## THE PRESENT AND FUTURE

### STATE-OF-THE-ART REVIEW

# Management of Pulmonary Embolism
## An Update

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### ABSTRACT

Pulmonary embolism (PE) remains a major contributor to global disease burden. Risk-adapted treatment and follow-up contributes to a favorable outcome. Age-adjusted cutoff levels increase D-dimer specificity and may decrease overuse of imaging procedures and overdiagnosis of PE. Primary systemic fibrinolysis has an unfavorable risk–benefit ratio in intermediate-risk PE; catheter-directed techniques are an option for patients with hemodynamic decompensation and high bleeding risk. New oral anticoagulant agents are effective and safe alternatives to standard anticoagulation regimens. Recent trial data do not support insertion of cava filters in patients who can receive anticoagulant treatments. Remaining areas of uncertainty include the therapeutic implications of subsegmental PE, the optimal diagnostic approach to the pregnant patient with suspected PE, and the efficacy and safety of new oral anticoagulant agents in patients with cancer. Campaigns to increase awareness combined with strategies to implement guideline recommendations will be crucial steps towards further optimizing management of acute PE.  (J Am Coll Cardiol 2016;67:976–90) © 2016 by the American College of Cardiology Foundation.

Venous thromboembolism (VTE), which encompasses deep vein thrombosis (DVT) and its most dangerous complication, acute pulmonary embolism (PE), represents a major threat to the health, the well-being, and occasionally, the lives of a large number of patients worldwide. The annual incidence rate of VTE ranges between 75 and 269 cases per 100,000 persons, as shown by studies in Western Europe, North America, Australia, and southern Latin America, with subjects 70 years of age or older having an incidence of up to 700 per 100,000 (1). As the risk of VTE approximately doubles with each decade after the age of 40 years, it is to be expected that an increasing number of people in aging societies throughout the world will be diagnosed with the disease in the years to come. Despite the epidemiological relevance of PE and its high short-term mortality, a relative lack of public awareness was demonstrated by a global survey that included more than 7,200 responders (2). In particular, the level of awareness was clearly lower than that for other thrombotic disorders, such as heart attack and stroke, or compared with diseases previously addressed by sensitization campaigns, such as breast cancer, prostate cancer, and acquired immunodeficiency syndrome (2).

The present paper critically reviews recent data that have contributed to substantial improvement of

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management strategies for acute PE in past years, while also highlighting areas that remain to be clarified or resolved by ongoing and future research.

## EVOLVING STRATEGIES FOR DIAGNOSIS AND RISK ASSESSMENT

**APPROPRIATE TRIAGE OF PATIENTS FOR IMAGING TESTS.** In the absence of hemodynamic instability at presentation, the diagnostic work-up of a patient with suspected acute PE begins with the assessment of the clinical or pre-test probability of PE (**Figure 1**). Standardized prediction rules integrating baseline clinical parameters and the patient's history permit the classification of patients into distinct categories of clinical probability of the disease. Whichever prediction rule (e.g., Wells or revised Geneva) or version (original or simplified) is used, the proportion of patients with confirmed PE is expected to be approximately 10% in the low-probability category, 30% in the intermediate-probability category, and 65% in the high-clinical probability category when using the 3-level classification; if a 2-level classification is used, PE will be confirmed in around 12% and 50% of patients in the PE-unlikely and PE-likely categories, respectively (3).

Whereas patients with high clinical probability for PE (or "PE-likely," if dichotomized prediction rules are used) should directly undergo an imaging test, D-dimer testing is recommended as the next diagnostic step in patients with low or intermediate pre-test probability (or PE-unlikely, if dichotomized prediction rules are used) (4). Although a negative test safely excludes PE without further testing in these cases, the specificity of a positive D-dimer test is low and decreases steadily with age. This might result in too many positive tests and, consequently, in overuse of diagnostic imaging, particularly in the elderly. A multicenter, prospective management study evaluated age-adjusted (age × 10 μg/l, above 50 years) cutoff levels in a cohort of 3,346 patients with suspected PE. Patients with a normal age-adjusted D-dimer value did not undergo computed tomographic (CT) pulmonary angiography; these patients were left untreated and followed over a 3-month period. Using the age-adjusted (instead of the standard 500 μg/l) D-dimer cutoff increased the number of patients in whom PE could be excluded from 6.4% to 30% in patients aged 75 years or older, without a significant increase in the rate of VTE events during follow-up (5).

In most countries and hospitals, CT pulmonary angiography has become the preferred imaging method for the diagnosis of acute PE in patients with either a high clinical (pre-test) probability or low/intermediate probability and elevated D-dimer levels (**Figure 1**). However, pitfalls and errors resulting in misdiagnosis of PE may be frequent in clinical practice. In a retrospective review of 937 pulmonary CT examinations performed in a tertiary-care university hospital over a 12-month period, 3 experienced chest radiologists retrospectively reinterpreted studies originally reported as positive for PE (174, 19%). Overall, discordance between the reviewing subspecialists and the original radiologist was reported in 45 (26%) cases. Retrospective rejection of the diagnosis occurred more often when the reported PE was solitary (46% of original PE diagnoses) or located in a segmental or subsegmental pulmonary artery (27% and 59%, respectively). The most frequent explanation for discrepancies was breathing motion artifact, followed by beam-hardening artifact from adjacent high-density structures (superior vena cava, right atrium, right ventricle) (6). The debate surrounding the perceived trends in (over)diagnosis of PE in the era of CT angiography, and the clinical significance of isolated subsegmental PE, will be discussed later.

