as soon as possible after the diagnosis of VTE, preferably on the same day as the parenteral anticoagulant. Warfarin, acenocoumarol and phenprocoumon remain the anticoagulants most frequently prescribed for VTE. Their target is vitamin K epoxide reductase (VKOR), the enzyme that produces the active form of vitamin K. Mutations in VKOR may lead to various degrees of VKA resistance. In addition, polymorphisms in the gene encoding for the cytochrome P-450 enzyme CYP2C9 may change daily VKA requirements. In a previous review article,[44] we highlighted the possible value of pharmacogenetic testing (*CYP2C9* and *VKORC1* genotyping) for optimizing the precision of

Table 1 Classification of patients with acute pulmonary embolism based on early mortality risk [adapted from (ESC Guidelines 2014 citation)]

Early mortality risk		Risk parameters and scores			
		Shock or Hypotension	PESI class III-V or sPESI ≥1[a]	Signs of RV dysfunction on an imaging test[b]	Cardiac laboratory biomarkers[c]
High		+	(+)[d]	+	(+)[d]
Intermediate	Intermediate–High	–	+	Both positive	
	Intermediate–Low	–	+	Either one (or none) positive[e]	
Low		–	–	Assessment optional; if assessed, both negative[e]	

PE, pulmonary embolism; PESI, Pulmonary Embolism Severity Index; RV, right ventricular; sPESI, simplified Pulmonary Embolism Severity Index.
[a]PESI classes III–V indicate moderate to very high 30-day mortality risk; sPESI ≥1 point(s) indicate high 30-day mortality risk.
[b]Echocardiographic criteria of RV dysfunction include RV dilatation and/or an increased end-diastolic RV/LV diameter ratio (in most studies, the reported threshold value was 0.9 or 1.0); hypokinesia of the free RV wall; increased velocity of the tricuspid regurgitation jet; or combinations of the above. On computed tomographic (CT) angiography (four-chamber views of the heart), RV dysfunction is defined as an increased end-diastolic RV/LV diameter ratio (with a threshold of 0.9 or 1.0).
[c]Markers of myocardial injury (e.g. elevated cardiac troponin I or T concentrations in plasma), or of heart failure as a result of (right) ventricular dysfunction (elevated natriuretic peptide concentrations in plasma).
[d]Neither calculation of the PESI (or sPESI) nor laboratory testing are considered necessary in patients with hypotension or shock.
[e]Patients in the PESI class I–II, or with sPESI of 0, and elevated cardiac biomarkers or signs of RV dysfunction on imaging tests, are also to be classified into the intermediate–low-risk category. This might apply to situations in which imaging or biomarker results become available before calculation of the clinical severity index.

VKA dosing. In 2013, three large randomized trials expanded our knowledge on this topic.[45–47] All used the percentage of time in therapeutic range (TTR) for the INR during the first 4–12 weeks of therapy, a surrogate for the quality of anticoagulation (in terms of both efficacy and safety), as the primary endpoint. In one of these trials, which included 455 patients, genotype-guided dosing of warfarin with a point-of-care test resulted in a significant, albeit modest, increase in TTR over the first 12 weeks compared with a fixed 3-day loading-dose regimen (67.4 vs. 60.3%; $P < 0.001$).[46] However, two other trials enrolling 1015[45] and 548[47] patients, respectively, failed to show an additional benefit of genotype data to information derived from clinical variables (age, sex, height, weight, amiodarone use) when deciding on the warfarin loading-dose regimen. Taken together, these results allow the prediction that pharmacogenetic testing used on top of clinical parameters is unlikely to gain wide acceptance. They also point out the need to place emphasis on improving the infrastructure of anticoagulation management by optimizing the procedures, which link INR measurement to provide feedback to the patient and individually tailoring dose adjustments.

