# Incidence of recurrent venous thromboembolism and of chronic thromboembolic pulmonary hypertension after a first episode of

# The incidence of recurrent venous thromboembolism and chronic thromboembolic pulmonary hypertension following a first episode of pulmonary embolism

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**Purpose of review**

Pulmonary embolism is the most serious complication of venous thromboembolism, with an elevated case/fatality rate. Patients who survived a first episode of pulmonary embolism should be evaluated for the risk of recurrence and of chronic thromboembolic pulmonary hypertension (CTEPH).

**Recent findings**

The risk of recurrence is higher in patients with unprovoked pulmonary embolism than in those with transient risk factors. Persistent risk factors, such as active cancer and antiphospholipid antibodies, are associated with high risk of recurrence. Recently, elevated D-dimer levels after discontinuation of therapy have been identified as a risk factor for recurrence. CTEPH is characterized by intravascular organization of emboli and occurs in 0.5–1% of cases. Some patients with CTEPH have impaired fibrinolysis, likely due to a structural abnormality of fibrin or fibrin clot. Echocardiography often reveals signs of pulmonary hypertension. This should be confirmed by direct measurement of pulmonary artery pressures at right heart catheterization.

**Summary**

CTEPH patients should receive life-long anticoagulation for preventing recurrent pulmonary embolism. Pulmonary endarterectomy is the treatment of choice for patients with proximal pulmonary vascular occlusion. Patients with predominantly distal pulmonary vascular occlusion are candidates for pharmacological treatment. All patients with unprovoked pulmonary embolism should be evaluated for long-term anticoagulation.

**Keywords**

chronic thromboembolic pulmonary hypertension, D-dimer, fibrin, pulmonary embolism, venous thromboembolism recurrence

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## Introduction

Venous thromboembolism (VTE) is a common disease, with an incidence of about one in 1000 per year [1–3] and with a progressive increase with increasing age. Deep vein thrombosis (DVT) and pulmonary embolism are generally considered to be two clinical manifestations of the same disease. However, pulmonary embolism is the most serious complication of VTE with an elevated case/fatality rate. These patients have a risk of early death from VTE, due to either the initial acute episode or recurrent VTE, which is substantially higher for patients with pulmonary embolism than for those with DVT only.

If a patient survives a first acute episode of pulmonary embolism and adequate anticoagulant treatment is started, two major problems arise: the risk of recurrence when anticoagulation is stopped and the risk of developing chronic thromboembolic pulmonary hypertension (CTEPH).

## Risk of recurrence of venous thromboembolism

Several trials [4–6] and observational studies [7,8] indicate that the risk of recurrent VTE after stopping anticoagulant therapy was much lower if VTE had been provoked by a reversible risk factor, such as surgery, rather than if the episode of VTE was unprovoked [7,9]. Reversible provoking risk factors include major and minor conditions. Major factors are surgery, hospitalization, or plaster cast immobilization, all within 1 month, and pregnancy. Other conditions, such as oral contraceptive treatment, traveling over long distances, or major risk factors occurring between 1 and 3 months before the diagnosis of VTE are considered minor risk

factors. Their role in determining an acute VTE event is still debated. The risk of recurrent VTE after stopping oral anticoagulant treatment (OAT) in patients with a first episode of VTE associated with a major transient risk factor is about 3% per year [3,10•]. By contrast, patients with unprovoked VTE have a high risk for recurrent VTE, estimated as 17.5% in the first 2 years with a persistent increase for many years [7]. In a patient-level meta-analysis of seven prospective studies in patients with a first VTE followed after anticoagulation withdrawal, the 5-year cumulative rate of recurrent VTE in patients with pulmonary embolism was 22.0% for any recurrence (DVT or pulmonary embolism) and 10.6% for pulmonary embolism recurrence. The risk of recurrent pulmonary embolism was 3.1-fold higher in patients presenting with pulmonary embolism than in patients with proximal DVT [hazard ratio 3.1; 95% confidence interval (CI) 1.9–5.1] [11••].

## Factors affecting recurrence

The association between malignancy and VTE is well established, and cancer patients with venous thromboembolism are more likely to develop recurrent VTE than those without [12]. The elevated risk of VTE recurrence in patients with malignancy leads to the recommendation to prolong anticoagulant therapy indefinitely or until the cancer is resolved [13].