Planar ventilation/perfusion (V/Q) lung scans represent an alternative imaging method to CT angiography in patients with a high clinical probability of PE or those with a positive D-dimer test. The main limitations of planar V/Q scans are the high proportion of non-conclusive results, especially in patients older than 75 years of age, often requiring additional testing. V/Q single-photon emission computed tomography (SPECT) is a new method of scintigraphic acquisition that has been reported to improve diagnostic performance and reduce the number of nonconclusive tests (7). However, the diagnostic criteria need to be standardized (8). Moreover, head-to-head comparison of V/Q SPECT with CT pulmonary angiography needs to be performed, including follow-up of patients left without anticoagulant treatment on the basis of negative V/Q SPECT findings.
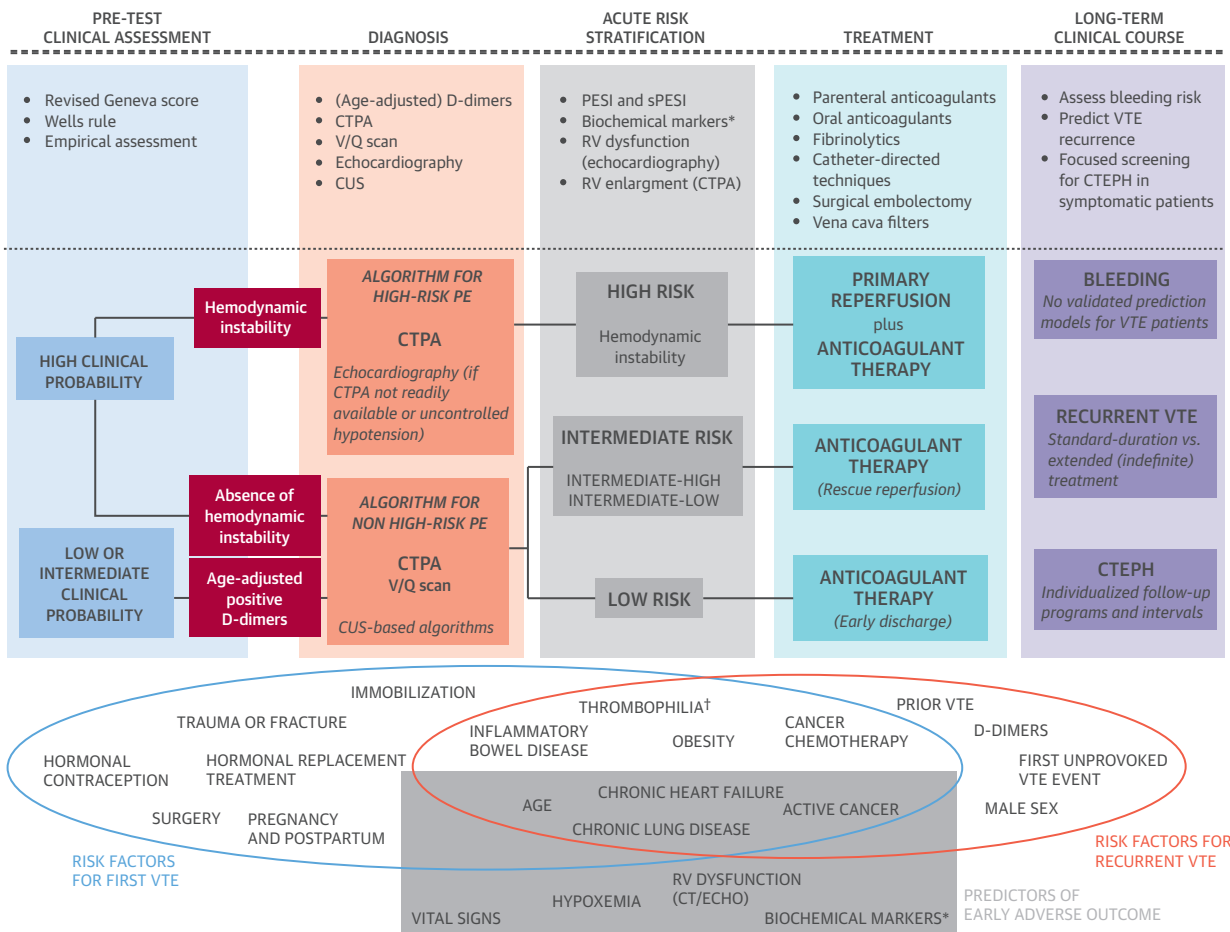
Of note, V/Q lung scans are an important early step for ruling out chronic thromboembolic pulmonary hypertension (CTEPH) in the diagnostic work-up of patients with persistent dyspnea after acute PE and at least 3 months of anticoagulation treatment (4).

**RISK STRATIFICATION: IDENTIFYING HIGH- AND LOW-RISK PE.** Clinical classification of the severity

**FIGURE 1** PE: Risk-Adjusted Management in the Acute Phase and Over the Long Term



*Biochemical markers include markers of myocardial injury (troponins, heart-type fatty acid-binding protein) and markers of heart failure (BNP or N-terminal-proBNP). †Only antiphospholipid syndrome and high-risk inherited thrombophilia (i.e., homozygosity for factor V Leiden, homozygosity for prothrombin G20210A mutation, double heterozygosity, antithrombin deficiency) are considered. Nevertheless, routine thrombophilia testing is not indicated in PE patients. BNP = B-type natriuretic peptide; CT = computed tomography; CTEPH = chronic thromboembolic pulmonary hypertension; CTPA = computed tomographic pulmonary angiogram; CUS = compression ultrasound; Echo = echocardiography; N-terminal-proBNP = N-terminal pro-B-type natriuretic peptide; PE = pulmonary embolism; PESI = pulmonary embolism severity index; RV = right ventricular; sPESI = simplified pulmonary embolism severity index; V/Q scan = ventilation/perfusion lung scan; VTE = venous thromboembolism.

of acute PE is on the basis of the estimated early death risk (**Figure 1**). It has been established that the presence of right ventricular dysfunction and failure resulting from acute pressure overload is the principal determinant of the patient's early clinical course and risk of an adverse outcome (reviewed in [4,9]). Accordingly, high-risk or massive PE refers to the presence of shock or persistent arterial hypotension as a result of overt right ventricular failure. This is clearly a life-threatening situation, in which prompt reperfusion treatment (as discussed later) is needed, along with circulatory and respiratory support in order to break the spiral of

hemodynamic deterioration and to increase the chances of survival (4,10,11).

More than 95% of patients with acute PE are (or appear to be) hemodynamically stable at presentation and are thus not considered to be at high risk (12). Within this large group, the next challenging step is to determine which patients will need hospitalization and possibly initial monitoring, and to distinguish them from those who are at truly low risk and may qualify for early discharge and outpatient treatment. To be used as risk stratification tools for this purpose, baseline clinical parameters and prediction scores derived from them should reliably exclude severe

acute illness and the presence of significant comorbidity. The Pulmonary Embolism Severity Index (PESI) has been extensively validated and shown to fulfill these requirements; patients in PESI risk strata I and II were at low risk of 30-day mortality [13]. The simplified version of the Pulmonary Embolism Severity Index (sPESI) also possessed a high negative predictive value for ruling out an adverse early outcome [14,15]. Thus, a substantial proportion (between 25% and 46%, depending on the cohort studied) of all patients with acute PE can be classified as being at low risk on the basis of a PESI risk class of I or II, or a sPESI score of 0 [14–16]. Although the negative predictive value of the index may rise even further when it is combined with the (negative) result of a high-sensitivity cardiac troponin assay [17], it is uncertain how often this extra reassurance is really needed in clinical practice.

Despite the uncontested prognostic value of the PESI, it should be kept in mind that this was primarily designed as an epidemiological tool, and not as a direct guide to PE management. The only prospective trial that used this severity index to randomize patients to outpatient versus in-hospital treatment of PE required numerous additional eligibility criteria, including a supportive social environment [18]. Other groups, particularly in the Netherlands, chose to develop explicit home treatment-oriented clinical criteria, either alone (Hestia criteria) [19] or in combination with biomarker testing (N-terminal pro–B-type natriuretic peptide [NT-proBNP] plasma levels <500 pg/ml) [20], which they tested successfully in small- to medium-sized (150 to 300 patients) prospective cohort trials. These criteria await validation in larger cohorts and further countries. Importantly, and in view of first reports that severe right ventricular dysfunction may occasionally be present in a patient with a negative sPESI [21], it will also need to be determined in this context whether CT or echocardiographic imaging of the right ventricle should be added to clinical eligibility criteria for immediate or early discharge in order to maximize patient safety.

