Pulmonary embolism

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Abstract | Pulmonary embolism (PE) is caused by emboli, which have originated from venous thrombi, travelling to and occluding the arteries of the lung. PE is the most dangerous form of venous thromboembolism, and undiagnosed or untreated PE can be fatal. Acute PE is associated with right ventricular dysfunction, which can lead to arrhythmia, haemodynamic collapse and shock. Furthermore, individuals who survive PE can develop post-PE syndrome, which is characterized by chronic thrombotic remains in the pulmonary arteries, persistent right ventricular dysfunction, decreased quality of life and/or chronic functional limitations. Several important improvements have been made in the diagnostic and therapeutic management of acute PE in recent years, such as the introduction of a simplified diagnostic algorithm for suspected PE as well as phase III trials demonstrating the value of direct oral anticoagulants in acute and extended treatment of venous thromboembolism. Future research should aim to address novel treatment options (for example, fibrinolysis enhancers) and improved methods for predicting long-term complications and defining optimal anticoagulant therapy parameters in individual patients, and to gain a greater understanding of post-PE syndrome.

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Acute venous thromboembolism (VTE), which includes deep-vein thrombosis (DVT) and acute pulmonary embolism (PE), is a leading cause of cardiovascular mortality, exceeded only by stroke and myocardial infarction[1]. PE occurs when an embolus breaks off a thrombus (blood clot) in a vein and occludes blood vessels of the pulmonary artery tree (FIG. 1). Thrombosis is regulated by a multistep coagulation cascade, involving multiple factors, and can be triggered by plasma hypercoagulability, changes to blood flow and endothelial cell dysfunction. Untreated, PE confers a high mortality, especially in the presence of right ventricular (RV) impairment. In an acute PE event, arrhythmia or massive RV failure, or a combination of the two, can cause acute haemodynamic collapse leading to inadequate arterial blood flow to organs and, ultimately, death. Even after successful acute PE treatment, up to 10% of PE survivors will die within 1 year[2,3].

PE survivors can develop post-PE syndrome, with a higher risk of developing recurrent PE and functional impairments[4,5]. Within the post-PE syndrome, two specific conditions have been described: chronic thromboembolic vascular disease (CTED) and chronic thromboembolic pulmonary hypertension (CTEPH). CTED has been defined as functional impairment due to chronic thromboembolic remains in the pulmonary artery tree without pulmonary hypertension, that is, a mean pulmonary systolic pressure <25 mmHg. CTEPH is defined as a mean pulmonary artery pressure of ≥25 mmHg, a pulmonary capillary wedge pressure of ≤15 mmHg and the presence of multiple chronic or organized occlusive thrombi in the pulmonary artery tree after at least 3 months of anticoagulant treatment[6]. In this Primer, PE and CTEPH are presented as a continuum, but it is important to note that 25–30% of patients with CTEPH do not report any episode of symptomatic VTE[7].

Given the prevalence of this disease, it is remarkable that, in contrast to myocardial infarction and stroke, there is a lack of awareness of VTE[8]. A 2014 population-based study in the United States showed that despite advances in prophylaxis and treatment, the annual rate of VTE remains high[9].

Three key steps are vital in the management of PE: first, the prognosis of patients depends on a rapid, simple and accessible diagnosis[10]; second, accurate triaging of PE according to risk of acute complications, such as RV failure, will allow for appropriate treatment based on the triaging[6]; third, estimating the optimal duration of treatment requires a precise assessment of the long-term risks of recurrent VTE and/or anticoagulation-associated bleeding for the individual patient with PE[6,11]. Much progress has been made regarding these steps in recent years; however, outstanding problems still remain, including the prevention and/or early detection of CTEPH[12,13]. In this Primer, we provide an overview of the current knowledge of the development and clinical consequences of PE, including acute PE and post-PE syndrome. In addition, we highlight new and emerging treatment options for PE and its complications.

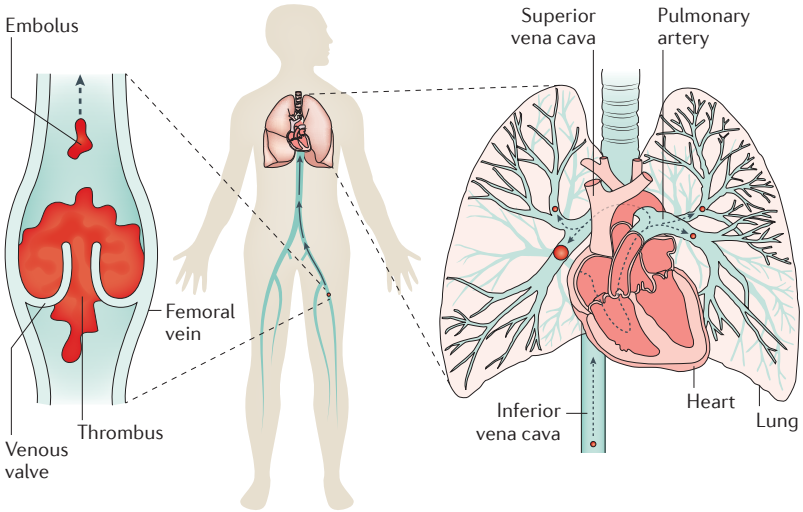

Figure 1 | **Mechanisms of PE.** After travelling to the pulmonary arteries, emboli may either break down and lodge in the peripheral pulmonary arteries or, alternatively, if very large, remain at the main pulmonary artery bifurcation, which then gives rise to a 'saddle embolism'; this latter event causes severe haemodynamic compromise, collapse and severe dyspnoea. PE, pulmonary embolism.

Epidemiology

Incidence and mortality

In the United States and Europe, the incidence of VTE is 1–2 cases per 1,000 inhabitants per year — a figure that rises exponentially with age[14]. Although the overall incidence of VTE has remained more or less stable over time, the contribution of PE to this figure is increasing whereas that of DVT is decreasing, which is possibly partly owing to an increase of incidental PE findings detected using thoracic CT[9,15]. The use of CT pulmonary angiography (CTPA) to diagnose PE has increased as this technique is also useful for diagnosing other causes of PE-like symptoms. Moreover, CT image quality is continuously improving, resulting in the diagnosis of an increased number of small (subsegmental) pulmonary emboli and, hence, an increase in incidence[16]. Both sexes have shown a substantial increase in age-standardized incidence rates over time, but the mean observed annual change was +1.2% in men and +0.6% in women[17].

VTE contributes to a major burden of disease across low-income, middle-income and high-income countries and is a leading cause of disability-adjusted life years lost[18]. The 30-day case mortality of PE is approximately three to four times higher than that of DVT, at 6.8% for PE versus 1.8% for DVT (excluding patients with cancer) in a Norwegian study[2]. Similar figures were reported in a Canadian study (3.9% PE versus 1.3% DVT)[19]. The non-cancer-related 1-year mortality was higher for PE than for DVT in the Norwegian study (15.5% PE versus 11.1% DVT), again similar to the figures from Canada (12.9% PE versus 7.8% DVT)[2,19]. Long-term mortality data (up to 8 years of follow-up) show no difference between patients with DVT or PE, but mortality risk is twofold higher in individuals post-VTE than in age-matched and sex-matched individuals without VTE[20].

The recurrence rate of PE is ~22% after 5 years[21]. In observational studies, patients with an initial PE are approximately three times more likely to develop a recurrent PE than patients with an initial DVT; this finding was confirmed in a meta-analysis of nine randomized controlled trials[21–24]. In addition to recurrent VTE, patients who survived acute PE have an increased risk of arterial cardiovascular disease, cancer and chronically reduced quality of life owing to lasting functional limitations[3,25,26]. As such, the evolving definition of 'the post-PE syndrome' includes various long-term complications of acute PE that cause functional limitations[4,12,27–29]. Several studies report that up to half of individuals who have survived PE reported symptoms of exercise intolerance corresponding to a New York Heart Association (NYHA) heart failure score of ≥11 after a 6-month follow-up period[28,30,31]. The 2-year incidence of CTEPH after symptomatic acute PE has been reported to be 0.6% (95% CI 0.1–1.0) in all individuals with PE, 3.2% (95% CI 2.0–4.4) in individuals who have survived PE and 2.8% (95% CI 1.5–4.1) in individuals who have survived PE without cardiopulmonary, malignant and/or other severe comorbidities[32–34]. The incidence of CTED is currently unknown, and it remains unclear whether CTED is a precursor of CTEPH.

Risk factors

Risk factors for VTE. Many risk factors for VTE have been identified and can be divided into genetic, acquired and mixed-origin (for example, high levels of procoagulant factors) risk factors[35]. The strongest genetic risk factors fall into two categories. The first category comprises loss-of-function mutations in genes encoding natural anticoagulants such as *PROC*, *PROS1* and *SERPINC1* (respectively encoding protein C, protein S and antithrombin)[36]. The mutations in these genes are very heterogeneous; thus, affected families have a specific mutation that is relatively rare in the general population. Heterozygosity for a risk allele may increase risk of VTE up to tenfold in affected families[36]. Homozygosity for a loss-of-function mutation is very rare and either results in severe thrombotic disease that manifests immediately postpartum, or has never been observed (for example, such mutations in antithrombin are embryonically lethal). The prevalence of mutations in anticoagulant genes seems largely independent of ethnic origin; however, one study demonstrated evidence for a high prevalence of protein S deficiency in Japanese people[37].

The second category encompasses more common gain-of-function mutations in genes encoding procoagulant proteins, such as *F5* and *F2* (respectively encoding coagulation factor V and prothrombin), and *FGA*, *FGB* and *FGG* (collectively encoding fibrinogen)[36]. The factor V Leiden mutation occurs in ~3% of white individuals and increases thrombotic risk approximately 3-fold in heterozygous individuals, and up to 50-fold in homozygous individuals, but symptoms occur relatively late in life[38]. The factor V Leiden mutation is very rare in populations other than of white origin[39], as is the prothrombin A20210G mutation[40].

Common single-nucleotide polymorphisms may also weakly influence thrombotic risk and are clinically irrelevant[36,41]. Moreover, almost all of these weak risk factors have not been studied specifically in the context of PE; therefore, they fall outside the scope of this Primer.