Trials on new oral anticoagulants

The design and principal findings of the phase 3 clinical trials on the treatment of VTE with new oral anticoagulants are summarized in *Table 2*. In the RE-COVER trial programme, the direct thrombin inhibitor dabigatran was compared with warfarin for the treatment of VTE. The primary outcome was the 6-month incidence of recurrent symptomatic or fatal VTE. Recently, a pooled analysis of the results of the 'twin' studies RECOVER I and II was published, including a total of 5109 patients.[49] With regard to the primary efficacy endpoint, dabigatran was non-inferior to warfarin (observed incidence, 2.4 vs. 2.2%; HR: 1.09, 95% CI: 0.76–1.57). Major bleeding occurred with a lower frequency in the dabigatran group, both during the period starting at first intake of study drug (which included the initial warfarin loading together with heparin treatment in the control arm as opposed to heparin alone until the switch to the oral anticoagulant in the dabigatran arm; HR: 0.73 for dabigatran, 95% CI: 0.48–1.11), and during the double-dummy phase (comparing monotherapy of dabigatran vs. warfarin; HR: 0.60, 95% CI: 0.36–0.99).

In the EINSTEIN-DVT[50] and EINSTEIN-PE[54] trials, single-oral drug treatment with the direct factor Xa inhibitor rivaroxaban was tested in patients with VTE using a randomized, open-label, non-inferiority design (*Table 2*). Recently, a pooled analysis of the results of both studies was published, including a total of 8282 patients.[55] Rivaroxaban was non-inferior to the standard therapy for the primary efficacy outcome (observed incidence, 2.1 vs. 2.3%; HR: 0.89, 95% CI: 0.66–1.19). Major bleeding occurred with a lower frequency in the rivaroxaban group (HR: 0.54, 95% CI: 0.37–0.79). In a pre-defined safety analysis of the EINSTEIN-PE study including 350 patients, rivaroxaban was non-inferior to the standard therapy in reducing pulmonary vascular obstruction (PVO; assessed with the same imaging method as the baseline diagnostic test) at the 3-week follow-up; PVO decreased by 62% on CT angiography and by 71% on the perfusion scan.[56] In a

Table 2 Overview of phase 3 clinical trials with new oral anticoagulants for standard duration anticoagulation in patients with venous thrombo-embolism

Drug	Trial	Duration	Efficacy			Safety		
			VTE recurrence NOAC (%, n/n)	VTE recurrence VKA (%, n/n)	Hazard ratio (95% CI)	Major bleeding NOAC (%, n/n)	Major bleeding VKA (%, n/n)	Hazard ratio (95% CI)
Dabigatran	RE-COVER[48]	6 months	2.4% (30/1274)	2.1% (27/1265)	1.10 (0.65–1.84)	1.6% (20/1274)	1.9% (24/1265)	0.82 (0.45–1.48)
	RE-COVER II[49]		2.3% (30/1279)	2.2% (28/1289)	1.08 (0.64–1.80)	1.2% (15/1279)	1.7% (22/1289)	0.69 (0.36–1.32)
Rivaroxaban	EINSTEIN-DVT[50]	3–12 months	2.1% (36/1731)	3.0% (51/1718)	0.68 (0.44–1.04)	0.8% (14/1731)	1.2% (20/1718)	0.65 (0.33–1.30)
	EINSTEIN-PE[51]	3–12 months	2.1% (50/2419)	1.8% (44/2413)	1.12 (0.75–1.68)	1.1% (26/2419)	2.2% (52/2413)	0.49 (0.31–0.79
Apixaban	AMPLIFY[52]	6 months	2.3% (59/2609)	2.7% (71/2635)	0.84 (0.60–1.18)	0.6% (15/2676)	1.8% (49/2689)	0.31 (0.17–0.55)
Edoxaban	HOKUSAI-VTE[53]	3–12 months	3.2% (130/4118)	3.5% (146/4122)	0.89 (0.70–1.13)	1.4% (56/4118)	1.6% (66/4122)	0.84 (0.59–1.21)

CI, confidence interval; NOAC, new oral anticoagulant; VKA, vitamin K antagonist; VTE, venous thrombo-embolism.

further subgroup analysis of 1472 patients included in EINSTEIN-DVT, rivaroxaban significantly improved patient-reported satisfaction with treatment compared with warfarin as assessed by the Anti-Clot Treatment Scale.[57]

The Apixaban for the Initial Management of Pulmonary Embolism and DVT as First-line Therapy (AMPLIFY) study compared single-oral drug treatment with the direct factor Xa inhibitor apixaban with the standard therapy in 5395 patients with acute VTE.[52] Apixaban was non-inferior to conventional treatment for the primary efficacy; major bleeding occurred less frequently under apixaban compared with heparin/VKA therapy (*Table 2*). A significant difference in favour of apixaban was also observed for the composite outcome of major or clinically relevant non-major bleeding (observed incidence, 4.3 vs. 9.7%; RR: 0.44, 95% CI: 0.36–0.55).