### EVOLVING DEFINITION OF INTERMEDIATE-RISK PE.
What are the next steps if a normotensive patient is not classified into the low-risk category on the basis of the clinical criteria described previously? With the objective of further developing the concept of intermediate-risk PE, the 2014 European Society of Cardiology (ESC) guidelines critically reviewed the combinations of imaging (echocardiographic or CT angiographic) parameters and laboratory biomarkers that can be used to detect right ventricular dysfunction and/or myocardial injury [4]. Taking into account that imaging and laboratory tests have consistently been shown to have prognostic values additive to each other and to those of clinical parameters [22,23], and aiming to discourage uncritical time- and resource-consuming laboratory and/or echocardiographic testing in every patient with confirmed PE without prior clinical triage, the updated ESC guidelines proposed a stepwise classification of early risk, as displayed in the **Central Illustration** [4]. Although supported by evidence from cohort studies and validated (at least in a modified form) in a large randomized therapeutic trial [24], the current risk stratification scheme will almost certainly need further improvement in the following years. In particular, the definition and positive prognostic value of the intermediate-high-risk class must be optimized to better identify candidates for reperfusion treatment among normotensive patients with PE. Promising steps in this direction include the use of age-adjusted cutoff values for high-sensitivity cardiac troponin T in patients age 75 years or older [25] and laboratory biomarkers more specific for relevant neurohumoral activation or for myocardial injury [26]. In 2,874 normotensive PE patients derived from 6 cohort studies, a multidimensional prognostic model on the basis of 4 variables (systolic blood pressure 90 to 100 mm Hg; heart rate ≥110 beats/min; elevated cardiac troponin; right ventricular dysfunction on imaging) was constructed, yielding 3 risk strata [27]. The rate of an adverse 30-day outcome was 29% in the high-risk stratum (>4 points) of the derivation population [27], and up to 42% in a validation cohort of 1,083 patients [28]. External validation and implementation of new prediction rules in prospective management trials are necessary steps before these can be integrated into future risk stratification algorithms.

## ADVANCES IN ANTICOAGULATION TREATMENT

In patients with acute VTE (presenting either as PE or proximal DVT), the duration of anticoagulation treatment should cover at least 3 months [4,10,11,29]. Within this period, traditional regimens of acute-phase treatment consist of parenteral anticoagulation (intravenous unfractionated heparin, subcutaneous low-molecular-weight heparin, or fondaparinux) over the first 5 to 10 days, overlapping and followed by a vitamin K antagonist (VKA), which is adjusted to obtain a therapeutic (2.0 to 3.0) international normalized ratio. Advances in knowledge and the remaining open questions related to determining the optimal duration (beyond the first 3 months) of anticoagulation after PE are discussed separately in this review, in the

**CENTRAL ILLUSTRATION**   Acute PE: Current Risk Stratification

| Early Mortality Risk | | Risk Parameters and Scores | | | |
|---|---|---|---|---|---|
| | | Shock or Hypotension | PESI Class III-V or sPESI ≥1 | Signs of RV Dysfunction on an Imaging Test | Cardiac Laboratory Biomarkers* |
| High | | + | (+) | + | (+) |
| Intermediate | Intermediate-high | – | + | Both positive | |
| | Intermediate-low | – | + | Either 1 (or none) positive | |
| Low | | – | – | Assessment optional: If assessed, both negative | |

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*Markers of myocardial injury (e.g., elevated cardiac troponin or heart type-fatty acid-binding [H-FABP] plasma concentrations), or of right ventricular dysfunction (elevated natriuretic peptide plasma concentrations). Adapted with permission from the 2014 European Society of Cardiology Guidelines on the Diagnosis and Management of Pulmonary Embolism (4). PE = pulmonary embolism; PESI = Pulmonary Embolism Severity Index; RV = right ventricular; sPESI = simplified Pulmonary Embolism Severity Index.

section titled *Current Controversies and Areas of Ongoing Research.*

Phase 3 trials investigating the new, non–vitamin K-dependent oral anticoagulant agents (NOACs) apixaban (30), dabigatran (31,32), edoxaban (33), and rivaroxaban (34,35) in the treatment of VTE have been completed and published. A meta-analysis showed that these agents are noninferior to the standard heparin/VKA regimen, in terms of prevention of VTE recurrence (relative risk [RR]: 0.90; 95% confidence interval [CI]: 0.77 to 1.06), and that they are probably safer in terms of major bleeding (RR: 0.61; 95% CI: 0.45 to 0.83), particularly intracranial (RR: 0.37; 95% CI: 0.21 to 0.68) and fatal (RR: 0.36; 95% CI: 0.15 to 0.84) hemorrhage (36). As a result, NOACs are recommended in the 2014 ESC Guidelines as an alternative to the standard heparin/VKA treatment (4). All 4 NOACs mentioned earlier are now licensed for treatment of VTE in the United States and the European Union (edoxaban still awaits approval in Canada); the approved regimens are summarized in **Table 1**.

Post-marketing experience with these drugs in clinical practice (under "real-world" conditions) appears reassuring in the setting of stroke prevention in atrial fibrillation, and has also begun to accumulate in VTE. In a prospective German registry of patients treated with rivaroxaban, rates of major bleeding for patients with VTE were 4.1% per year (95% CI: 2.5% to 6.4% per year), and case fatality rates were low (approximately 5% at 30 days) (37). Importantly, available data suggest that the first reversal agent against a NOAC, the monoclonal antibody idarucizumab, which binds the thrombin inhibitor dabigatran, is effective in emergency situations (38); this agent is expected to obtain U.S. Food and Drug Administration approval soon. In parallel, phase 3 clinical trials are currently being conducted with andexanet, a modified recombinant form of factor Xa, which is catalytically inactive (39) and may serve as a reversal agent for rivaroxaban, apixaban, and edoxaban.