Of the acquired VTE risk factors, the strongest are factors that are related to other morbidities such as surgery and extended hospital admission. Furthermore, in the outpatient scenario, various diseases increase the risk of VTE, including cancer[42], inflammatory disorders such as inflammatory bowel disease[43], infection such as respiratory or urinary tract infection[44], hyperthyroidism[45] and kidney disease[46]. The use of female hormones for oral contraception and hormone replacement therapy leads to minor hypercoagulable states and an increased risk of VTE in otherwise healthy women, as do pregnancy and puerperium[47–49]. Last, obesity is consistently associated with increased VTE risk, but it is unclear whether this is owing to a hypercoagulable state or to other mechanisms, such as decreased mobility, venous compression or related comorbidity[50,51].

Risk factors for PE versus DVT. The risk factors for PE largely overlap with those for DVT, but striking differences have been reported, the best known of which is the 'factor V Leiden paradox'. Since 1996, it has been consistently reported that patients with DVT are more likely to carry the gain-of-function factor V Leiden mutation than patients with PE. Hence, for individuals with the factor V Leiden mutation, the relative risks (compared with individuals with wild-type factor V) are higher for DVT and lower for PE. A similar pattern has been described for a few other risk factors, such as hormonal-related risk factors (for example, pregnancy, puerperium and use of oral contraceptives), obesity and leg trauma[51–53].

The factor V Leiden mutation and hormonal risk factors both increase VTE risk by inducing resistance to activated protein C (an anticoagulant); a similar mechanism has been proposed for obesity[54]. Activated protein C resistance may preferentially increase the risk of DVT and not the risk of PE through decreased fibrinolysis and thereby decreased embolization[55,56]. The reason for the increased risk of DVT in leg injuries may be due to the local development of thrombi associated with tissue damage and restrained mobility. In addition, the risk of PE may be reduced as patients with leg trauma are likely to be otherwise healthy and may be mobile again fairly quickly.

Other risk factors lead to a higher risk of PE than for DVT — for example, chronic obstructive pulmonary disease (COPD)[57], pneumonia[58] and sickle cell disease[59]. These factors have little to no effect on the risk of DVT. In sickle cell disease, sickle-shaped red blood cells have a tendency to form clots, which are easily trapped in the small pulmonary arteries; an acute chest syndrome can occur in which hypoxia further enhances coagulation, eventually leading to clots in the larger pulmonary arteries. Sickle cell trait has a high prevalence in black people, which could in part explain the higher risk of PE than DVT in black people than in white people[60].

Last, atrial fibrillation might be related to the occurrence of PE. Epidemiological studies have shown a higher risk of PE than for DVT in patients with atrial fibrillation, particularly in the weeks after a recent diagnosis of atrial fibrillation[61,62]. A potential mechanism for this is that abnormal blood flow in the right atrium could lead to clot formation and embolization.

Considering the differential effect of several risk factors on PE and DVT, it might be considered that the aetiology of these diseases is not always the same. This consideration is confirmed by the pattern of recurrent VTE events: if DVT and PE are different expressions of the same disease, the anatomic location of recurrence would be expected to be random (thus, independent of the location of the first event); however, this is not the case. This observation calls for studies further unravelling the mechanisms underlying the two conditions.

Risk factors for post-PE syndrome. Several factors have been associated with post-PE syndrome. First, deconditioning occurring after hospital admission and the cardiovascular effect of acute PE are likely relevant to the level of physical recovery of the patient, as well as the presence of other cardiopulmonary comorbid conditions, such as COPD or coronary artery disease[63–66]. Second, persistent pulmonary perfusion defects have been described in 20–30% of patients with PE despite adequate anticoagulant therapy. Persistent blood clots cause pulmonary perfusion defects, which may cause increased physiological dead space (lacking tissue functionality) in the lung, and ventilatory insufficiency[4,28,67]. Third, persistent RV dysfunction has been detected in up to 44% patients 6–12 months after an acute PE event[30,31,68]. Severe RV dysfunction at baseline, known cardiovascular comorbidities, persistent perfusion

Box 1 | **Risk factors for CTEPH**

- Thyroid replacement therapy
- Malignancy
- Venous thromboembolism (acute or recurrent)
- Antiphospholipid antibodies
- High serum levels of factor VIII
- Non-O blood group
- Ventriculo-atrial shunt
- Infected pacemaker leads
- Indwelling venous catheters and leads
- Splenectomy
- Chronic inflammatory disorders

Mechanisms of thrombus non-resolution implicated with CTEPH pathophysiology

- Defective angiogenesis
- Systematic inflammation
- Fibrinogen abnormalities and/or impaired fibrinolysis
- Misguided immune response to venous clots
- Hypoxia-induced endothelial and mesenchymal cell activation

CTEPH, chronic thromboembolic pulmonary hypertension.

defects and older age were associated with a higher risk of persistent RV functional impairment in these patients. Last, as described above, CTEPH is a chronic condition associated with post-pulmonary syndrome. The risk factors for CTEPH are summarized in BOX 1.

Mechanisms/pathophysiology

Aetiology of acute PE

PE is defined by a process of venous thrombi dislodging from their origin (usually from the deep leg veins, rarely the pelvic, renal and upper extremity veins and very rarely the right atrium of the heart) and travelling as emboli through the vena cava and right side of the heart to the pulmonary arteries (FIG. 1). After travelling to the pulmonary arteries, thrombi may either break down and lodge into the peripheral pulmonary arteries or, alternatively, if very large, remain at the main pulmonary artery bifurcation, which then gives rise to a 'saddle embolism'; this latter event may cause severe haemodynamic compromise, collapse and severe dyspnoea. If the thrombi travel further to smaller arteries and end arteries, the latter may cause pulmonary infarction, which causes severe pain that typically increases on respiration.

Pathophysiology of RV failure

Relevance of RV failure. RV dysfunction and failure is the primary cause of death in PE[69–71] (FIG. 2). Under normal conditions, the pulmonary vascular system has a low resistance, which explains the properties of the right ventricle (thin walled and a decreased contractility compared with the left ventricle)[72]. In addition, the RV contractility reserve to pressure or volume overload is small owing to the low RV mass, making the right ventricle vulnerable to a sudden increase in RV afterload, as can occur in acute PE.

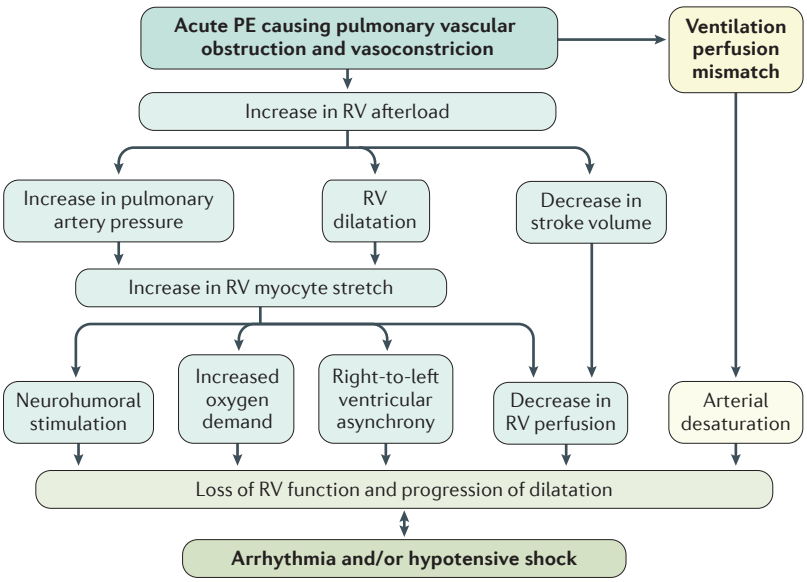

Figure 2 | **The sequence of RV failure in acute PE.** Acute pulmonary embolism (PE) will induce pulmonary vascular obstruction and, to a lesser extent, pulmonary vasoconstriction. As a consequence, the increased pulmonary vascular resistance, which is the main component of right ventricular (RV) afterload, leads to an increase in pulmonary artery pressure, RV dilatation and a decrease in stroke volume. The increase in pulmonary artery pressure and RV dilatation will increase the stretch on the RV myocyte. The impact of this sudden increase on the RV myocardium is neurohumoral stimulation, increased oxygen demand of the myocardium, prolonged RV contraction time leading to right-to-left ventricular asynchrony and decreased coronary perfusion to the right ventricle. As a consequence, RV failure will occur, which will be further provoked if hypotension and low arterial oxygen saturation are present. An increased ventilation perfusion mismatch may lead to arterial desaturation also leading to low arterial oxygen saturation.

Mechanisms of RV failure. The increase in RV afterload in acute PE is due to mechanical obstruction of the pulmonary vasculature by emboli and, to a lesser extent, by obstruction-associated vasoconstriction triggered by vasoactive mediators released by endothelial cells and platelets (among others thromboxane A2 and serotonin)[73,74]. The resulting sudden increase in pulmonary artery pressure leads to an increase in RV dilatation, with both contributing to the increase in stretch of the RV myocyte, which is reflected by increases in serum N-terminal pro-brain-type natriuretic peptide (NT-proBNP) and troponin levels (biomarkers of myocardial stretch and damage) in acute PE[75,76]. To match the increase in afterload, RV contractility must increase by an increase in neurohumoral activation (an increase in the activity of the renin–angiotensin system, sympathetic nervous system, vasopressin and atrial natriuretic peptide) and RV dilatation (Frank–Starling mechanism). If this increase in contractility does not match, the increased afterload stroke volume will drop, leading to a systemic decrease in blood pressure, which triggers the production of catecholamines and the neurohumoral system[77]. The mechanism of RV dilatation will, according to the Frank–Starling mechanism, maximize contractility by optimizing the length–tension relationship of cardiac muscle fibres only to a certain threshold. Further dilation beyond this point will lead to failure[72]. Because the RV mass is low in healthy individuals, the ability of the right ventricle to adapt is limited: upon increased afterload, a previously healthy non-hypertrophied right ventricle can acutely generate a mean pulmonary artery pressure of up to 40 mmHg (normal pulmonary artery pressure at rest is between 8 and 15 mmHg)[78]. With further increases in afterload, RV dilatation becomes maladaptive, leading to RV failure.