The most recently published study, Hokusai-VTE, compared the direct factor Xa inhibitor edoxaban with conventional therapy in 8240 patients with VTE who had initially received heparin for at least 5 days.[53] Patients received edoxaban at a dose of 60 mg once daily (reduced to 30 mg once daily in the case of creatinine clearance of 30–50 mL/min or a body weight $<$60 kg), or warfarin. In contrast to the fixed anticoagulation period(s) followed in previous trials, the study drug was administered for 3–12 months based on the investigators' judgement; all the patients were followed for 12 months. Edoxaban was non-inferior to warfarin with respect to the primary efficacy outcome of recurrent symptomatic VTE (*Table 2*). Major bleeding or clinically relevant non-major bleeding was less frequently observed in the edoxaban group (HR: 0.81, 95% CI: 0.71–0.94).

In summary, and as confirmed by a meta-analysis,[58] the results of the trials using new oral anticoagulants in the treatment of VTE indicate that these agents are at least as effective and probably safer (in terms of major bleeding) than the standard heparin/VKA regimen. Experience with handling of these drugs in different clinical scenarios, and with the management of their bleeding complications, continues to accumulate, and useful practical recommendations have recently been published by the European Heart Rhythm Association.[59] At present, rivaroxaban is the only new oral agent approved for treatment of VTE in Europe, but it is expected that the other agents will follow in 2014–15.

Thrombolytic and interventional treatment for acute pulmonary embolism

Thrombolytic treatment has been available for acute PE for more than four decades. In an epidemiological report, in-hospital mortality attributable to PE was lower in unstable patients who received thrombolytic therapy compared with those who did not (RR: 0.20, 95% CI: 0.19–0.22, $P < 0.0001$).[60] Accordingly, thrombolysis remains first-line treatment for high-risk PE. It should be considered even in the presence of an increased risk of bleeding, such as after recent surgery or trauma (except for those affecting the central nervous system), especially, if surgical embolectomy or catheter-directed treatment is not immediately available. Under these circumstanes, serious bleeding must be anticipated and preventive measures should be taken before it occurs. These include preparation for surgical management of bleeding sites and rapid blood transfusion.

In non-high-risk PE, the clinical benefits of thrombolysis have remained controversial for many years.[61] Recently, a large multicentre, randomized European trial compared, in a double-blind manner, thrombolysis with tenecteplase plus heparin vs. placebo plus heparin in 1006 patients with intermediate-risk PE.[30] Eligible patients had RV dysfunction, confirmed by echocardiography or CT angiography, and myocardial injury confirmed by a positive troponin I or T test. The primary efficacy outcome, a composite of all-cause death or haemodynamic decompensation/collapse within 7 days of randomization, was significantly reduced with tenecteplase (2.6 vs. 5.6% in the placebo group; OR: 0.44, 95% CI: 0.23–0.88). The clinical benefit was driven mainly by a significant reduction in the rate of haemodynamic collapse (1.6 vs. 5.0%, $P = 0.002$); all-cause mortality was 1.2% in the tenecteplase group and 1.8% in the placebo group ($P = 0.43$).[30] Tenecteplase is currently not approved for clinical use in acute PE.

Thrombolytic treatment carries a risk of major bleeding, including intracranial haemorrhage. Increasing age and the presence of co-morbidity have been associated with a higher risk of bleeding complications.[62] The Pulmonary Embolism Thrombolysis (PEITHO) trial demonstrated a 2% risk of haemorrhagic stroke after thrombolytic treatment with tenecteplase in patients with intermediate–high-risk PE; major non-intracranial bleeding events were also increased in the tenecteplase compared with the placebo group (6.3 vs. 1.5%; $P < 0.001$).[30] These results confirm historical data (reviewed by Konstantinides[63]) and underline the need to improve the safety of thrombolytic treatment before it can be considered for normotensive patients with PE, unless they show clinical signs of haemodynamic decompensation. Preliminary evidence suggests that a reasonable strategy might consist of reducing by 50% (or even more) the dosage of the thrombolytic agent used. In a randomized pilot trial of 118 patients with high- or intermediate-risk PE, half-dose recombinant tissue-type plasminogen activator (rtPA) was equally effective with the full dose in terms of improving PVO, and it appeared to cause less bleeding.[64] In another small study of 121 patients with (arbitrarily defined) 'moderate' PE, reduced-dose rtPA appeared to be safe in the acute phase and to reduce the persistence of echocardiographically assessed pulmonary hypertension at 28 ± 5-month follow-up.[65]