Evidence from prospective studies [14,15] suggests that the presence of hereditary thrombophilia is not a critical determinant of the risk of recurrence. The recurrence risk is increased only in patients who have at least two abnormalities. Patients should be evaluated also for the identification of acquired thrombophilia. The antiphospholipid antibodies syndrome is diagnosed when a patient who suffered from a thrombotic event presents positivity for lupus anticoagulant and/or antiphospholipid antibodies against cardiolipin or β(2)-glycoprotein I (confirmed in at least two blood samples 12 weeks apart). These patients carry an elevated risk of recurrence and, therefore, need life-long anticoagulant treatment with vitamin K antagonists (VKAs) [International Normalized Ratio (INR) 2.0–3.0] [16].

Sex is also a determinant of the risk of recurrent VTE. In patients with a first unprovoked VTE, men have a 2.2-fold higher risk of recurrence than women. The risk of recurrence remained 1.8-fold higher in men than in women, even after adjustment for women with initial hormone-associated events [17••].

Recently, it has been demonstrated that clotting activation, detected after withdrawal of anticoagulant therapy, is associated with recurrence. Palareti *et al.* [18] observed that elevated D-dimer levels, measured 1 month after stopping warfarin in patients who undergo a standard period of anticoagulation after a first episode of VTE, were associated with an increased risk of recurrent VTE. This observation was confirmed by several studies [19]. Overall, it was confirmed that in patients who have completed at least 3 months of anticoagulation after a first episode of unprovoked VTE, a negative D-dimer result measured 1 month after anticoagulation withdrawal is associated with a 3.5% annual risk of recurrent disease, whereas a positive D-dimer result is associated with an 8.9% annual risk of recurrence. In particular, in a group of patients with pulmonary embolism as the index event, the finding of abnormal D-dimer levels at 1 month after anticoagulant treatment withdrawal was an independent risk factor for recurrent VTE [20]. In this study, the rate of recurrence was 11.3 per 100 patient-years in patients with elevated D-dimer levels and 2.6 per 100 patient-years in those with normal D-dimer levels. Management studies are now underway to assess the value of D-dimer test in predicting VTE recurrence in clinical practice (DULCIS Study, D-dimer and ULtrasonography in Combination Italian Study; ClinicalTrials.gov identifier: NCT00954395).

**Key points**

- The risk of recurrent pulmonary embolism was 3.1-fold higher in patients presenting with pulmonary embolism than in patients with proximal deep vein thrombosis.
- Abnormal D-dimer levels at 1 month after anticoagulant treatment withdrawal was an independent risk factor for recurrent venous thromboembolism.
- Several prospective studies report an incidence of chronic thromboembolic pulmonary hypertension (CTEPH) ranging from 0.6 to 1.3%.
- Fibrin resistance to lysis occurs in patients with CTEPH.
- Pulmonary endarterectomy is the treatment of choice for CTEPH.

## Oral anticoagulant treatment

Patients presenting with pulmonary embolism have a higher incidence of fatal recurrent VTE than those with isolated DVT. Therefore, defining the duration of anticoagulant treatment is particularly important for patients suffering from pulmonary embolism. The efficacy of oral anticoagulants in preventing recurrent VTE is well known. Data from the literature indicate that indefinite treatment with conventional-intensity VKA (target INR 2.5) reduces recurrent VTE by approximately 90% [21,22]. However, the treatment is associated with a significant risk of major bleeding. In specialized anticoagulation services, this risk ranges from 0.32 to 2.1% per year, with the risk of fatal bleeding ranging

from 0 to 0.25% per year [23]. A significant clinical impact of bleeding in patients anticoagulated for VTE has been demonstrated in a recent meta-analysis, which reported a case-fatality rate of major bleeding of 13.4% [95% confidence interval (CI) 9.4–17.4], with a rate of intracranial hemorrhage of 1.15% per 100 patient-years (95% CI 1.14–1.16) [24].

There has been only one evaluation of the duration of VKA therapy in a large sample of patients with proven pulmonary embolism [25]. After 3 months of successful anticoagulation, patients were randomly assigned to discontinue therapy immediately or extend therapy to 6 months or 1 year. Extending the duration of treatment beyond 3 months did not reduce the recurrence rates.