In acute PE, the oxygen supply to the right ventricle is limited and leads to further impairments in contractility. Two factors are associated with reduced oxygen supply: impaired coronary perfusion and hypoxaemia. Under healthy conditions, the right ventricle is perfused during systole and diastole. However, under conditions of increased RV afterload, systolic coronary perfusion is reduced or even absent (FIG. 2). In addition, severe acute PE is often accompanied by a drop in systemic blood pressure, which further reduces myocardial blood supply to both ventricles. The primary gas exchange disturbance in acute PE is caused by increased dead space ventilation in pulmonary tissue, and hypoxaemia (low blood oxygen) frequently occurs (BOX 2).

As a consequence of increased RV wall tension, a reduced oxygen supply to the myocardium and increased oxygen demand, further neurohumoral activation will occur at a systemic and intracardiac level. Neurohumoral overstimulation may induce an inflammatory

response — a hypothesis that is supported by studies of tissues from patients who died of acute PE that showed extensive influx of inflammatory cells (mainly mononuclear cells and neutrophilic granulocytes) into the right ventricle, mimicking the picture of catecholamine-induced myocarditis[79–81]. Moreover, the increase in troponin levels in severe PE indicates cardiomyocyte death. Interestingly, treatment of an animal model of acute RV pressure overload with blocking antibodies to a neutrophil chemoattractant, cytokine-induced neutrophil chemoattractant 1 (CINC1; also known as CXCL1), leads to suppression of neutrophilic accumulation in the right ventricle and a reduction of the plasma concentration of troponin I (REF.[82]), highlighting the potential importance of inflammation in RV injury.

Another important mechanism of RV failure is ventricular interdependence — the concept that the size, shape and compliance of one ventricle affect the properties of the other ventricle by mechanical interactions. As a consequence of increased RV wall tension, RV contraction time will increase and continue while the left ventricle is already in its early diastolic phase, leading to a leftward shift of the interventricular septum (the wall separating the left and right ventricles), thereby compromising left ventricular filling and cardiac output and adding mechanical inefficiency to the right ventricle[83] (FIG. 2). Progression of RV failure will bring the heart into a fatal feedback loop in which increasing oxygen demand and decreasing oxygen supply trigger the haemodynamic instability and tachyarrhythmias that are responsible for death in acute PE.

In the case of a gradual increase in pulmonary artery pressure as in CTEPH, the right ventricle can adapt. The first step in this process is RV hypertrophy (thickening) leading to a reduction in wall tension and increased RV contractility (up to five times higher)[84]. However, if the increase of the pressure load exceeds the adaptational ability of the right ventricle, it will enter a failure feedback loop characterized by progressive RV dilatation, a decrease in stroke volume and an increase in heart rate[72]. In contrast to RV failure in acute pressure overload, the right ventricle in chronic pressure overload does not show signs of inflammation[81].

Post-PE syndrome

Post-PE syndrome encompasses the chronic conditions CTED and CTEPH. The mechanism for functional impairment in CTED is heterogeneous and includes pulmonary ventilatory dead space, RV dysfunction (for example, decreased contractile reserve), exercise-induced pulmonary hypertension and abnormal pulmonary flow dynamics. In CTEPH, which is the more severe presentation, the exact pathophysiological mechanism that prevents the complete resolution of an acute thrombus is unclear, although a pro-inflammatory state in the setting of autoimmune disease or cancer, abnormal fibrinogen variants, aberrations in angiogenesis and mesenchymal cell activation have been implicated in poorer pulmonary thrombus resolution[85–93]. In addition to chronic blood clots, patients with CTEPH usually exhibit widespread pulmonary microvasculopathy, which resembles other pulmonary arterial hypertension subtypes[85,94] and may be caused by altered blood flow from multiple anastomoses between the systemic and pulmonary circulation through hypertrophic bronchial arteries. This hypothesis is supported by the observation that 19–63% of patients with confirmed CTEPH lack a history of symptomatic PE or DVT; as some patients with CTEPH lack evidence of PE, other mechanisms of disease may be involved. It can be speculated that these latter patients suffered one or more episodes of 'silent PE' or, alternatively, have a pronounced prothrombotic phenotype of idiopathic pulmonary hypertension with extensive in situ thrombosis.

Box 2 | **Mechanisms of hypoxaemia in PE**

The most important factor contributing to hypoxaemia in pulmonary embolism (PE) appears to be overperfusion of non-embolic, non-occluded regions, leading to abnormal increased perfusion in relation to ventilation. Another factor is the collapse of lung tissue (atelectasis) leading to pulmonary shunt, which is defined as pulmonary perfusion to non-ventilated areas near occluded embolic regions due to selective bronchial constriction. Possible mechanisms of atelectasis include alveolar hypocapnia (termed hypocapnic bronchoconstriction)[73,202], serotonin release from lysed platelets of the embolus[203], loss of surfactant[204] and abnormal breathing pattern (splinting) due to pleuritic pain[73]. Finally, opening of a patent foramen ovale (a blood-flow pathway between right and left atriums, normally naturally closed after birth) leading to an intracardial right–left shunting has been described in up to 35% of patients with acute PE[205].

Diagnosis, screening and prevention

Diagnosis of acute PE

Signs and symptoms. The symptoms of acute PE include chest pain, shortness of breath, palpitations, syncope (fainting) and haemoptysis (coughing up blood) as well as DVT symptoms such as leg swelling, pain and redness. Clinical signs comprise tachycardia, tachypnoea, elevated jugular pressure and in the most severe cases signs of shock with cyanosis and hypotension. PE shares symptoms and signs with other conditions, including acute coronary syndrome, dissection of the thoracic aorta, pneumothorax and pneumonia. Many patients in the emergency room exhibit one of these symptoms and are subsequently investigated for PE, with a low proportion of confirmed cases. In recent studies, <20% (in some studies only 5%) of patients investigated for a suspected PE actually have the disease[95].

The clinical signs and symptoms of PE lack diagnostic accuracy, being neither sensitive enough nor specific enough to diagnose or exclude the condition in most cases[96]. The use of a combination of risk factors, signs and symptoms could be more predictive. For example, the Pulmonary Embolism Rule-out Criteria (PERC) rule, consists of eight criteria (age ≥50 years, heart rate ≥100 bpm, oxygen saturation <95%, previous VTE, recent surgery or trauma, haemoptysis, oestrogen use and unilateral leg swelling[97]). Two recent prospective studies showed that it is possible to exclude PE on clinical grounds alone in patients with a low gestalt clinical

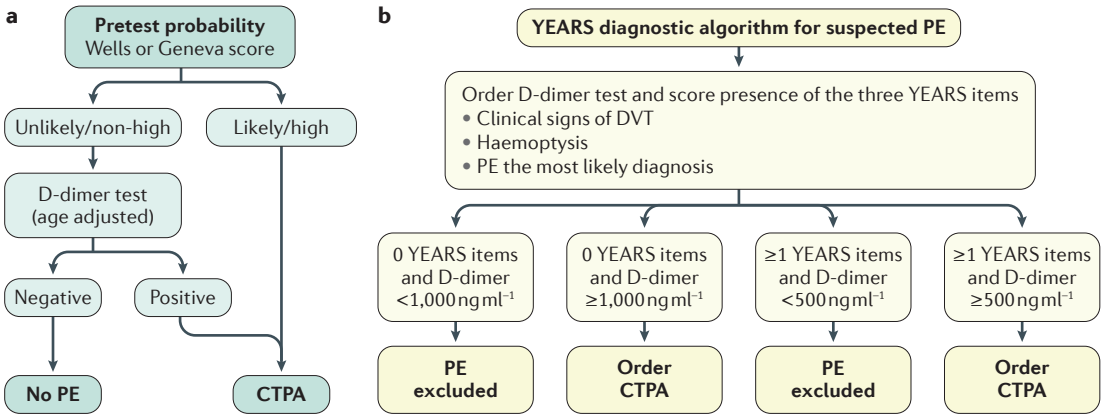

Figure 3 | **Validated diagnostic algorithms for suspected acute PE. a** | Conventional algorithm. After applying the Wells criteria or revised Geneva score, patients are allocated to either 'unlikely/non-high' probability or 'likely/high' probability categories. In the case of unlikely/non-high probability, a normal D-dimer test safely rules out pulmonary embolism (PE), whereas radiological imaging is required in all other patients. **b** | YEARS algorithm. D-Dimer tests are performed in all patients, and three clinical criteria are scored. PE is safely excluded in patients with none of the criteria and a D-dimer level <1,000 ng ml^{-1} and in patients with one or more of the criteria and a D-dimer level <500 ng ml^{-1}, whereas radiological imaging is required in all other patients. Compared with the conventional algorithm, the YEARS algorithm spares the need for CT pulmonary angiography (CTPA) in an additional 14% of patients with suspected PE. DVT, deep-vein thrombosis. Data from REFS[6,105].

probability (thus, on the basis of the estimation of the physician) and none of the PERC criteria[98,99], although it remains to be determined how PERC should be used together with other decision rules[100]. All other patients with clinically suspected PE should undergo objective testing with biomarkers of acute thrombosis (for example, D-dimer) and/or diagnostic imaging. Current diagnostic algorithms are based on the sequential use of pretest probability assessment, D-dimer testing and chest imaging when necessary[10] (FIG. 3).

Pretest probability assessment. Pretest probability assessment is the first step in the evaluation of patients with suspected PE. Best practice is to use a validated clinical decision rule, which combines the most discriminant and independent predictors of PE, and provides a standardized and reproducible estimate of the pretest probability of disease. The most widely validated clinical decision rules (the Wells criteria and the revised Geneva score) are summarized in BOX 3 (REFS[66,101–103]). Pretest probability assessment is mainly used to select patients for non-invasive testing with a D-dimer test. Patients who have low or intermediate scores are referred for the D-dimer test, whereas patients who score highly could be sent directly for chest imaging[10].

D-dimer test. D-Dimers are fibrin degradation products that are generated by the fibrinolytic process. The D-dimer test is highly sensitive for the presence of an acute thrombosis, and a negative D-dimer test (D-dimer serum level <500 µg l^{-1} for most commercial assays) enables the exclusion of PE in patients with a non-high pretest probability of disease (FIG. 3). However, the D-dimer test lacks specificity and has a high rate of false-positive results. D-dimers are increased in many other conditions, such as infection, inflammation, cancer, pregnancy or ageing. An age-adjusted cut-off addresses the latter: among patients >50 years of age, it is possible to exclude PE in those with a D-dimer level that falls below their age multiplied by 10 (for example, <730 µg l^{-1} for a 73-year-old patient)[104]. Newer promising approaches tailor D-dimer cut-off values according to the pretest probability (YEARS algorithm[105] (FIG. 3) and the PEGED study[106]).