An alternative approach to 'safer' thrombolysis may consist of local, catheter-delivered, ultrasound-assisted thrombolysis using small doses of a thrombolytic agent, provided that local availability and expertise are available. This procedure was recently reviewed in the Engelberger and Kucher.[66] In a phase 2 clinical trial, 59 patients, aged 63 ± 14 years, with acute main or lower lobe PE and echocardiographic right-to-left ventricular dimension ratio ≥1.0 were randomized to receive unfractionated heparin and an ultrasound-assisted thrombolytic regimen of 10–20 mg rtPA plus unfractionated heparin over 15 h as opposed to unfractionated heparin alone. Reduced-dose local thrombolysis significantly reduced, compared with heparin alone, the subannular right-to-left ventricular dimension ratio from baseline to 24 h without an increase in bleeding complications.[29] The efficacy and safety of local, 'pharmacomechanical' thrombolysis appears to be further supported by the results of a recently presented prospective, single-arm multicentre trial which enrolled 150 patients with submassive or massive PE (Clinicaltrials.gov identifier: NCT01513759).

In patients with absolute contraindications to thrombolysis, other catheter-based techniques such as thrombus fragmentation, rheolytic or rotational thrombectomy, or suction thrombectomy may be applied. Again, local availability and expertise are a prerequisite. Overall, evidence for these procedures remains weak, being based on single-centre case series.[67] This also remains true for surgical pulmonary embolectomy.

Despite the increasing use of retrievable vena cava filters in some countries, the indications for their implantation in acute PE have not changed and remain confined to patients with absolute contraindications to anticoagulant drugs as well as those with objectively confirmed recurrence despite adequate anticoagulation treatment. Observational studies suggest that venous filters might reduce PE-related mortality rates in the acute phase at the cost of a possible increase in the risk of recurrence later on.[68,69] The results of a large multicentre randomized trial evaluating the risk–benefit ratio of retrievable filters in addition to anticoagulation (Clinicaltrials.gov identifier: NCT00457158) have not been published yet, but no significant differences in symptomatic PE recurrence are to be expected. No solid evidence exists to support the routine use of venous filters in patients with free-floating thrombi in the proximal veins, or in those scheduled for systemic thrombolysis, surgical embolectomy, or pulmonary thromboendarterectomy.

Early discharge and outpatient treatment of pulmonary embolism

While the majority of patients with acute DVT is currently being treated on an outpatient basis in many countries, early discharge or entirely ambulatory treatment of patients with PE generally remains the exception despite the accumulating evidence that it may be safe under certain circumstances.[70] When considering this option in acute PE, the first important step is to select those patients who are at low risk of an adverse early clinical outcome. As discussed above, the PESI is, at present, the most extensively validated prognostic score, and the largest randomized trial performed to date used a low PESI as the main inclusion criterion for home treatment of acute PE.[20] In an alternative approach, a relatively small (152 patients) single-arm management study employed a laboratory marker, namely natriuretic peptide levels, as the main criterion for selecting 'low-risk' candidates for home treatment.[33] It remains questionable, however, whether biomarker testing may possess an additive (negative) prognostic value in patients with a low PESI score.

Beyond identifying a low early PE-related death or complication risk *per se*, it is also crucial to include criteria guaranteeing the feasibility and safety of the intensified anticoagulation treatment which is necessary during the acute phase, both in the in-hospital and in the outpatient setting. Data from a prospective multicentre single-armed (management) trial on 297 patients suggested that the so-called Hestia criteria, a set of clinical parameters that can be obtained at the bedside, may be helpful in this regard; the rate of recurrent VTE was 2.0% (0.8–4.3%) in patients with acute PE discharged within 24 h.[71] The Hestia criteria have not yet been externally validated.