Single oral drug regimens for PE might be expected to improve (reduce) patients' perceived burden of

**TABLE 1  Non–Vitamin K-Dependent Oral Anticoagulant Agents in the Treatment and Secondary Prevention of VTE**

| | Dosage and Interval | | | |
|---|---|---|---|---|
| | Initial Phase | Long-Term Phase | Extended Phase | Not Recommended or Contraindicated* |
| Rivaroxaban† | 15 mg twice daily with food for 21 days | 20 mg once daily with food | | • CrCl <30 ml/min<br>• Moderate or severe hepatic impairment (Child-Pugh B and C), or hepatic disease associated with coagulopathy<br>• Concomitant use of combined P-gp and strong CYP3A4 inhibitors or inducers |
| Dabigatran etexilate‡ | Initial therapy with parenteral anticoagulation for 5-10 days should precede administration of dabigatran etexilate | 150 mg twice daily | | • CrCl <30 ml/min<br>• Concomitant treatment with P-gp inhibitors in patients with CrCl <50 ml/min<br>• Concomitant treatment with P-gp inducers (i.e., rifampin) |
| Apixaban | 10 mg twice daily for 7 days | 5 mg twice daily | 2.5 mg twice daily after at least 6 months of treatment | • CrCl <15 ml/min<br>• Severe hepatic impairment (Child-Pugh C), or hepatic disease associated with coagulopathy<br>• Strong dual inhibitors or inducers of CYP3A4 and P-gp |
| Edoxaban§ | Initial therapy with parenteral anticoagulation for 5-10 days should precede administration of edoxaban | 60 mg once daily<br>30 mg once daily can be considered in patients with ≥1 of the following factors: CrCl 15-50 ml/min; body weight ≤60 kg; concomitant use of P-gp inhibitors, cyclosporin, dronedarone, erythromycin, or ketoconazole | | • CrCl <15 ml/min<br>• Moderate or severe hepatic impairment (Child-Pugh B and C), or hepatic disease associated with coagulopathy<br>• Concomitant treatment with rifampin |

The table displays drugs and regimens on the basis of U.S. FDA approval for the treatment of acute VTE. *In addition to the specific conditions listed here, all mentioned anticoagulant agents should be avoided in patients: 1) with hemodynamically unstable acute pulmonary embolism for whom thrombolysis or pulmonary embolectomy may be required; 2) requiring dialysis; 3) at significant risk of bleeding or with active pathological bleeding; 4) treated with a concomitant anticoagulant agent; 5) with known hypersensitivity to the agent; and 6) in pregnant women or during breast feeding. Moreover, all mentioned anticoagulant agents should be administered with caution in patients with an increased bleeding risk, including those receiving concomitant treatment with NSAIDs, acetylsalicylic acid, and platelet aggregation inhibitors. †According to the EMA product information, rivaroxaban 15 mg should be considered for the long-term phase if the patient's assessed risk for bleeding outweighs the risk for recurrent venous thromboembolism. In the European Union, rivaroxaban is contraindicated in patients with CrCl <15 ml/min and should be used with caution in patients with CrCl 15-30 ml/min. ‡According to the EMA product information, dabigatran etexilate 110 mg twice daily can be considered in patients ≥80 years of age; for those under concomitant treatment with moderate P-gp inhibitors (i.e., amiodarone, quinidine, verapamil); at higher risk of bleeding, including elderly patients >75 years of age with >1 risk factor for bleeding; and with CrCl 30-50 ml/min. In the European Union, dabigatran etexilate is not recommended in patients with elevated liver enzymes >2× upper limit of normal or with liver disease expected to have any impact on survival. §Although a separate extension trial was not conducted for edoxaban, >40% of patients included in the HOKUSAI-VTE study received an extended anticoagulant treatment with edoxaban for up to 12 months.

CrCl = creatinine clearance; CYP3A4 = cytochrome P450-3A4; EMA = European Medicines Agency; FDA = Food and Drug Administration; NSAID = nonsteroidal anti-inflammatory drug(s); P-gp = P-glycoprotein; VTE = venous thromboembolism.

anticoagulation therapy and, possibly, the costs related to prolonged hospitalization and bleeding complications. As part of the open-label EINSTEIN-PE (Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Pulmonary Embolism) rivaroxaban phase 3 trial, 2,397 patients in 7 countries completed a validated measure of treatment satisfaction, the Anti-Clot Treatment Scale (ACTS); rivaroxaban treatment was reported to result in improved treatment satisfaction compared with enoxaparin/VKA, particularly by reducing the patient-reported anticoagulation burden (40). In an analysis of data from the EINSTEIN trials, rivaroxaban was associated with greater discounted quality-adjusted life-expectancy, as well as per-patient cost savings for each treatment duration modeled (3, 6, and 12 months); the benefits were greatest with shorter durations (41).

Further specific aspects of NOAC treatment that were beyond the scope of the phase 3 trials are currently under investigation. For example, the safety and efficacy of NOACs in patients with intermediate-risk PE have not been systematically addressed thus far (42). One of the phase 3 clinical trials investigating the use of NOACs in patients with VTE reported efficacy results for the subgroup of patients with acute PE and right ventricular dysfunction; the latter was defined either as NT-proBNP levels >500 pg/ml, or as a right-to-left ventricular dimension ratio >0.9 on CT pulmonary angiography (33). Among patients with elevated NT-proBNP levels, recurrent VTE occurred in 15 of 454 patients in the edoxaban arm and in 30 of 484 patients in the warfarin arm, with a hazard ratio of 0.52 (95% CI: 0.28 to 0.98) (33). These findings are to be regarded as hypothesis-generating at the present stage; a prospective, multicenter management trial will focus on the safety, efficacy, and cost-effectiveness of dabigatran in the treatment of patients with acute intermediate-risk PE, defined by imaging (echocardiographic or CT) and laboratory

(circulating levels of cardiac troponins and natriuretic peptides) parameters, and their combinations, as proposed by the ESC guidelines (4). The study planned to enroll its first patient in the fourth quarter of 2015 (EudraCT 2015-001830-12).

The available data from cohort studies suggest, as a whole, that a shift towards ambulatory treatment might affect a substantial proportion (up to 50%) of patients with PE (reviewed in [43]). A prospective multicenter management trial has set out to determine whether early discharge and out-of-hospital treatment with rivaroxaban of patients with "low-risk" PE (on the basis of the Hestia criteria (19), combined with the exclusion of right ventricular dysfunction and intracardiac thrombi) is feasible and safe; the trial will also obtain health economic variables as the basis for description of resource utilization (EudraCT 2013-001657-28).

The advances and outlook of anticoagulation in patients with PE and cancer are discussed separately in the section *Current Controversies and Areas of Ongoing Research*.

## REPERFUSION STRATEGIES

**SYSTEMIC FIBRINOLYTIC TREATMENT.** Fibrinolytic agents have been tested in randomized trials over almost one-half a century, and those currently approved for clinical use were recently reviewed (4). A meta-analysis of 15 trials involving a total of 2,057 patients showed that fibrinolysis reduced overall mortality (odds ratio [OR]: 0.59; 95% CI: 0.36 to 0.96) and achieved a significant reduction in the combined endpoint of death or treatment escalation (OR: 0.34; 95% CI: 0.22 to 0.53), PE-related mortality (OR: 0.29; 95% CI: 0.14 to 0.60), and PE recurrence (OR: 0.50; 95% CI: 0.27 to 0.94). At the same time, however, major hemorrhage (OR: 2.91; 95% CI: 1.95 to 4.36) and fatal or intracranial bleeding (OR: 3.18; 95% CI: 1.25 to 8.11) were significantly more frequent among patients receiving thrombolysis (44). Of note, interpretation of meta-analyses in this field should be extremely cautious, considering the marked heterogeneity of: 1) trial size and patient selection (PE severity) criteria; 2) the fibrinolytic agents, doses, and regimens tested; and 3) drug application modalities and duration of treatment. These differences become even more pronounced and critical if trials on full-dose or reduced-dose (see later discussion) fibrinolysis, and on systemically or locally infused fibrinolytic agents, are analyzed together (45).