Recently, the American College of Chest Physicians recommended that patients with unprovoked VTE should receive at least 3 months of anticoagulation and should then be evaluated for the risk–benefit ratio of long-term therapy [13]. Long-term treatment is recommended in the patients in whom risk factors for bleeding are absent and in whom a good anticoagulant monitoring is achievable. However, the decision about treatment is ultimately left to the attending physician, who should assess the risk–benefit ratio in an individual case, and to patient willingness to prolong treatment. The results of ongoing management strategies, based on D-dimer levels, measured after stopping a standard period of anticoagulant therapy, will probably offer the clinicians a valid support for decision making.

## Chronic thromboembolic pulmonary hypertension

CTEPH is a rare complication of pulmonary embolism that is associated with severe morbidity and high mortality [26]. In the United States, an incidence of 0.1–0.5% was estimated, based on the number of cases diagnosed as having CTEPH and the annual rate of patients surviving an acute embolic event [27,28]. This low incidence rate has been questioned, and the actual incidence of CTEPH is still a matter of controversy.

In a small prospective study comprising 78 cases of pulmonary embolism, CTEPH was diagnosed in three (8.8%) of the 34 patients who had a pulmonary artery systolic pressure (PASP) higher than 30 mmHg as estimated by Doppler echocardiography at 1 year of diagnosis [29]. However, the data set is incomplete, with 39% of the eligible patients not included in the study and 14% lost to follow-up [29]. Pengo *et al.* [30] found a cumulative incidence rate of 1% at 6 months, 3.1% at 1 year, and 3.8% at 2 years, with no subsequent increase in incidence. In that study, the investigation for CTEPH was prompted by the occurrence of unexplained exertional dyspnea. However, no lung scan follow-up was pursued to evaluate the restoration of pulmonary perfusion, which would have allowed them to identify previous unrecognized episodes of pulmonary embolism.

Several broad prospective studies, published between 2006 and 2010, were in agreement in reporting an incidence of CTEPH in the range of 0.6–1.3% [31,32, 33•,34••], which is probably the real incidence of the disease.

### Pathophysiology

CTEPH is characterized by intravascular organization of emboli that may yield a complete fibrotic obliteration of the vascular lumen. If obliteration is extensive, it brings about an increase in pulmonary vascular resistance (PVR), which, in turn, determines sustained pulmonary arterial hypertension. Notably, pulmonary vascular lesions, very similar to those of idiopathic pulmonary hypertension, are found in the pulmonary vessels free of embolic material [35]. Such widespread arteriopathy contributes to the elevation of the pulmonary artery pressure [36].

The pathogenesis of CTEPH is still largely unknown. The prevalence of hereditary thrombophilia (deficiencies of antithrombin, protein C or protein S, or factor II and V mutations) is not significantly higher in CTEPH as compared with idiopathic pulmonary hypertension, or healthy individuals [36]. Antiphospholipid antibodies are detected in 21% of the patients [36] and elevated levels of factor VIII were found in 41% of the patients with CTEPH [37].

In 2006, Morris *et al.* [38] first reported that fibrin isolated from 10 patients with CTEPH is resistant to plasmin-mediated lysis, as compared with controls. In particular, cleavage of the amino terminus of the β chain was significantly slower in CTEPH than in controls. It was hypothesized that persistence of the amino terminus residues within the pulmonary vessels could promote the organization of thromboemboli into chronic intravascular scars, thereby determining sustained elevation of PVR [38].

Recently, we confirmed that fibrin resistance to lysis uniformly occurs in patients with established CTEPH [39•]. Such abnormality was also found in idiopathic and in some forms of acquired pulmonary hypertension [39•]. In pulmonary hypertensive patients, the resistance of fibrin to lysis was observed shortly after the incubation with plasmin. This suggests a structural abnormality of the fibrin molecule itself, or a modification in the overall architecture of the fibrin clot that makes it resistant to lysis. The above data may be relevant to the pathogenesis of pulmonary hypertension, as it is recognized that prolonged exposure to fibrin or fibrin fragments stimulates

in-vitro platelet adhesion and proliferation of endothelial cells, fibroblasts and pulmonary arterial smooth muscle cells, thereby suggesting a potential role in vascular remodeling and angiogenesis [40,41].

### Clinical presentation and diagnosis

The clinical presentation of CTEPH is nonspecific, featuring progressive dyspnea on exertion, palpitations, hemoptysis, syncope, and, when right heart failure occurs, dilated neck veins and ankle edema. Usually, there is a clinically 'silent' period that may last from a few months to many years, as the acute embolic event. However, a substantial proportion of the patients with proven CTEPH have no known history of pulmonary embolism [42]. In fact, pulmonary embolism is still a largely underdiagnosed clinical entity [2].