An ongoing multicentre prospective single-armed phase 4 trial (EudraCT number 2013-001657-28) will determine whether early discharge and out-of-hospital treatment of patients with low-risk acute PE with the recently approved oral factor Xa inhibitor rivaroxaban is feasible, effective, and safe. The study will further investigate whether early discharge and out-of-hospital treatment can result in good quality of life and patient satisfaction, and it will obtain health economic variables as a basis for description of resource utilization. Definition of low-risk PE is mainly based on the absence of haemodynamic instability at presentation; RV dysfunction or free-floating right-heart thrombi on echocardiography or CT angiography; and need for parenteral analgesia or severe comorbidity requiring hospitalization.

Progress in therapeutic strategies

An algorithm for the risk-adjusted management of acute PE as recommended in the recently updated ESC Guidelines(ESC Guidelines 2014 citation) is shown in *Figure 2*.

Extended anticoagulation after venous thrombo-embolism

Current guidelines recommend a 'standard' anticoagulation period of 3 months for patients with VTE provoked by surgery or a non-surgical transient risk factor.[6,72] Patients with unprovoked VTE will need evaluation for the risk–benefit ratio of extended anticoagulation therapy after the first 3 months of treatment. For many of these latter patients, the question on the optimal duration of anticoagulation remains unresolved. The reason for this uncertainty is that, although several pre-disposing factors and conditions have been identified, the relative weight of these factors (or possible combinations thereof) on the risk of VTE recurrence remains partly