Imaging. Patients with a positive D-dimer test and patients with a high pretest probability should undergo chest imaging with CTPA[10] (FIG. 4). CTPA enables the detection of clots in the pulmonary arteries and can be used to diagnose acute PE. CTPA became the most commonly used chest imaging test mainly for convenience: CT machines are widely available; CT-based diagnostic algorithms are simpler than ventilation–perfusion (V/Q) scan-based algorithms; and CTPA can be used to diagnose other conditions, including pneumonia, rib fracture or pneumothorax. However, the use of CTPA may be associated with overdiagnosis of PE. V/Q-based algorithms have similar diagnostic accuracy but are more complex to follow, mainly owing to the higher proportion of indeterminate, non-normal or non-high probability scans, thereby requiring the combined use of bilateral leg ultrasonography. Single-photon emission CT (SPECT) V/Q scans could address this limitation, but they lack clinical validation[107,108]. Importantly, whereas the diagnosis of PE is based on identifying clots in the pulmonary arteries, RV functionality is the main determinant of the short-term prognosis of PE patients. Compression ultrasonography (CUS) of leg veins enables diagnosis in individuals with suspected PE when a proximal DVT is found. However, CUS has a low yield (that is, is not often positive in this setting) and low cost effectiveness; therefore, its use is limited to patients in whom physicians want to avoid the use of chest imaging (for example, those with renal failure or pregnancy) or to patients with indeterminate chest imaging test results.

Diagnosis of RV failure in acute PE. All patients with CTPA-confirmed acute PE should be assessed for RV failure. Heart rate and blood pressure are the most clinically relevant parameters to assess RV function in acute PE because both parameters reflect forward failure (insufficient cardiac output) and sympathetic nervous system overdrive. The amount of RV dilatation and leftward movement of the septum observed using radiographic imaging are strong indicators of RV myocardial stretch. RV function can be assessed by the volumetric assessment of the right and left ventricles either by CT angiography or transthoracic echocardiography (TTE). Observation of any global right ventricle wall movement during systole and diastole using TTE, together with an underfilling pattern of the left ventricle, helps to support the diagnosis of severe RV dysfunction in patients with haemodynamic instability. In addition, the measurement of tricuspid annular plane systolic excursion (TAPSE) helps to quantify RV systolic function.

Box 3 | **Clinical decision rules for diagnosis of acute PE**

Wells criteria[101]

- Presence of active malignancy: +1
- Haemoptysis: +1
- History of previous DVT or PE: +1.5
- Heart rate >100 bpm: +1.5
- Surgery or bed rest ≥3 days in 1 month: +1.5
- Clinical signs and symptoms of DVT: +3
- No presence of an alternative diagnosis as likely as or more likely than PE: +3

Pretest probability	Points	Prevalence of PE (%; 95% CI)
Low	<2	5.7 (3.7–8.2)
Intermediate	2–6	23.2 (18.3–28.4)
High	>6	49.3 (42.6–56.0)
Unlikely	≤4	8.4 (6.4–10.6)
Likely	>4	34.4 (29.4–39.7)

Revised Geneva score[102]

- Age >65 years: +1
- Presence of active malignancy: +2
- Haemoptysis: +2
- History of previous DVT or PE: +3
- Surgery or lower limb fracture within previous month: +2
- Unilateral oedema and pain at palpation: +4
- Spontaneously reported calf pain: +3
- Heart rate between 75 and 94 bpm: +3
- Heart rate ≥95 bpm: +5

Pretest probability	Points	Prevalence of PE (%; 95% CI)
Low	0–3	9.0 (7.6–10.6)
Intermediate	4–10	26.2 (24.4–28.0)
High	≥11	75.7 (69.0–81.8)

Simplified versions of these two clinical decision rules exist in which all items are scored 1 point regardless of their weight in the original clinical decision rules. Simplified versions may be used without altering the predictive accuracy. DVT, deep-vein thrombosis; PE, pulmonary embolism.

In haemodynamically stable patients, the value of TTE is less clear. A 2018 analysis of the use of TTE to evaluate patients with haemodynamically stable acute PE showed that practice varied widely among hospitals in the United States[109]. In addition, hospitals with a high use of TTE had a similar PE mortality and higher costs than hospitals that did not use TTE — a finding that supports the current PE guidelines, which do not recommend routine use of TTE to risk-stratify patients with haemodynamically stable PE. Finally, an increase in serum biomarkers of myocardial stretch (such as NT-proBNP) or myocardial damage (such as troponin T) indicates that normal adaptation mechanisms of the right ventricle are failing and places the patients at an increased risk of haemodynamic decompensation[71,75,76,110].

Diagnosis of CTEPH

All patients who have survived acute PE that have symptoms of functional impairment should be assessed for CTEPH. Diagnosis of CTEPH starts with echocardiography (to assess the peak velocity of tricuspid valve regurgitation) and the detection of indirect signs of pulmonary hypertension[111]. The next step is a V/Q scan, of which a normal result excludes CTEPH[112]. In cases of echocardiographic findings and abnormal V/Q results consistent with a CTEPH diagnosis, an assessment of pulmonary haemodynamics by right heart catheterization is mandatory to confirm the diagnosis[111]. Pulmonary angiography is also required to confirm the diagnosis of CTEPH (FIG. 5).

Within Western Europe, a diagnostic delay for CTEPH of >1 year exists[7]; therefore, the ability to predict CTEPH, as well as improved early recognition of CTEPH, will likely improve CTEPH prognosis[13]. Therefore, physicians should have a low threshold for testing for CTEPH in patients with post-PE syndrome who report persistent dyspnoea. Of note, evidence for strategies of CTEPH risk prediction are scarce. In 2016, a CTEPH prediction score was developed to overcome this issue but has not yet been externally validated, although trials are under way[113]. An alternative strategy would be studying the added value of reassessing the baseline CTPA scans used for the diagnosis of acute PE to detect signs of chronic PE or pulmonary hypertension, such as RV hypertrophy, webs and bands, convoluted bronchial arteries or mosaic perfusion[114] (FIGS 4,5). However, it remains unclear which radiological sign is most sensitive or specific for a future CTEPH diagnosis.

Screening

In general, there is no indication to screen for PE, even in asymptomatic high-risk individuals. An acute thrombus usually develops over a few hours or days. Most thrombi originate from the calf veins and can be detected by ultrasonography. However, a single screening test is unlikely to detect a thrombus early enough before it becomes symptomatic. Studies of high-risk patients showed that most cases of VTE occur before the screening test is performed or during follow-up after a negative screening result[115].

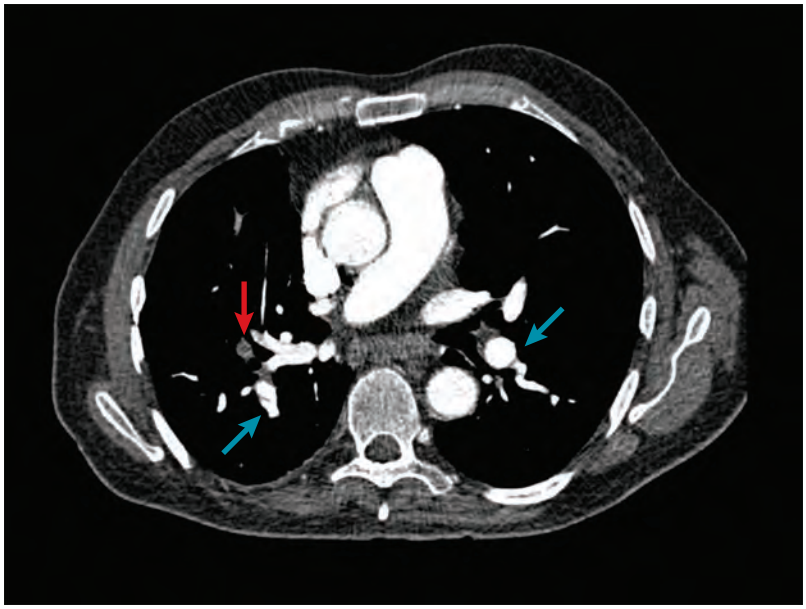

Figure 4 | **CTPA of a patient with acute and chronic signs of PE.** Red arrow denotes acute pulmonary embolism (PE). The blue arrows point at webs in the pulmonary artery tree suggestive of chronic thrombus remains. CTPA, CT pulmonary angiography.

Many efforts have been made to identify individuals at high risk of VTE in the general population, mainly through screening for the genetic predisposition to thrombosis. However, the impact for primary prevention remains limited in clinical practice[116]. The incidence rate of VTE is low even in the presence of predisposing risk factors (for example, <2% per year with the most high-risk genetic thrombophilias), the risk–benefit ratio of lifelong primary thromboprophylaxis is not favourable and it is unclear whether heightened awareness of the symptoms of PE can lead to more benefit from earlier diagnoses than harm (for example, medical costs and patient anxiety). Moreover, many patients with PE, including patients from families containing several members with PE, do not have any of the known genetic predispositions, suggesting that there are unknown risk factors.

Prevention

Sudden death may be the first symptom of PE, and non-fatal PE can have considerable impact on short-term and long-term quality of life. Thus, primary prevention is and must be a key component of strategies aimed at reducing the global burden of VTE. PE prevention measures are the same as those recommended for VTE prevention. Pharmacological thromboprophylaxis with anticoagulants is the main therapy for PE prevention. Other strategies include reducing immobilization, tailoring oral contraceptives or hormonal replacement therapy use on the basis of PE risk and increasing awareness of PE symptoms so that PE is diagnosed and treated promptly.