With all of the previously mentioned limitations in mind, there is consensus that immediate reperfusion treatment using systemic fibrinolysis is indicated in patients who present with high-risk or massive PE, that is, those with persistent arterial hypotension or shock (4,10,11). This is in contrast to the controversy that, until recently, surrounded the possible net clinical benefit of fibrinolysis in apparently stable patients with intermediate-risk or submassive PE. The international PEITHO (Pulmonary Embolism Thrombolysis) trial (24) compared a single intravenous bolus of tenecteplase plus heparin with placebo plus heparin in 1,006 patients with confirmed PE, right ventricular dysfunction detected by echocardiography or CT, and a positive troponin I or T test (partly corresponding to the ESC category of intermediate-high-risk PE [4]). In the fibrinolysis group, the primary outcome of all-cause death or hemodynamic decompensation/collapse within 7 days occurred less frequently than in the group receiving heparin alone (2.6% vs. 5.6%; OR: 0.44; 95% CI: 0.23 to 0.88). In parallel, a higher incidence of hemorrhagic stroke (2.0%) and major nonintracranial bleeding (6.3%) was observed in patients allocated to tenecteplase than in the placebo group (0.2% and 1.5%, respectively) (24). In view of these latter data, it becomes clear that full-dose systemic thrombolysis cannot be recommended as routine primary treatment for patients with intermediate-risk or submassive PE, even if signs of both right ventricular dysfunction and myocardial injury are initially present. Patients belonging to this risk group should receive parenteral heparin anticoagulation and be monitored closely over at least 48 to 72 h, and rescue fibrinolysis should be considered if clinical signs of hemodynamic decompensation appear (4).

**WEAK EVIDENCE FOR REDUCED-DOSE FIBRINOLYSIS.** The life-threatening bleeding complications that have consistently been associated with full-dose systemic fibrinolysis (reviewed in [46]) raise the question of whether reduced doses might improve safety without loss of efficacy. In a randomized pilot trial of 118 patients with either hemodynamic instability or "massive" pulmonary artery obstruction (without a standardized definition of clinical severity), half-dose recombinant tissue-type plasminogen activator (rtPA) was noninferior to the full dose in terms of improving pulmonary vascular obstruction, and it appeared to cause less bleeding (47). In another small study of 121 patients with "moderate" PE (also without a standardized definition of clinical severity), reduced-dose rtPA appeared to be safe in the acute phase and for reducing the persistence of echocardiographically assessed pulmonary hypertension at 28 ± 5 months of follow-up (48). The safety and efficacy of reduced-dose intravenous fibrinolytic regimens in patients 75 years of

age or older are also indirectly supported by the findings of a randomized controlled trial on acute ST-segment elevation myocardial infarction (49).

Although "half-dose" systemic fibrinolytic treatment appears appealing to many physicians, the evidence in its favor should be considered preliminary at best, and such off-label regimens cannot be recommended at the present stage. As an alternative option for PE patients who need reperfusion treatment due to initial or evolving hemodynamic decompensation, but present with absolute or relative contraindications to systemic fibrinolysis, catheter-based techniques may be considered, as will be explained later.

**CATHETER-DIRECTED REPERFUSION TECHNIQUES, WITH OR WITHOUT FIBRINOLYSIS.** Catheter-directed reperfusion techniques for removal of obstructing thrombi from the main pulmonary arteries may be an alternative to surgical embolectomy for patients with absolute or relative contraindications to thrombolysis (50). The phase 2 ULTIMA (Ultrasound Accelerated Thrombolysis of Pulmonary Embolism) trial randomized 59 patients with acute main- or lower-lobe PE and an echocardiographic right-to-left ventricular dimension ratio ≥1.0 to receive unfractionated heparin plus a catheter-directed, ultrasound-assisted thrombolytic regimen of 10 to 20 mg rtPA over 15 h, as opposed to heparin alone (51). Reduced-dose local thrombolysis significantly reduced the subannular right-to-left ventricular dimension ratio between baseline and 24-h follow-up, without an increase in bleeding complications (51). The efficacy and safety of pharmacomechanical thrombolysis is further supported by the results of a prospective, single-arm, multicenter trial from the United States that enrolled 150 patients with submassive or massive PE (52). A recent multicenter registry on catheter-directed mechanical or pharmacomechanical thrombectomy reported clinical success (defined as all of the following: stabilization of hemodynamics; improvement in pulmonary hypertension and/or right heart strain; and survival to hospital discharge) in 86% of 28 included patients with massive PE and 97% of 73 patients with submassive PE. No hemorrhagic strokes were observed (53).

The obvious need for local expertise and a high institutional volume to ensure satisfactory outcomes of catheter-directed treatment (54), along with the high costs of the equipment for ultrasound-assisted pharmacomechanical fibrinolysis and the lack of reimbursement by the health systems of several countries, still limit the widespread use of this technique outside of selected specialized centers. Moreover, it remains to be confirmed that ultrasound is indeed necessary to enhance the efficacy of the locally delivered low-dose fibrinolytic agent. In a recently published controlled clinical trial, 48 patients with acute iliofemoral DVT (but *not* PE) were randomized to receive ultrasound-assisted catheter-directed fibrinolysis versus catheter-directed fibrinolysis alone (55). The thrombolysis regimen (20 mg alteplase over 15 h) was identical in all patients. The percentage of thrombus load reduction was 55 ± 27% in the ultrasound-assisted versus 54 ± 27% in the conventional catheter-directed thrombolysis group (p = 0.91). At the 3-month follow-up, primary venous patency was 100% in the ultrasound-assisted and 96% in the conventional catheter-directed thrombolysis group (p = 0.33), and there was no difference in the severity of the post-thrombotic syndrome (55).