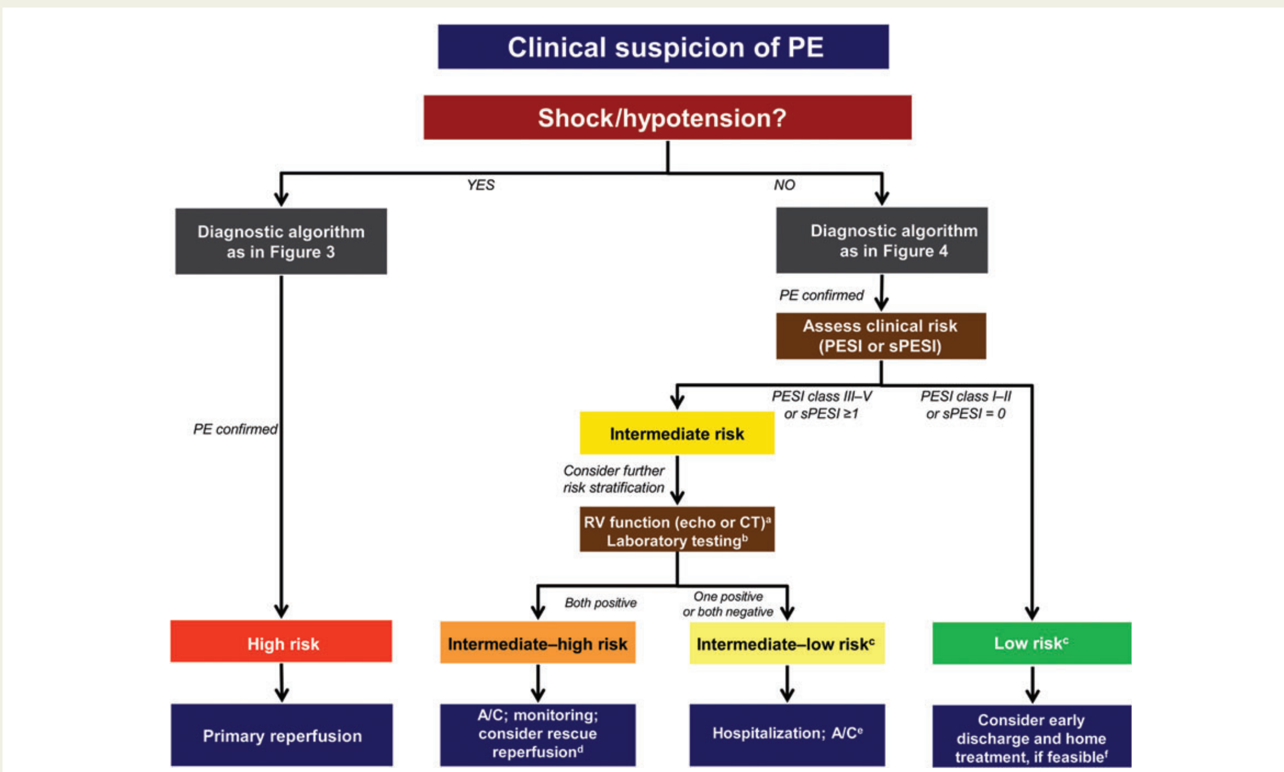

Figure 2 Risk-adjusted therapeutic strategies in acute pulmonary embolism [adapted from (ESC Guidelines 2014 citation)]. A/C, anticoagulation; CT, computed tomographic pulmonary angiography; PE, pulmonary embolism; PESI, Pulmonary Embolism Severity Index; RV, right ventricular; sPESI, Simplified Pulmonary Embolism Severity Index. [a]If echocardiography has already been performed during diagnostic work up for pulmonary embolism and detected right ventricular dysfunction, or if the CT already performed for diagnostic work up has shown right ventricular enlargement (RV/left LV ratio $\geq$0.9), a cardiac troponin test should be performed except for cases in which primary reperfusion is not a therapeutic option (e.g. due to severe comorbidity or limited life expectancy of the patient). [b]Markers of myocardial injury (e.g. elevated cardiac troponin I or T concentrations in plasma), or of heart failure as a result of (right) ventricular dysfunction (elevated natriuretic peptide concentrations in plasma). If a laboratory test for a cardiac biomarker has already been performed during initial diagnostic work up (e.g. in the chest pain unit) and was positive, then an echocardiogram should be considered to assess right ventricular function, or right ventricular size should be (re)assessed on CT. [c]Patients in the Pulmonary Embolism Severity Index class I–II, or with Simplified Pulmonary Embolism Severity Index of 0, and elevated cardiac biomarkers or signs of right ventricular dysfunction on imaging tests, are also to be classified into the intermediate–low-risk category. This might apply to situations in which imaging or biomarker results become available before calculation of the clinical severity index. These patients are probably no candidates for home treatment. [d]Thrombolysis, if (and as soon as) clinical signs of haemodynamic decompensation appear; surgical pulmonary embolectomy or percutaneous catheter-directed treatment may be considered as alternative options to systemic thrombolysis, particularly if the bleeding risk is high. [e]Monitoring should be considered for patients with confirmed PE and a positive troponin test, even if there is no evidence of right ventricular dysfunction on echocardiography or CT. [f]The simplified version of the Pulmonary Embolism Severity Index has not been validated in prospective home treatment trials; inclusion criteria other than the Pulmonary Embolism Severity Index were used in two single-armed (non-randomized) management studies.

controversial;[73,74] in addition, the relatively high bleeding rates related to chronic anticoagulation with VKA need to be taken into account in treatment decisions.[75]

The apparently improved safety profile of new oral anticoagulants compared with VKA might facilitate decision-making in the future. The new oral direct thrombin inhibitor dabigatran was compared with warfarin, or with placebo, in two studies on patients who had completed the standard anticoagulation treatment. In RE-MEDY, a trial on patients estimated to be at a higher risk of recurrence, 2866 patients were randomized to receive dabigatran 150 mg twice daily, or warfarin. Dabigatran was non-inferior to warfarin for the prevention of confirmed recurrent symptomatic VTE or VTE-related death.[76] The rate of major bleeding was 0.9% under dabigatran vs. 1.8% under warfarin (HR: 0.52, 95% CI: 0.27–1.02). In RE-SONATE, 1353 patients were randomized to dabigatran or placebo for an additional anticoagulation period of 6 months.[76] Dabigatran was associated with a 92% relative risk reduction in symptomatic recurrent VTE. A 0.3% rate of major bleeding was observed in the dabigatran vs. 0% in the placebo group; clinically relevant non-major bleeding occurred in 5.3 and 1.8% of the patients, respectively.

The randomized, double-blind EINSTEIN Extension study assessed the efficacy and safety of rivaroxaban in the extended treatment of VTE.[50] An additional 6- or 12-month course of rivaroxaban (20 mg once daily) was compared with placebo in patients who had completed 6–12 months of anticoagulation treatment for a first VTE event. Rivaroxaban had superior efficacy over placebo (1.3 vs. 7.1%, HR: 0.18, 95% CI: 0.09–0.39). Non-fatal major bleeding occurred in 0.7% of patients in the rivaroxaban arm vs. none in the placebo arm. The incidence of clinically relevant non-major bleeding was 5.4% in the rivaroxaban group and 1.2% in the placebo group.