The main disadvantage of pharmacological thromboprophylaxis is that its use is associated with an increased risk of bleeding. The risk–benefit ratio of antithrombotic therapy for PE primary prevention needs to be considered for each at-risk patient[117]. Risk factors contribute to the risk of PE to varying degrees. Some result in high absolute PE risk, in which thromboprophylaxis is clearly warranted (for example, hip fracture surgery), whereas others do not (for example, airline travel). The ideal targets for primary prevention are individuals who are transiently exposed to a major risk factor, such as surgery, trauma with fracture and/or immobilization or admission to hospital for an acute medical condition[118,119]. In patients with permanent or extended exposures to risk factors, the benefits of thromboprophylaxis usually do not outweigh the risks (for example, in patients with genetic thrombophilia, pregnant women or patients with inflammatory bowel disease). Ongoing studies aim to assess whether certain patients with cancer who have high risk of PE might benefit from primary prevention[120,121].

Low-molecular-weight heparins, administered subcutaneously, have been the cornerstone of PE prevention for the past few decades. Subcutaneous unfractionated heparin is used in some settings, mainly in patients with severe renal failure because low-molecular-weight heparins are contraindicated in these patients. Oral vitamin K antagonists (VKAs; for example, warfarin) may be used in patients requiring extended thromboprophylaxis because long-term injections with low-molecular-weight heparins may lead to lower patient compliance. More recently, direct oral anticoagulants (DOACs) have been approved by health authorities, including the US FDA and the European Medicines Agency (EMA), for PE prevention in a few indications, including patients undergoing hip or knee replacement surgery. Whenever antithrombotic therapy is contraindicated (for example, in patients with active or high risk of bleeding, such as those with thrombocytopenia), mechanical methods, such as elastic stockings or intermittent compression devices, may be used, although their efficacy and cost effectiveness remain less well established than pharmacological prophylaxis[118,122].

Many challenges remain for PE prevention. Complications of hospital admissions still account for up to 20% of all VTE events[15], and the number of hospital-acquired VTEs is not decreasing despite increased awareness and implementation of thromboprophylaxis strategies[123]. Prevention efforts should focus on improving the identification of high-risk patients and strict adherence to thromboprophylaxis guidelines in these patients. A better understanding of the pathophysiology and epidemiology of VTE might help in designing primary prevention strategies for the general population. Prevention is particularly challenging knowing that currently, no major risk factor is identified for the majority of patients with VTE.

Management

Risk stratification

An adequate risk stratification of patients with confirmed acute PE is important for tailoring their initial management. The characteristics of clinical presentation, including patient history and concomitant diseases, and the presence and severity of RV dysfunction

represent the key prognostic determinants. According to current European Society of Cardiology (ESC) guidelines[6], patients with RV dysfunction resulting in reduced cardiac output, persistent arterial hypotension and signs of end-organ hypoperfusion (thus, haemodynamic instability) are categorized into the high risk of mortality category (<5% of all patients with PE). These are the patients expected to benefit most from immediate reperfusion treatment (see below).

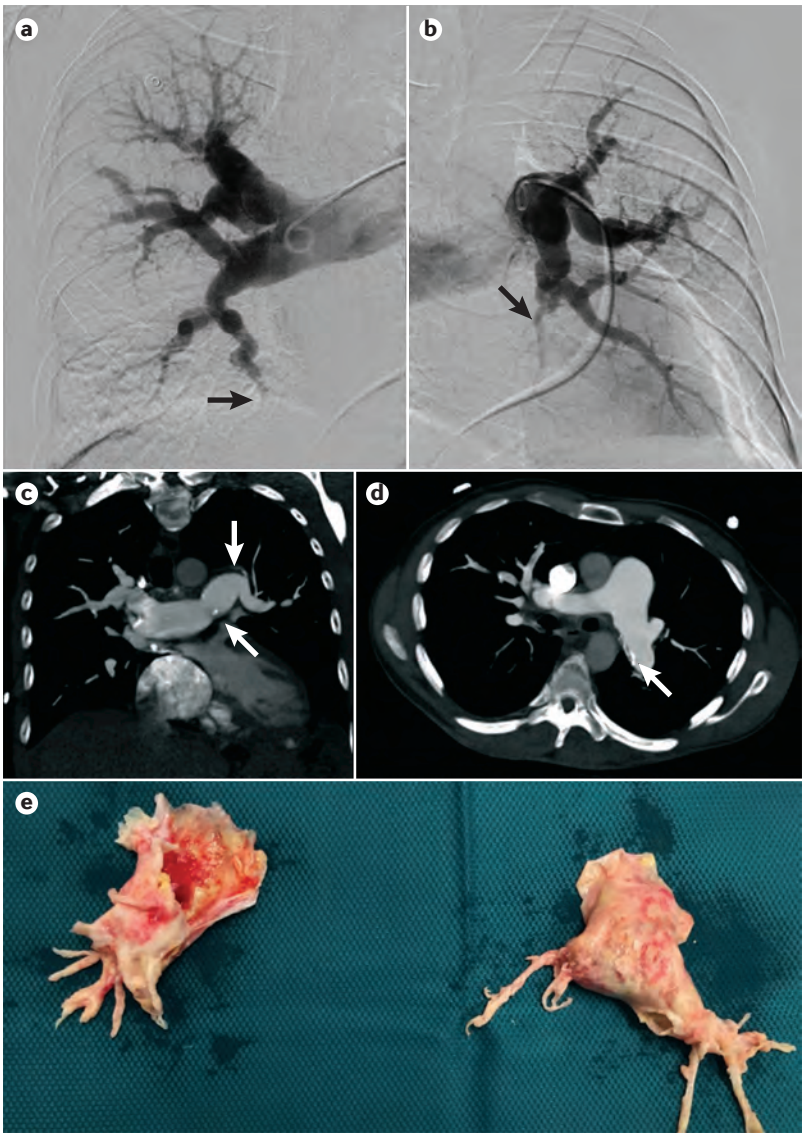

Figure 5 | **Radiological findings in a patient with CTEPH. a** | An A–P (anterior–posterior) angiogram of the right pulmonary artery with a complete perfusion defect of the right lower lobe (black arrow). **b** | An A–P pulmonary angiogram with a complete perfusion defect in the apical segment of the left upper lobe and a large web in the lower lobe artery (black arrow). **c** | A coronal image of a contrast-enhanced CT showing a partially calcified thrombus in the left pulmonary artery with total occlusion of the apical branch of the left upper lobe (white arrows). **d** | An axial image of a contrast-enhanced CT with a partially calcified thrombus in the left pulmonary artery (white arrow) with a dilated truncus pulmonalis. **e** | A pulmonary endarterectomy surgical specimen removed from a patient with CTEPH showing the fibrotic vascular occlusion with fresh thrombus characteristic of CTEPH. CTEPH, chronic thromboembolic pulmonary hypertension.

Most patients present without haemodynamic instability and should be further stratified using two categories of tools: clinical criteria (for example, the (simplified) Pulmonary Embolism Severity Index (sPESI) or the HESTIA decision rule) and the detection of RV dysfunction by imaging and/or laboratory tests. The sPESI primarily serves to identify patients who are at low risk of 30-day mortality. Only the HESTIA decision rule, which consists of a set of 11 criteria from which a physician can decide to send a patient home and treat out of the hospital or not, has been validated as a triage instrument for home treatment of PE. If no HESTIA criterion is present, a patient can be safely treated out of hospital[124,125]. For the remaining patients at intermediate risk, in-hospital management is recommended. Moreover, patients with RV dysfunction and elevated biomarkers of myocardial injury can by classified as intermediate high risk and might need early haemodynamic monitoring and possibly rescue reperfusion treatment in the case of haemodynamic collapse[6].

Anticoagulant therapy

Anticoagulant therapy is essential for preventing acute and chronic complications following an acute PE, including recurrent PE (with resultant haemodynamic failure), recurrent DVT of the legs (often the origin of PE) and post-PE syndrome. Treatment consists of three phases: an acute phase comprising the first 5–10 days after presentation of PE, an intermediate phase between 10 days and 3 months after presentation and an extended long-term phase beyond this period[6].

Conventional therapy. Before introduction of the DOACs, acute therapy for PE is initiated with a parenteral anticoagulant, usually low-molecular-weight heparin, as a bridging treatment together with a VKA (VKAs only reach full activity after 5–7 days). This bridging treatment modality is very effective and safe in patients with PE and DVT; the 3-month recurrent VTE rate during VKA treatment is 3.4% (up to 20% in untreated people) (95% CI 2.9–4.0) and the 3-month major bleeding rate is 1.6% (95% CI 1.3–2.0)[126]. However, practical management of VKA therapy is problematic as frequent international normalized ratio testing and multiple dose adjustments are required to ensure that the drug stays within the safe therapeutic range. In addition, there are many interactions between VKAs and other drugs, including antibiotics and anti-epileptic agents, as well as with certain foods, including vegetables rich in vitamin K (for example, broccoli and cauliflower).

DOACs. The introduction from 2012 onwards of DOACs has simplified the anticoagulant treatment of VTE. DOACs can be given in fixed doses without the requirement for routine monitoring and have fewer interactions with other medications[127]. Four DOACs are available for treatment of PE: dabigatran, a specific thrombin inhibitor, and three factor Xa blockers, apixaban, rivaroxaban and edoxaban[6]. In addition, betrixaban is another factor Xa inhibitor with very low dependence on renal clearance (7–14%), but it has not been tested for PE treatment[128].