## CONTINUING DISCUSSION ON THE UTILITY OF INFERIOR VENA CAVA FILTERS

Venous filters are usually placed in the infrarenal portion of the inferior vena cava. A reasonable general recommendation is to use them in patients with acute PE who have absolute contraindications to anticoagulant drugs, in those experiencing major bleeding events during the acute phase, and in patients with objectively confirmed recurrent PE, despite adequate anticoagulation treatment (4). However, in some countries, particularly in the United States, a growing liberalization of indications for both permanent and retrievable filters is observed; this trend is highlighted by a 3-fold increase in their use between 2001 and 2006 according to data from the National Hospital Discharge Survey (56). Epidemiological data from the U.S. Nationwide Inpatient Sample, analyzing almost 298,000 filter implantations, suggest that cava filters may be associated with an improved outcome (57); registry data from Europe (albeit with fewer patients) have been less convincing (58). The PREPIC (Prévention du Risque d'Embolie Pulmonaire par Interruption Cave) 2 trial, a randomized, open-label, blinded endpoint trial with a 6-month follow-up, was more recently published (59). Hospitalized patients with acute, symptomatic PE associated with lower-limb vein thrombosis and at least 1 criterion for severity were assigned to retrievable inferior vena cava filter implantation plus anticoagulation (n = 200) or anticoagulation alone with no filter implantation (n = 199). Anticoagulant treatment was not interrupted during filter placement, and access site hematomas were observed in only 2.6% of the patients. By 3 months, recurrent PE had occurred in 6 patients (3.0%; all events fatal) in the filter group and in 3 patients (1.5%; 2 fatal) in the control group (RR with filter: 2.0;

**FIGURE 2   Global Trends in PE Incidence and Case Fatality Rates**
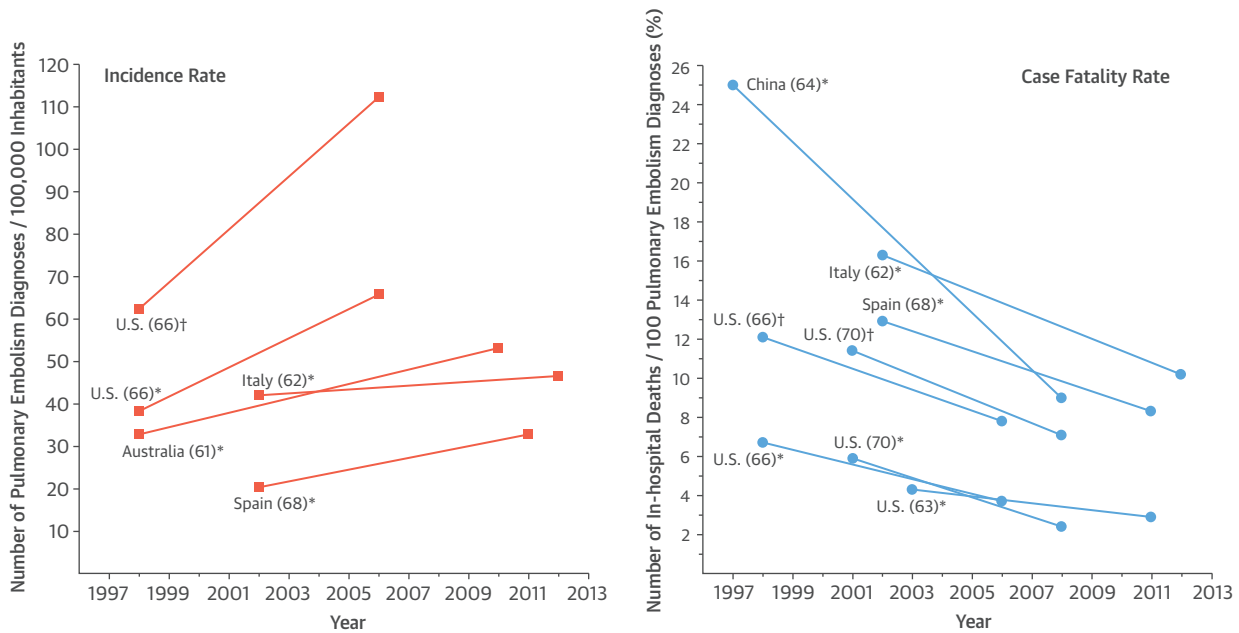


(Left) Pulmonary embolism (PE) incidence. (Right) Case fatality rates. Data shown here were retrieved from studies of trends in pulmonary embolism (61-64,66,68,70). In case of duplicate or overlapping data, only the most recent publication was included. *Pulmonary embolism was listed as principal diagnosis. †Any listed code for pulmonary embolism was considered.

95% CI: 0.51 to 7.89); results were similar at 6 months (59). In this context, it should also be borne in mind that cava filter placement is not free of complications, which may include penetration of the caval wall or embolization to the right heart cavities and occasionally require emergency treatment (60). Moreover, and importantly, the high success rates of filter retrieval (153 of 164 patients in whom it was attempted) reported in the PREPIC 2 trial (59) will be very difficult to reproduce in the real world, probably increasing the rate of long-term complications. In conclusion, the evidence derived from trial data does not support the liberalization of cava filter use beyond the strict indications listed previously.

## IMPACT OF EVOLVING MANAGEMENT STRATEGIES: TRENDS IN MORTALITY AND THE ECONOMIC BURDEN OF PULMONARY EMBOLISM

Evidence published in the past decade and continuing to accumulate consistently indicates a progressive reduction of case fatality rates among patients with acute PE (Figure 2). Data obtained from the U.S. Nationwide Inpatient Sample during the 8-year period between 1998 and 2005 were used to investigate the outcomes of patients with a primary or secondary PE diagnosis who had been discharged from acute care hospitals. The number of patients increased from 126,546 to 229,637 annually during that period; at the same time, in-hospital case fatality rates for these patients decreased from 12.3% to 8.2%, and the length of hospital stay decreased from 9.4 to 8.6 days (65). Another study, using both the U.S. Nationwide Inpatient Sample cohort and the Multiple Cause-of-Death database, reported that the incidence of diagnosed PE increased by as much as 81% (from 62.1 to 112.3 per 100,000) following the introduction of CT angiography, in comparison to the earlier reference period (1998 to 2006 vs. 1993 to 1998); in parallel, case fatality rates decreased before (from 13.2% to 12.1%) and, particularly, in the era of CT angiography (from 12.1% to 7.8%). Over the entire observation period, mortality related to PE dropped from 13.4 to 11.9 per 100,000 (66). Similar trends were reported from Germany (67), and also on the basis of the National Hospital Discharge Database, covering the entire Spanish population (68). In the latter study, in-hospital case fatality rates of PE decreased from 12.9% in 2002 to 8.3% in 2011 in parallel with a decrease in mean length of hospital stay from 12.7 to 10 days.

An obvious conclusion from dropping case-fatality rates could be that diagnosis and treatment of PE have both improved substantially, likely due to a combination of a higher level of suspicion, standardized clinical prediction rules and use of D-dimer testing, high accuracy of multidetector CT angiography, and the efficacy of low-molecular-weight heparins (population data reflecting the impact of NOACs on VTE-related mortality are not yet available). Evolution and broad implementation of multidisciplinary programs, such as the Pulmonary Embolism Response Team (PERT), which bring together a team of specialists to rapidly evaluate intermediate- and high-risk patients with PE, formulate a treatment plan, and mobilize the necessary resources, may contribute to even better patient outcomes in the future (69). It can also be argued that the parallel increase in the annual incidence of VTE (68), and the rather subtle (66) or absent (70) changes in PE-related annual mortality over time, reflect the increasing comorbidity in aging populations. However, overdiagnosis of PE with the liberal use of multidetector CT is an alarming alternative explanation (66,71), and it needs to be addressed by concerted efforts to increase the implementation of evidence-based guidelines.