Simple laboratory tests, such as electrocardiogram and chest radiograph, are helpful in strengthening the suspicion of CTEPH [26]. Electrocardiographic signs of right ventricular overload, although nonspecific, may prompt further investigation by transthoracic echocardiography. Chest radiographic abnormalities in chronic pulmonary embolism were first described some 50 years ago [43]. They include dilatation on the pulmonary artery trunk (Fleischner sign) and of the hilar arteries with abrupt tapering of the distal arteries. Increased translucency, due to focal oligoemia of the lung, usually coexists. Dilatation of the right ventricle is best recognized by the increased area of contact between the heart and the anterior chest wall in the lateral roentgenogram [43].

Perfusion or ventilation–perfusion scintigraphy is an important step in the diagnostic work-up of CTEPH [43,44]. Multiple segmental or lobar perfusion defects with preserved ventilation are strongly suggestive of chronic pulmonary embolism, particularly when they remain unchanged in sequential lung scans. Such finding mandates further objective testing for suspected CTEPH.

In clinical practice, pulmonary hypertension is often found, unexpectedly, on transthoracic Doppler echocardiography requested for another indication. Even though echocardiography is very useful in the evaluation of suspected CTEPH, it should be considered that Doppler echocardiography estimates of PASP are often inaccurate [45,46] due to a poor visualization of the tricuspid regurgitation jet, or to an unreliable estimation of the right atrial pressure from the compressibility of the inferior vena cava [46,47].

Therefore, physicians should not be overly reliant on such estimates in their approach to patients with suspected CTEPH, or in assessing changes in PASP in response to therapy.

The definitive confirmation or exclusion of CTEPH rests on the direct measurement of pulmonary artery pressures at right heart catheterization. Hemodynamic criteria to establish a diagnosis of precapillary pulmonary hypertension include a mean pulmonary arterial pressure of more than 25 mmHg at rest with a pulmonary occlusion pressure of 15 mmHg or less and a normal or reduced cardiac output [48]. Hemodynamic assessment should also include the vasoreactivity test with inhaled nitric oxide to identify the patients who retain some degree of active pulmonary vasodilation [48]. In a recent study, a decrease in the mean pulmonary arterial pressure higher than 10.4%, with inhaled nitric oxide, was found to be a strong predictor of long-term survival and freedom from lung transplantation in patients with CTEPH undergoing pulmonary endarterectomy (PEA) [49].

### Treatment

Even though patients with CTEPH should receive lifelong anticoagulation for preventing recurrent pulmonary embolism, such treatment cannot in itself halt the disease progression. PEA is regarded as the treatment of choice for CTEPH patients with proximal pulmonary vascular occlusion [48]. When considering the option of PEA, it is necessary to visualize the location and the extent of pulmonary intraluminal occlusion. In this regard, selective or superselective pulmonary angiography is the modality of choice [48]. Multidetector computed tomography angiography is becoming a valid alternative to selective angiograms, as it provides a detailed three-dimensional reconstruction of the pulmonary vascular tree.

PEA is contraindicated in the patients with predominantly distal pulmonary vascular occlusion and in those with severe comorbidities associated with an increased risk of perioperative mortality (particularly, chronic obstructive or restrictive lung diseases).

Such patients, and those with persistent pulmonary hypertension after PEA, are candidates for pharmacological treatment [48]. As of now, only one randomized clinical trial has been conducted in patients with inoperable CTEPH [50]. In that study, a 16-week oral therapy with bosentan (a dual endothelin receptor antagonist) resulted in a significant reduction of PVR and NT-proBNP levels as compared with the placebo group [50]. It is, however, unknown whether pharmacotherapy is capable of improving survival in the patients with inoperable CTEPH and in those who have persistent elevation of the mean pulmonary arterial pressure after PEA.

## Conclusion

Patients who survive a first episode of pulmonary embolism should be evaluated for the occurrence of CTEPH and to define optimal duration of anticoagulant treatment

to prevent recurrence, balancing the risk–benefit ratio of therapy. In particular, patients with an unprovoked pulmonary embolism should be carefully evaluated for long-term treatment.

## Acknowledgement

### Conflicts of interest

D.P. and M.M. have no conflicts to report.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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