Table 1 | **Overview of phase III trials using DOACs for the treatment of acute VTE**

Trial	Intervention	Study duration; number of patients	Study design	Efficacy outcome	Safety outcome
Dabigatran					
RE-COVER[206]	Dabigatran[a] versus warfarin[a]	6 months; 2,539 patients with acute VTE	Double blind	Recurrent VTE or fatal PE: 2.4% for dabigatran versus 2.1% for warfarin	Major bleeding: 1.6% for dabigatran versus 1.9% for warfarin
RE-COVER II (REF.[207])	Dabigatran[a] versus warfarin[a]	6 months; 2,589 patients with acute VTE	Double blind	Recurrent VTE or fatal PE: 2.3% for dabigatran versus 2.2% for warfarin	Major bleeding: 15 patients for dabigatran versus 22 patients for warfarin
Rivaroxaban					
EINSTEIN-DVT[147]	Rivaroxaban versus warfarin[a]	3–12 months; 3,449 patients with acute DVT	Open label	Recurrent VTE or fatal PE: 2.1% for rivaroxaban versus 3.0% for warfarin	Major bleeding or CRNM bleeding: 8.1% for rivaroxaban versus 8.1% for warfarin
EINSTEIN-PE[208]	Rivaroxaban versus warfarin[a]	3–12 months; 4,832 patients with acute PE, with or without DVT	Open label	Recurrent VTE or fatal PE: 2.1% for rivaroxaban versus 1.8% for warfarin	Major bleeding or CRNM bleeding: 10.3% for rivaroxaban versus 11.4% for warfarin
Apixaban					
AMPLIFY[209]	Apixaban versus warfarin[a]	6 months; 5,395 patients with acute DVT and/or PE	Double blind	Recurrent VTE or fatal PE: 2.3% for apixaban versus 2.7% for warfarin	Major bleeding: 0.6% for apixaban versus 1.8% for warfarin
Edoxaban					
Hokusai-VTE[210]	Edoxaban combined with LMWH versus UFH or LMWH with warfarin	3–12 months; 8,240 patients with acute DVT and/or PE	Double blind	Recurrent VTE or fatal PE: 3.2% for edoxaban versus 3.5% for warfarin	Major bleeding or CRNM bleeding: 8.5% for edoxaban versus 10.3% for warfarin

In the trials on acute treatment, dabigatran (twice daily) and edoxaban (once daily) were started after a minimum 5-day period of therapeutic dose of LMWH, which was followed by a continuous direct oral anticoagulant (DOAC) dose for both drugs, whereas apixaban (twice daily) and rivaroxaban (once daily) were given in a higher loading dose (for 7 days for apixaban and for 21 days for rivaroxaban) followed by a lower continued dose. CRNM, clinical-relevant non-major; DVT, deep-vein thrombosis; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; UFH, unfractionated heparin; VTE, venous thromboembolism. [a]Combined with enoxaparin. Table adapted from REF.[6].

The approval of DOACs for the treatment of PE was based on phase III trials in acute treatment as well as extended treatment, which demonstrated that DOACs are as effective as conventional therapy but are associated with less major bleeding[129,130] (TABLE 1). In the first meta-analysis, the incidences for recurrent VTE and VTE-related death over 6 months were 2.0% in patients treated with DOACs and 2.2% in patients treated with VKAs (relative risk of DOACs 0.88; 95% CI 0.74–1.05)[129]. Major bleeding occurred in 1.1% of patients treated with DOACs and in 1.7% of patients treated with VKAs (relative risk 0.60; 95% CI 0.41–0.88). Compared with patients treated with VKAs, patients treated with DOACs had a significant 62% reduction in major bleeding occurring in a critical site (for example, brain or pericardium), a significant 61% reduction in intracranial bleeding (relative risk 0.37; 95% CI 0.21–0.68) and a significant 64% reduction in fatal bleeding. On the basis of these results and the practicalities of DOACs (fixed dosage, oral administration and no monitoring required), the most recent American College of Chest Physicians (ACCP) guidelines suggest the use of DOACs over VKA in patients with PE but without active cancer[131].

The choice of whether or not to start a DOAC in a patient with PE in the acute phase of treatment is influenced by the clinical situation and comorbidity. A high-risk patient with haemodynamic instability, in whom thrombolytic therapy is considered, is usually given low-molecular-weight heparin or unfractionated heparin, and DOACs can be started upon haemodynamic stabilization[6]. Only patients with severe renal impairment, defined as creatinine clearance of <15 ml min^{-1} for apixaban, rivaroxaban and edoxaban and <30 ml min^{-1} for dabigatran, or severe hepatic impairment should be excluded from DOAC treatment. Moreover, DOACs are contraindicated in pregnant or breastfeeding women as all DOACs can pass through the placenta and into the mother's milk and no safety data during pregnancy or lactation are available. In patients with cancer, DOAC treatment of PE in phase III trials is favourable, but few patients were included; consequently, guidelines still advocate low-molecular-weight heparin as the first-line treatment[131,132]. A very recent trial showed non-inferiority of edoxaban versus dalteparin for the combined end point of major bleeding and recurrent VTE in patients with PE and/or DVT and active cancer, suggesting that DOACs can be used in that patient category as well[133]. Patients with known antiphospholipid syndrome and arterial thrombosis should be excluded from DOAC treatment as sufficient clinical outcome data are unavailable for DOAC use in these patient groups. Finally, patients with a weight of >120 kg should be excluded from DOAC treatment as there are insufficient data for efficacy[134].

Duration of anticoagulant treatment

Beyond the initial 3-month treatment period with anticoagulant drugs, the risk of recurrent VTE when therapy is stopped versus the risk of major bleeding associated with anticoagulation treatment should be assessed.

Bleeding risk. As a rule, patients deemed at high risk of anticoagulation-associated major bleeding, such as elderly patients or patients with a history of major bleeding, should discontinue anticoagulant therapy after the first 3 months[6]. However, it remains unclear how bleeding risk assessment should be performed in the individual patient considering the lack of sufficiently validated risk assessment scores or models, as well as outcome trials successfully applying risk assessment models. However, current studies aim to solve this issue[135–138]. Patients with unprovoked VTE (that is, VTE in the absence of any known risk factors) who do not have a high bleeding risk should continue anticoagulant treatment as these patients have a high risk of recurrent VTE (see below).

Risk of recurrent VTE. It has been repeatedly demonstrated that patients with unprovoked VTE have a considerable risk of developing recurrent VTE after stopping anticoagulant treatment. In a landmark cohort follow-up study in 1,625 patients with unprovoked PE, the risk of recurrent VTE after 3 months of anticoagulant treatment was 11% (95% CI 9.5–12.5) after 1 year and 40% (95% CI 35–44) after 10 years[139]. The adjusted hazard ratio for recurrent VTE was 2.30 (95% CI 1.8–2.9) in patients whose first VTE was unprovoked[139]. In a meta-analysis involving 2,925 patients with various types of VTE from randomized studies, recurrent VTE incidence was lower after isolated distal DVT (DVT below the level of the knee) than after proximal DVT (DVT at the level of the knee or more proximal) (HR 0.49; 95% CI 0.34–0.71)[140]. Similarly, recurrent VTE incidence was higher after PE and proximal DVT (HR 1.19; 95% CI 0.87–1.63) and lower after thrombosis provoked by a temporary risk factor (such as hospitalization or surgery) than after unprovoked thrombosis (HR 0.55; 95% CI 0.41–0.74)[140]. The risk of recurrent VTE in patients with a temporary risk factor was higher if anticoagulation was stopped at 1 or 1.5 months compared with at 3 months or later (HR 1.52; 95% CI 1.14–2.02) and similar if treatment was stopped at 3 months compared with at 6 months or later (HR 1.19; 95% CI 0.86–1.65)[140]. From these data, and in line with international guidelines, patients who present with a first episode of unprovoked PE are recommended to continue anticoagulant therapy beyond 3 months; if PE was provoked by a major risk factor, then anticoagulant therapy should be stopped after 3 months[6,131].

Several risk scores have been developed to predict the risk of recurrent VTE after stopping anticoagulant treatment, including the D-dimer, Age, Sex, Hormones (DASH) score, the Vienna prediction rule, and the Hyperpigmentation, Edema or Redness in either leg; D-dimer level ≥250 μg/L; Obesity with body mass index ≥30; or older age, ≥65 years (HERDOO2) rule[141–143]. Of these, only the HERDOO2 rule has been validated prospectively[144]. In low-risk women who had stopped anticoagulant treatment, recurrent VTE was 3.0% per patient year (95% CI 1.8%–4.8%)[144]. In high-risk women and in men who stopped anticoagulants, the recurrence rate was 8.1% per patient year (95% CI 5.2%–11.9%), whereas the rate was 1.6% per patient year (95% CI 1.1%–2.3%) in men and women who continued anticoagulant therapy[144]. For women >50 years old who stopped anticoagulant therapy, the risk of recurrent VTE was higher than expected (~5.7%). Therefore, further validation of the HERDOO2 rule in postmenopausal women is required.

Evidence from clinical trials. Apixaban (in two doses), rivaroxaban and dabigatran have been compared with placebo for extended therapy beyond 6 months[145–147]. All three trials revealed a statistically significant reduction in the rate of recurrent VTE but an increased risk of combined major and clinically relevant non-major bleeding. Dabigatran is the only DOAC to have been compared with a VKA in the RE-MEDY trial[146]. Rivaroxaban has been tested in two different doses versus aspirin for extended treatment in VTE[148]; aspirin was inferior for preventing recurrent VTE, and major bleeding was not different between rivaroxaban-treated and aspirin-treated patients.

Reperfusion therapy

Reperfusion therapy for acute PE involves the induction of systemic thrombolysis by using intravenously administered thrombolytic agents such as tissue plasminogen activator to restore blood flow. Mechanical and pharmacomechanical modalities are an option for those with high-risk, haemodynamically unstable PE in whom bleeding risk is deemed too high for systemic full-dose fibrinolytic therapy.

Systemic thrombolysis. Contemporary guidelines recommend prompt reperfusion therapy in patients with high-risk PE, provided that no absolute contraindications, such as recent stroke, major bleeding or surgery, are present[6,131,149]. These recommendations are mostly based on small studies that demonstrated rapid improvement of surrogate haemodynamic parameters, such as right-to-left ventricle end-diastolic dimension ratio, after thrombolysis (reviewed in REF.[150]) and appear to be supported by epidemiological data[151]. Despite the lack of large-scale studies based on clinical outcomes, the indication for systemic thrombolysis in acute high-risk PE is universally accepted, as only a rapid reversal of an acute RV pressure overload can prevent early death in these patients. Interestingly, the use of systemic thrombolysis in patients with PE-related non-shockable sudden cardiac arrest admitted to hospital before the onset of cardiac arrest has also been associated with improved survival[152].