Costs related to the management of acute PE (and VTE in general) have long been assumed to be substantial, but it was only recently that they were systematically calculated in the United States (72). In a cost model built on adult incidence-based events and potential complications, total annual VTE costs ranged from $13.5 to $69.3 billion, with preventable costs of $4.5 to $39.3 billion (72). These data highlight the potential for cost savings in the future by: 1) improving VTE preventive measures in hospitalized patients; 2) implementing evidence-based, risk-adjusted management algorithms, as recommended by current guidelines; 3) identifying candidates for early discharge and ambulatory treatment; 4) using anticoagulant agents with an improved safety profile; and 5) increasing VTE awareness in the population (2).

## CURRENT CONTROVERSIES AND AREAS OF ONGOING RESEARCH

**MAGNETIC RESONANCE IMAGING.** Five years after the disappointingly low rate of technically adequate images reported in the PIOPED (Prospective Investigation of Pulmonary Embolism Diagnosis) III study, an ongoing prospective management study, is investigating the performance of magnetic resonance imaging in combination with lower-limb compression ultrasound in the diagnostic workup of suspected PE (NCT02059551). Beyond angiographic techniques and the detection of filling defects, a study using an experimental mouse model of VTE, as well as ex vivo-generated human clots, investigated a novel technique for the sensitive and specific identification of developing thrombi (73). The study used background-free $^{19}F$ magnetic resonance imaging, together with alpha2-antiplasmin peptide-targeted perfluorocarbon nanoemulsions (PFCs) as a contrast agent cross-linked to fibrin by active factor XIII. Developing thrombi with a diameter <0.8 mm could be visualized in vivo in the murine inferior vena cava as hot spots by simultaneous acquisition of anatomic matching (73). If further developed and tested in humans, this method may offer the potential to visualize fresh, developing thrombi that are still susceptible to pharmacological intervention.

**SIGNIFICANCE OF SUBSEGMENTAL PE.** The clinical significance and therapeutic implications (i.e., need for anticoagulation treatment) of isolated subsegmental PE on CT pulmonary angiography remain subjects of debate. A meta-analysis reported that the rate of subsegmental PE diagnosis has doubled in parallel with advances in CT technology, rising from 4.7% (95% CI: 2.5% to 7.6%) of patients undergoing single-detector CT angiography to 9.4% (5.5% to 14.2%) of those submitted to multidetector CT (71). The 3-month VTE recurrence risk in patients who were left untreated on the basis of a negative CT angiography remained unaffected by the use of multidetector CT (71), and it is possible that at least some of the tests were false positive because the positive predictive value is low and the interobserver agreement poor at this distal level (6,74). Compression ultrasound of the leg veins can be helpful in this situation, because the confirmation of proximal DVT in a patient with isolated subsegmental PE sets the indication for anticoagulant treatment, whereas the exclusion of DVT could support a decision against treatment; these latter cases should be managed on an individual basis, taking the clinical probability and the bleeding risk into account (4). An ongoing prospective cohort study is currently investigating the safety of withholding anticoagulation in patients with subsegmental PE and no cancer, who have negative serial bilateral lower extremity ultrasound tests and are carefully followed over 3 months (NCT01455818).

**SUSPECTED VTE IN PREGNANCY.** PE is the leading cause of pregnancy-related maternal death in developed countries; at the same time, pregnancy is 1 of the main risk factors for inappropriate management of suspected PE (75). These facts emphasize the

importance of the recommendation that suspicion of PE in pregnancy warrants formal diagnostic assessment with validated methods (4). This may be easy to say, but it is much more difficult to implement in practice, because individual symptoms and clinical signs are even less specific than in nonpregnant patients, and clinical prediction rules are lacking. As D-dimer levels increase during pregnancy, adapted cutoff values might help increase specificity, but these have not been tested in outcome trials. Finally, controversy persists on the appropriate imaging test(s) for PE, and VTE in general, due to the questionable performance of leg vein compression ultrasound in this setting and the (partly justified) fears of fetal and maternal irradiation (overview of absorbed doses provided in [4]). An ongoing multicenter outcome study in pregnant patients is currently investigating a PE diagnostic strategy on the basis of 4 sequential steps: assessment of clinical probability; D-dimer measurement; compression ultrasonography; and CT pulmonary angiography (NCT00771303).

**OPTIMAL MANAGEMENT OF PATIENTS WITH CANCER.** The epidemiological and clinical relevance of the association between VTE and cancer is well documented. Overall, the risk of VTE in cancer patients is 4× as high as in the general population (76). Conversely, the proportion of a first VTE event that could be attributed to cancer was consistently around 20% in population-based studies and registries (reviewed in [77]). Importantly, unprovoked VTE may be the earliest sign of cancer, and up to 10% of patients with VTE may be diagnosed with cancer within 1 year following the index event. Nevertheless, a multicenter randomized open-label trial of 854 patients with first unprovoked VTE recently showed that extended occult cancer screening, including comprehensive CT of the abdomen and pelvis, does not reduce the number of missed occult cancers, the mean time to cancer diagnosis, or cancer-related mortality by the end of the 1-year follow-up, compared with a limited screening strategy (78).

The consensus that weight-adjusted subcutaneous low-molecular-weight heparin should be considered for the first 3 to 6 months, instead of oral anticoagulant agents, for patients with PE and cancer has remained unchanged in the past years (4,10). The results of the recently published CATCH (Comparison of Acute Treatments in Cancer Hemostasis) trial on 900 patients randomized to tinzaparin (175 IU/kg once daily) versus international normalized ratio–adjusted warfarin treatment over 6 months generally support the efficacy and safety of this approach, although the study did not, by itself, show superior efficacy of tinzaparin over warfarin in preventing VTE

recurrence or overall mortality (79). Post hoc analysis of the patients with active cancer or history of cancer included in the EINSTEIN-PE and -DVT phase 3 rivaroxaban trials (80), as well as a meta-analysis of the cancer patients included in all phase 3 NOAC trials on the treatment of VTE (81), suggest a good efficacy and safety profile for target-specific oral anticoagulant agents as compared with VKA. However, the existing evidence must be considered preliminary, and further data, including a comparison between NOACs and low-molecular-weight heparins, are needed to determine the optimal anticoagulation strategy in this patient population. The ongoing HOKUSAI-cancer (Cancer Venous Thromboembolism [VTE]) randomized controlled trial is aiming to evaluate whether the oral factor Xa inhibitor edoxaban is noninferior to the low-molecular-weight heparin dalteparin for treating acute VTE in cancer patients over a 12-month period (NCT02073682) (82).