In the double-blind AMPLIFY Extension trial, patients with VTE were randomized to two different doses of apixaban or placebo for a period of 12 months.[77] Symptomatic recurrent VTE or death from VTE occurred in 8.8% of patients receiving placebo compared with 1.7% of those receiving 2.5 mg of apixaban twice daily (a difference of 7.2 percentage points; 95% CI: 5.0–9.3, $P < 0.001$) and with 1.7% of the patients who were receiving 5 mg of apixaban twice daily (a difference of 7.0 percentage points; 95% CI: 4.9–9.1, $P < 0.001$). The rates of major bleeding were 0.5% in the placebo group, 0.2% in the 2.5 mg apixaban group, and 0.1% in the 5 mg apixaban group.

In two recent trials with a total of 1224 patients, extended therapy with aspirin was associated with a 30–35% reduction in the risk of recurrence after unprovoked DVT and/or PE.[78,79] This is clearly inferior to the protection offered by VKA or new oral anticoagulants.[50,75–77] The bleeding rates under aspirin treatment were low in these two (rather small) studies, but data obtained in larger numbers of patients with atrial fibrillation do not support the notion that chronic aspirin treatment is 'harmless' in terms of bleeding complications.[80] Consequently, aspirin may be considered for extended secondary VTE prophylaxis only in (the very few) cases in which patients refuse to take or are unable to tolerate any form of oral anticoagulants.

Chronic thrombo-embolic pulmonary hypertension

Most survivors of acute PE report returning to the previous functional capacity within weeks to months. However, some patients do not follow this path; in these cases, thrombo-emboli may fail to resolve but organize into fibrotic deposits permanently occluding pulmonary arteries. Moreover, increased flow in patent parts of the pulmonary arterial bed, to which blood is redistributed, augments shear stress and may lead to progressive pulmonary vascular disease similar to that found in the Eisenmenger syndrome.[81]

There is an ongoing debate regarding the true prevalence of CTEPH. While 30–50% of patients having suffered acute PE will have some thrombo-embolic remnants detectable with imaging tests, haemodynamics at rest and exercise tolerance remain unaffected in the majority of these cases. Most observational studies report a 0.5–5.0% prevalence of CTEPH among survivors of acute PE.[82] The disease may present either as persistent dyspnoea or as reappearence of symptoms after a 'honeymoon' (subclinical) period of variable duration. Prospective echocardiographic screening of unselected PE survivors for asymptomatic CTEPH appears to have a low diagnostic yield[83] and thus cannot recommended at present; however, clinical symptoms and signs suggestive of CTEPH should be sought in all survivors of PE and further evaluation should be ordered whenever deemed necessary.

Surgical pulmonary endarterectomy remains the treatment of choice for patients with CTEPH. However, according to a European registry, up to 40% of patients are not operated because of distal occlusions, comorbidity, or fear related to a major surgical intervention.[84] Such patients have a high (10%) annual mortality, similar to that of patients with pulmonary arterial hypertension. In a recent randomized trial including 261 inoperable patients with CTEPH, treatment with riociguat, a direct stimulator of guanylate cyclase, increased six-minute walking distance by 46 (95% CI: 25–67) m and improved functional class when compared with placebo; this was related to a significant decrease in pulmonar vascular resistance (by 226 dyn s cm$^{-5)}$ and a favourable safety profile.[85] These results have led to an FDA approval of riociguat for this indication.

Inoperable CTEPH patients might also benefit from pulmonary angioplasty of distally located post-embolic webs and bands (*Figure 3*). Introduced >10 years ago, the method re-emerged recently with the reporting of multiple clinical series, mostly from Japanese centres. The technique requires repeated interventions on the narrowed arteries in consecutive affected segments and lobes. To this date, over 500 procedures have been performed in >150 patients, and significant reductions in pulmonary artery pressure and vascular resistance were reported; procedural mortality rates ranged between 0 and 10%.[87–90] Such interventions require skill, not only in identifying and reaching distal culprit lesions but also in handling reperfusion oedema and life-threatening pulmonary bleeding. Accumulating experience beyond Japanese borders[86,90] will determine whether pulmonary angioplasty can become a useful therapeutic option for inoperable patients with CTEPH.