High-risk patients presenting with haemodynamic instability represent only a small minority of all PE patients. By contrast, haemodynamically stable patients with intermediate-risk PE constitute a larger group[153] in which systemic standard-dose thrombolysis is expected to exert beneficial haemodynamic and clinical effects[150,154]. However, an unfavourable risk–benefit ratio due to the risk of severe and potentially fatal haemorrhagic complications has precluded scientific societies from recommending the routine use of systemic thrombolysis in intermediate-risk and intermediate–high-risk patients[6,131,149]. In the intermediate–high-risk group,

the largest trial conducted thus far (the Pulmonary Embolism Thrombolysis (PEITHO) trial)[155] showed that intravenous thrombolysis with tenecteplase, a tissue plasminogen activator, resulted in lower rates of death or haemodynamic collapse (2.6% versus 5.6% in the group treated with anticoagulation alone) but was associated with significantly elevated rates of haemorrhagic stroke and major extracranial bleeding (TABLE 2). Notably, pooled safety data on other thrombolytic agents given at full dose (for example, the recombinant tissue plasminogen activator alteplase) are not available. However, the results of a trial enrolling 256 patients with intermediate-risk PE did not suggest an increased risk of intracranial or fatal bleeding after alteplase administration[156].

The possible effects of systemic thrombolysis on the long-term clinical outcome of patients after acute PE are unclear. It has been postulated that systemic thrombolytic treatment in the acute phase of PE may minimize residual or progressive thromboembolic pulmonary obstruction, thus protecting the patients from post-PE syndrome[113,157,158]. A prospective cohort study, which allocated 121 patients with extensive PE (defined as a large thrombus burden) to receive either reduced-dose systemic thrombolysis or anticoagulation alone, reported that thrombolysis was associated with reduced rates of pulmonary hypertension at 28 months[159]. However, follow-up of the patients with intermediate-risk PE included in the PEITHO trial for a median period of 38 months showed no differences in long-term survival

Table 2 | **Prospective trials and cohort studies investigating thrombolytic agents and regimens in patients with acute PE**

Reference and/or trial	Population	Groups	Outcome	Time of outcome assessment	Thrombolysis arm	Control arm	*P* value
PEITHO[149,153]	Intermediate-risk PE (*n* = 1,005)	Tenecteplase plus anticoagulation versus anticoagulation alone	Death or haemodynamic collapse	7 days	2.6%	5.6%	0.02
			CTEPH	38 months	2.1%	3.2%	NS
			NYHA III–IV	38 months	12%	10.9%	NS
			Echo parameters of RV dysfunction	38 months	–	–	NS
			Death	38 months	20.3%	18.0%	NS
TOPCOAT[188]	Intermediate-risk PE (*n* = 83)	Tenecteplase plus anticoagulation versus anticoagulation alone	NYHA III–IV	90 days	5.4%	20.5%	NS
			RV dilatation or hypokinesis	90 days	33.3%	37.8%	NS
			6-Minute walking distance <330 m	90 days	16%	28%	NS
TIPES[189]	Intermediate-risk PE (*n* = 58)	Tenecteplase plus anticoagulation versus anticoagulation alone	Reduction of RV/LV ratio, mean (s.e.)	24 hours	0.31 (0.08)	0.10 (0.07)	NS
			Hypokinesia of the RV free wall (s.e.)	7 days	0.47 (0.07)	0.34 (0.05)	NS
MAPPET-3 (REF.[190])	Intermediate-risk PE (*n* = 256)	Alteplase plus anticoagulation versus anticoagulation alone	Death or haemodynamic collapse	30 days	11%	24.6%	0.006
			Death	30 days	3.4%	2.2%	NS
MOPETT[152]	'Moderate PE' (*n* = 121)	Half-dose tPA plus anticoagulation versus anticoagulation alone	sPAP (mmHg), mean (s.d.)	6 months	31 (6)	49 (8)	<0.001
			sPAP (mmHg), mean (s.d.)	28 months	28 (7)	43 (6)	<0.001
			Death	28 months	1.6%	5.0%	NS
Wang et al.[191]	Intermediate-risk and high-risk PE (*n* = 118)	Half-dose tPA (50 mg) plus anticoagulation versus tPA (100 mg) plus anticoagulation	Echo parameters of RV dysfunction and pulmonary artery obstruction scores	24 hours and 14 days	–	–	NS
ULTIMA[157]	Intermediate-risk PE (*n* = 59)	CDT plus anticoagulation versus anticoagulation alone	RV/ LV ratio, mean difference (s.d.)	24 hours	0.30 (0.20)	0.03 (0.16)	<0.001
				90 days	0.35 (0.22)	0.24 (0.19)	NS
			Right ventricle–right atrium pressure gradient (mmHg), mean difference (s.d.)	24 hours	9.8 (9.9)	0.3 (10.9)	0.03
				90 days	12.3 (12.8)	11.6 (15.1)	NS
			TAPSE (mm), mean difference (s.d.)	24 hours	–3.1 (4.4)	0.9 (4.9)	0.02
				90 days	–6.1 (4.6)	–3.4 (5.4)	NS
SEATTLE II (REF.[156])	Intermediate-risk or high-risk PE (*n* = 150)	Low-dose CDT plus anticoagulation	RV/ LV ratio, mean (s.d.)	48 hours after CDT treatment	1.55 (0.39)	1.13 (0.2)	<0.0001
			sPAP (mmHg), mean (s.d.)	48 hours after CDT treatment	51.1 (16)	36.9 (14.9)	<0.0001

CDT, catheter-directed, ultrasonography-assisted thrombolysis; CTEPH, chronic thromboembolic pulmonary hypertension; MAPPETT-3, Management Strategies and Prognosis of Pulmonary Embolism-3 Trial; MOPETT, Moderate Pulmonary Embolism Treated with Thrombolysis; NS, not significant; NYHA, New York Heart Association; PE, pulmonary embolism; PEITHO, Pulmonary Embolism Thrombolysis; RV, right ventricular; RV/LV ratio, right-to-left ventricular diameter ratio; SEATTLE II, Submassive and Massive Pulmonary Embolism Treatment with Ultrasound Accelerated Thrombolysis Therapy; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TIPES, Tenecteplase Italian Pulmonary Embolism Study; TOPCOAT, Tenecteplase or Placebo: Cardiopulmonary Outcomes at Three Months; tPA, tissue-type plasminogen activator; ULTIMA, Ultrasound Accelerated Thrombolysis of Pulmonary Embolism.

between the thrombolysis treatment group and the heparin-only treatment group[68]. In addition, there appeared to be no effect of thrombolysis treatment on the long-term risk of persistent functional limitation, abnormal echocardiographic findings or diagnosis of CTEPH, although these latter findings should be interpreted with caution in view of missing data in some patients (TABLE 2). Future reperfusion trials for acute PE should aim to prospectively include a systematic, adequately long period of follow-up in addition to data on early efficacy and safety outcomes. This long follow-up will enable the assessment of the patients' clinical and haemodynamic course as well as their functional status and quality of life.

Mechanical and pharmacomechanical reperfusion modalities. According to 2014 ESC and 2016 ACCP guidelines, surgical embolectomy or catheter-directed interventions aiming at thrombus extraction or dissolution should be considered as alternative options to systemic thrombolysis in high-risk patients who require reperfusion treatment but have a high risk of bleeding complications[6,131]. Acute mechanical circulatory support of the right ventricle may be required in selected patients with high-risk PE. Extracorporeal membrane oxygenation, which can temporarily take over heart and lung function, can be considered for obtaining initial haemodynamic stabilization, as a bridge to stabilize a patient before catheter-based or operative mechanical interventions or postoperatively. Surgical pulmonary operative embolectomy and right heart exploration allow for a complete removal of an embolus in patients for whom systemic thrombolysis is contraindicated because of too high a bleeding risk.

Increasing attention has been focused on percutaneous catheter-directed treatment, either in the form of mechanical thrombus aspiration or as local pharmacomechanical (ultrasonography-assisted) low-dose thrombolysis[160]. In some centres, catheter-directed techniques are being used to treat haemodynamically unstable patients with high-risk PE, although it is not yet clear whether the slow infusion rate and low dose of thrombolytic agent associated with catheter-directed treatment possess sufficient efficacy to improve patient survival[161]. However, catheter-directed treatment has already been investigated in two interventional studies of patients with mainly[162] or exclusively[163] intermediate-risk PE, showing substantial improvement of surrogate outcome parameters, such as the subannular right-to-left ventricular dimension ratio, the estimated pulmonary artery pressure and the anatomic thrombus burden at 24–48 hours (TABLE 2). Importantly, the rates of intracerebral or other life-threatening bleeding are low on the basis of the existing trial data[162,163]. Adequately powered randomized controlled clinical trials with clinical efficacy and safety outcomes are needed before broader use of catheter-directed treatment can be recommended in high-risk and intermediate-risk PE.

Interdisciplinary management. A timely diagnosis, accurate risk stratification and the appropriate use of reperfusion techniques can be decisive for the early outcome of patients with high-risk and intermediate–high-risk PE. Off-office hours and weekend admissions have been associated with worse prognosis owing to the lack of prompt management provided by experienced physicians[164,165]. A new paradigm of coordinated care, the PERT, is developing in the United States and more recently in Europe; PERT streamlines the process from the first clinical suspicion of acute PE to multidisciplinary consultation and risk-adjusted treatment[166]. Many academic and community hospitals are currently in the process of coordinating the specialists involved in an attempt to ensure consensus on the management of challenging PE cases and to optimize the utilization of resources[166–169].

Treatment of CTEPH

All patients with CTEPH should be treated with long-term anticoagulant therapy. In addition, the gold-standard treatment for CTEPH is pulmonary endarterectomy, which can reduce mortality and improve right circulation haemodynamics. During pulmonary endarterectomy, thromboembolic material is removed from the pulmonary artery tree after median sternotomy and during deep hypothermic circulatory arrest[170] (FIG. 5). In high-volume referral centres, the in-hospital mortality is lower than 5%. Pulmonary endarterectomy is not an established therapeutic option for CTED, although it is occasionally performed for this indication[171]. A considerable subset of patients with CTEPH is considered inoperable because of peripheral thrombi or severe comorbidity and must be considered for pharmacological therapy[111].

Balloon pulmonary angioplasty is being increasingly explored as an alternative therapy for inoperable patients. In this procedure, small angioplasty balloons are introduced into segmental pulmonary artery branches and used to dilate webs and strictures[172] (FIG. 6). This procedure was first performed for the treatment of CTEPH in a Dutch patient in 1988; the patient developed non-lethal pulmonary oedema after two procedures[173]. Since then, the technique of balloon pulmonary angioplasty has been refined. However, large randomized studies are needed to define the efficacy of balloon pulmonary angioplasty and its place in the treatment algorithm of CTEPH. As with pulmonary endarterectomy, balloon pulmonary angioplasty has never been systematically evaluated in patients with CTED. Finally, and in contrast to patients with myocardial infarction or other severe cardiopulmonary conditions, cardiopulmonary rehabilitation is not routinely offered to patients with PE. However, available data, although scarce, suggest that cardiopulmonary rehabilitation is an effective intervention in patients with PE and CTEPH diagnosis in terms of exercise tolerance and quality of life.