**ANTICOAGULATION IN THE POST-NOAC ERA.** The ideal anticoagulant agent could be expected to effectively prevent or treat thrombosis without (significantly) increasing the risk of bleeding. Experimental data suggest that reduction of factor XI (FXI) levels might be a promising target in this regard (83,84). An open-label, parallel-group study randomly assigned 300 patients, who were undergoing elective primary unilateral total knee arthroplasty, to receive 1 of 2 doses of FXI antisense oligonucleotide (ASO) (200 mg or 300 mg), or 40 mg of enoxaparin once daily (85). The primary efficacy outcome, incidence of VTE (assessed by bilateral venography or report of symptomatic events), occurred in 36 of 134 patients (27%) who received 200 mg and 3 of 71 (4%) who received 300 mg of FXI-ASO, compared with 21 of 69 patients (30%) who received enoxaparin. The 200-mg regimen was thus noninferior, and the 300-mg regimen was superior, to enoxaparin (p < 0.001). Bleeding occurred in 3%, 3%, and 8% of the patients in the 3 study groups, respectively (85). These results await confirmation in larger trials and in further prophylactic or therapeutic indications.

**FOLLOW-UP AFTER PE: DURATION OF ANTICOAGULATION AND SEARCH FOR CHRONIC THROMBOEMBOLIC PULMONARY VASCULAR DISEASE.** The optimal duration of anticoagulation following the first episode of acute unprovoked VTE (i.e., VTE occurring in the absence of reversible risk factors such as surgery, trauma, immobilization, or contraception/hormonal replacement therapy in the 3 weeks to 6 months preceding diagnosis [29]) remains controversial. Beyond the "compulsory" 3-month anticoagulation treatment, decisions on extending VTE secondary prophylaxis for an indefinite period

should be made on an individual basis, after taking into consideration the patient's risk profile for recurrence without anticoagulant treatment and weighing it against the bleeding risk under anti-coagulation (4,29) (**Figure 1**). Although this approach sounds quite reasonable, it is often difficult to translate into clinical practice, because the proposed recurrence scores (86-88) still lack external valida-tion, and preliminary data suggest that the bleeding scores derived from atrial fibrillation may not perform adequately in patients with VTE (89,90). In this re-gard, it has been proposed that D-dimer testing may identify patients in whom anticoagulation can be safely discontinued, particularly with serial mea-surements combined with evidence of residual thrombosis (91) or when integrated into recurrence scores (86-88). However, a recently published pro-spective management study questioned the safety of this strategy (92). In 410 adults aged 75 years or younger with a first unprovoked proximal DVT or PE, who had completed 3 to 7 months of anticoagulant therapy, warfarin was stopped if D-dimer test results were negative and was not restarted if results were still negative after 1 month. The study showed that the risk for recurrence was, at least in men, not low enough to justify the discontinuation of anticoagu-lant therapy; there was imprecision and uncertainty in the female population (92). An ongoing prospective cohort study is investigating the value of a rule combining clinical data and D-dimer levels for pre-diction of a low recurrence risk after unprovoked VTE (NCT00261014).

In summary, considering: 1) the inconsistent re-ports on the influence of specific baseline or follow-up parameters on the risk of VTE recurrence (reviewed in [29]); 2) the lack of externally validated recurrence or bleeding scores for VTE; 3) the rise in recurrence risk as soon as anticoagulation is dis-continued, regardless of its previous duration (93-95); and 4) the good safety profile of extended NOAC treatment (35,94,96), but also of contemporary VKA-based anticoagulation (93), a progressive shift of anticoagulation strategies towards indefinite treat-ment periods after a first unprovoked PE can be anticipated, provided that it can be confirmed with real-world data that the favorable risk-to-benefit ratio of anticoagulation is maintained over the long term. An ongoing randomized double-blind study is inves-tigating the efficacy and safety of reduced-dose (10 mg once daily) versus standard-dose (20 mg once daily) rivaroxaban versus aspirin in the long-term prevention of recurrent symptomatic VTE in patients who have completed 6 or 12 months of anticoagulation after DVT or PE (NCT02064439).

Long-term follow-up studies indicate that as many as 50% of patients who have survived an acute PE episode report persistent functional limitation and/or reduced quality of life for long periods (up to several years) after the index event. We are still far from understanding how many of these patients experi-ence a "post-PE syndrome," and what the definition and pathophysiology of such a syndrome might be (97). So far, we have made progress in understanding and managing the far end of its severity spectrum, namely CTEPH. This debilitating and potentially life-threatening disease is caused by chronic obstruction of major pulmonary arteries and has a reported cu-mulative incidence of 0.1% to 9.1% within the first 2 years after a symptomatic PE event (98). This large margin of error is probably due to referral bias, absence of early symptoms, and the occasional diffi-culty in differentiating acute PE from an episode superimposed on pre-existing CTEPH (99). The 2014 ESC guidelines specify that CTEPH should be ruled out in patients with persistent dyspnea after acute PE and at least 3 months of anticoagulation treatment; however, routine screening for CTEPH is not recom-mended in asymptomatic survivors of PE on the basis of currently available data (4). Adequately powered multicenter prospective cohort studies with system-atic, multimodality follow-up programs are needed to identify the determinants of progressive clinical, functional, and hemodynamic impairment after PE, and the population in whom early signs of developing CTEPH should be sought.

## CONCLUSIONS

Recently published randomized trials and major cohort studies were able to clarify several important aspects related to the management of acute PE. In particular, age-adjusted D-dimer cutoff levels were helpful in optimizing the use of imaging procedures in patients with low pre-test clinical probability for the disease; the risks of full-dose systemic fibri-nolysis, administered as primary treatment, were shown to outweigh its benefits in patients with intermediate-risk PE; catheter-directed pharmaco-mechanical techniques emerged as a promising op-tion for patients with indications to reperfusion treatment and a high bleeding risk; 4 new oral anti-coagulant agents were approved for treatment and secondary prevention of VTE, showing noninferior efficacy and probably superior safety compared with traditional heparin/VKA regimens; retrievable vena cava filters were not found to improve 3-month or 6-month prognoses when inserted on top of anti-coagulation treatment; and further evidence was

provided in favor of extended or even indefinite anticoagulation for secondary prophylaxis after unprovoked PE. However, important issues that remain to be resolved include the therapeutic implications of subsegmental PE on CT pulmonary angiography; diagnostic algorithms adapted to pregnant patients; the efficacy and safety of new oral anticoagulant agents in patients with cancer; and the elaboration of follow-up strategies, in order to determine the optimal duration of anticoagulation and identify patients at risk of developing CTEPH. Overdiagnosis of PE is a growing challenge, as is the need to demonstrate the cost-effectiveness of new drugs and interventions. Updated guidelines recommending risk-adjusted diagnostic and therapeutic algorithms need to be implemented in clinical practice and accompanied by campaigns to increase the awareness of the disease; these measures will provide the basis for a sustainable decrease of both incidence and case fatality rates in the years to come.

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