Conclusions and outlook

Despite the continuous flow of data demonstrating its epidemiological relevance, VTE had received little attention from the scientific and medical community for decades, standing in the shadow of thrombosis in the arterial tree or the left atrial appendage. It was only recently that technical advances in diagnostic imaging followed by an

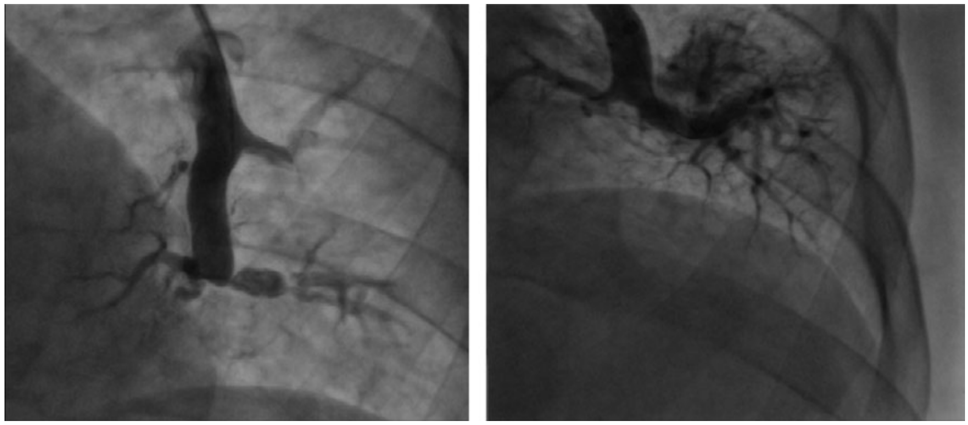

Figure 3 Ballon pulmonary angioplasty for inoperable chronic thrombo-embolic pulmonary hypertension. Angiography of the narrowed left lower segmental pulmonary artery before (left) and after (right) angioplasty. Reproduced from Darocha *et al.*[86] with permission.

ongoing revolution in therapeutics, led by new antithrombotic agents and strategies, increased the awareness of the importance of VTE, and began to improve patient outcomes in the acute phase and over the long term. The new evidence that accumulated in all these areas has provided a solid basis for the updated recommendations of the ESC Guidelines on the Management of Acute PE. (ESC Guidelines 2014 citation)

Resolution of case

This case highlights not only the frequent problem of correctly diagnosing PE in the emergency care setting, but also the uncharted waters and growing complexity of handling combinations of anticoagulant and antiplatelet agents in clinical practice. After the second episode of collapse, and in view of the echocardiographic and CT findings shown in *Figure 1*, it becomes evident that this is (and has most likely been from the beginning) a patient with high-risk PE. We assume that the coronary stenosis was an incidental finding and that she did not suffer an acute coronary syndrome. At the moment that PE is diagnosed, this patient is in need of prompt recanalization treatment; however, if at all possible, we would avoid administering full-dose systemic thrombolysis due to the high bleeding risk based on her advanced age and the dual antiplatelet therapy that she has already received for the presumed acute coronary syndrome and the percutaneous coronary intervention. It must be emphasized that reduced-dose systemic thrombolysis is *not* approved treatment for PE at present despite some encouraging preliminary data. Surgical embolectomy also does not seem to be an attractive option in this situation; instead, percutaneous catheter-directed treatment should be considered if local expertise is available. After stabilization, the optimal antithrombotic regimen also poses a challenge. Considering her high bleeding risk (her HAS-BLED score, although not explicitly validated in patients with PE, is ≥ 3), the probably low risk of myocardial ischaemia, and the fact that she has received a bare metal stent, the duration of combined anticoagulant and dual antiplatelet treatment can be limited to 2–4 weeks as derived from recommendations for patients with atrial fibrillation.[59,91] During this relatively short period, we would consider treating her with a low-molecular-weight heparin at a therapeutic dosage instead of starting a VKA; the latter step can follow as soon as the antiplatelet agents can be discontinued. As an alternative to VKA, this 'fragile' lady may receive rivaroxaban after the period of combined antithrombotic treatment is over and for a total of at least 3 months.

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Conflict of interest: The authors are responsible for the contents of this publication.

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