Quality of life

Patients who survive acute PE and develop post-PE syndrome are reported to have a lower quality of life than population controls or patients with PE who report a full physical recovery as assessed with generic or disease-specific questionnaires[4,25,28,64,65,174–181]. In particular, self-reported dyspnoea closely correlates with poor physical performance on the 6-minute walking test and

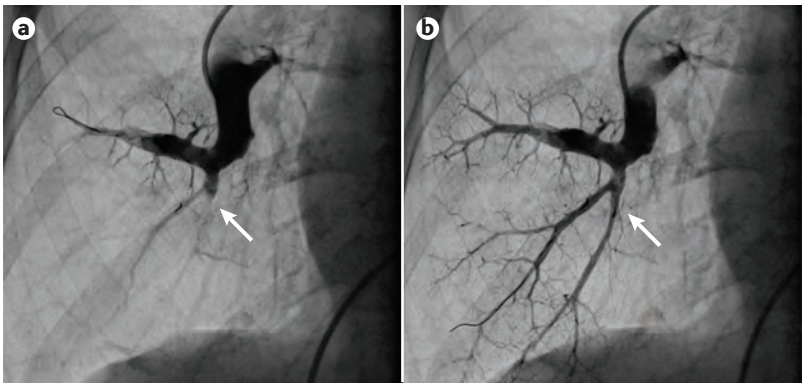

Figure 6 | **Pulmonary angiogram of a patient with inoperable CTEPH before and after BPA.** The figure clearly demonstrates a perfusion defect in the right lower lobe of the posterobasal, laterobasal and anterobasal branch (white arrow) (part **a**) and reperfusion after BPA (white arrow) (part **b**). BPA, balloon pulmonary angiography; CTEPH, chronic thromboembolic pulmonary hypertension.

low quality of life. In a 2017 prospective observational study of a Canadian cohort of 100 patients who had survived PE, 47% of the cohort had impaired exercise capacity and had worse generic and PE-specific quality of life[64,65]. A Norwegian study confirmed the association between persistent dyspnoea, exercise intolerance and decreased quality of life[177]. Moreover, an association was found between post-PE syndrome, lower quality of life and unemployment.

CTEPH is particularly associated with poor quality of life[63,179,180,182–184]. In patients with CTEPH, quality of life correlates with the degree of pulmonary functional capacity. In addition, when used as a proxy of severe CTEPH, poorer quality of life predicted a higher risk of mortality[182]. After successful treatment of CTEPH, quality of life improves, especially after pulmonary endarterectomy but also after treatment with vasoactive agents[183].

Outlook

Diagnosis

The diagnosis of PE during pregnancy presents particular difficulties to the clinician. The D-dimer test has not been evaluated to exclude PE, and clinical guidelines do not exist for the diagnosis of PE in pregnant women. Consequently, clinicians must use either CTPA or V/Q lung scanning, which is often inadequate for interpretation, to diagnose PE. Both imaging modalities are not ideal for use in pregnant women owing to exposure to radiation. Currently, two diagnostic studies during pregnancy are being performed. A Swiss study is evaluating the safety and efficacy of a diagnostic strategy of sequential clinical probability assessment, D-dimer measurement, lower limb CUS and multi-slice CT[185]. The Dutch–French–Irish ARTEMIS study will evaluate the safety and efficiency of the YEARS algorithm (FIG. 3b) in pregnant women. In this study, one exception to the normal YEARS algorithm is that patients presenting with symptomatic DVT will first undergo a CUS of the affected leg. When DVT is demonstrated, this means VTE is present and no CTPA is performed; subsequently, these women are treated with anticoagulants, as if they have PE[186].

Management

Direct comparative studies of DOACs for the treatment of VTE have not been performed. Currently, a US-based study (which is not yet recruiting patients), the North American Comparison of Oral Anticoagulants for Extended Venous Thromboembolism (COVET), will randomize patients to rivaroxaban, apixaban or warfarin for extended treatment of VTE[187]. In Europe, a non-inferiority study (the Reduced Dose Versus Full-Dose of Direct Oral Anticoagulant After Unprovoked Venous Thromboembolism (RENOVE) study) aims to evaluate the efficacy and safety of a reduced dose of apixaban versus full-dose apixaban in patients with unprovoked VTE after 6–24 months of anticoagulant treatment[188].

DOACs have been shown to reduce the risk of major intracranial and extracranial bleeding in patients with VTE compared with VKAs[129]; however, bleeding is still a problem in general practice. Thus, a search for safer anticoagulants is still warranted, and studying genetic variation in coagulation pathways may hold promise. Patients with congenital deficiency of factor XII do not display haemorrhagic diathesis (susceptibility for bleeding), whereas patients with factor XI deficiency seldom present with spontaneous bleeding. Furthermore, mice with factor XII or factor XI deficiency are less prone to thrombosis upon venous or arterial injury[189]. Several antisense oligonucleotides against factor XI or factor XII have been developed, which gradually lower factor XI or factor XII levels over time[190]. In a proof-of-principle phase II study in patients undergoing elective knee surgery, the factor XI-directed antisense oligonucleotide (ISIS-416858) was administered by regular subcutaneous injections from 36 days before surgery until 3 days after surgery. Mean plasma factor XI levels were substantially lower than baseline in the antisense oligonucleotide treatment groups[191]. Notably, venography-proven asymptomatic VTE occurred in 27% of patients in the lower dose and 4% of patients in the higher dose antisense oligonucleotide treatment groups versus VTE in 30% of patients receiving enoxaparin. Major or clinically relevant non-major bleeding occurred in 3% of patients in both antisense oligonucleotide treatment groups and in 8% of patients in the enoxaparin groups. These results indicate that it is possible to inhibit thrombosis formation without increasing the risk of bleeding. Future studies must demonstrate whether it is more efficient to reduce levels of factor XI or of factor XII. Owing to the slow onset of action of antisense oligonucleotides, their primary use may be in chronic indications, including secondary prevention of VTE and stroke prevention in atrial fibrillation, particularly in patients with a high risk of bleeding (for example, patients with advanced chronic kidney disease).

To improve the safety profile of thrombolytic treatment, a new generation of thrombolytic agents has been developed that act on targets other than plasminogen activators. For example, DS-1040 is a low-molecular-mass molecule inhibiting the activated form of thrombin-activatable fibrinolysis inhibitor (TAFI; also known as CBP2) that acts as an enhancer of endogenous fibrinolysis while normal haemostasis is preserved[192].

A phase Ib study evaluating DS-1040 is currently under way enrolling patients with acute PE[193]. In addition, an antibody that inactivates α2-antiplasmin, another natural inhibitor of fibrinolysis (DS-9231), specifically targets thrombi without degrading fibrinogen or enhancing experimental bleeding. This agent is currently being tested in phase I trials in healthy volunteers[194]. Furthermore, an engineered antibody heterodimer diabody (derived from two inhibiting monoclonal antibodies) bispecific inhibitor (Db^{-} TCK26D6×33H1F7) against TAFI and plasminogen activator inhibitor 1 (PAI1), a third naturally occurring fibrinolysis inhibitor, has been investigated in mouse models of thrombosis and showed profibrinolytic effects without increased bleeding[195]. Finally, inhibition of PAI1 activity by PAItrap (H37R)–HSA, a specific PAI1 antagonist derived from inactivated urokinase, appears to prevent thrombosis and accelerate fibrinolysis in murine models without impairing global haemostasis[196].

Long-term prognosis

Patterns of patient follow-up after acute PE vary substantially among different clinical practices with country-to-country variance, and high-quality evidence to provide clinical guidance is lacking. Patients, clinicians and health-care workers should be made aware of the long-term complications of acute PE. Furthermore, an urgent need exists for high-quality research to better define the optimal duration and intensity of medical follow-up after PE and for evidence-based treatment strategies for all stages of the post-PE syndrome. CTEPH should be included in the differential diagnosis of patients who develop chronic dyspnoea or functional impairment in the longer-term follow-up after PE, regardless of the presence of other cardiopulmonary comorbidities. The InShape II study is an international, multicentre intervention study that will prospectively validate a PE follow-up algorithm that is aimed at early diagnosis of CTEPH[197]. The algorithm consists of sequential application of the CTEPH prediction score, followed by the so called 'rule-out criteria' for patients either with a high clinical probability for CTEPH or with specific symptoms of CTEPH[113,198,199]. The rule-out criteria consist of measurement of the NT-proBNP biomarker and electrocardiogram assessment for three specific signs of pulmonary hypertension.

The first large randomized controlled trial to assess the benefits of pulmonary rehabilitation in patients with PE is being performed in Denmark[200]. The study aims to evaluate an 8-week home-based exercise intervention and whether it may improve physical capacity, improve quality of life, reduce sick leave and reduce the use of psychotropic drugs in patients with a history of acute PE. In addition, the RACE study[201] is a randomized open-label clinical trial in which patients with CTEPH who are not eligible for pulmonary endarterectomy will be randomized to riociguat, a novel vasodilator, which functions by stimulating soluble guanylate cyclase, or balloon pulmonary angiography as first-line treatment. The primary aim of the study is to establish the difference in pulmonary vascular resistance from baseline to the end of the 26-week follow-up period. This study will identify whether pharmacological treatment or balloon pulmonary angiography may be the better first-line treatment option in non-operable CTEPH patients.

Conclusions

Over time, many important improvements have been made in the diagnostic and therapeutic management of acute PE. However, several research questions remain. For example, is there a role for novel treatment options such as fibrinolysis enhancers? Can there be improvements in the methods for predicting long-term complications and defining the optimal duration and intensity of anticoagulant therapy in the individual patient? Can researchers finally unravel the full spectrum of the post-PE syndrome? Answering these questions will enable advancements in personalized treatment leading to improvements in the short-term and long-term prognosis of patients.

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