

# Long-term outcome of pulmonary embolism

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The risk of death after an episode of acute pulmonary embolism is less than 5%, provided that the patient is hemodynamically stable and free of major underlying disease. In unselected patients, pulmonary embolism and recurrent disease are responsible for a minority of deaths. Recurrent thromboembolism occurs in less than 5% of patients receiving anticoagulant therapy. The recurrence rate is higher during the first few months after termination of anticoagulant therapy, declining thereafter. At 10 years after the initial episode, the cumulative risk of recurrence is approximately 30%. In patients with a history of pulmonary embolism, recurrences are more likely to take the form of a new pulmonary embolism than deep venous thrombosis. Chronic thromboembolic pulmonary hypertension occurs in less than 5% of patients after pulmonary embolism, but most patients have persistent perfusion defects on lung scans several months after the initial episode. The significance of these findings remains unclear.

Patients presenting an episode of pulmonary embolism have an increased risk of dying during long-term follow-up, mostly due to underlying disease, whereas the frequency of fatal recurrent pulmonary embolism remains low, at least during anticoagulant treatment. The observed mortality differs considerably between information sources, being much higher in registries than in randomized clinical trials. Patients with pulmonary embolism may also suffer recurrent venous thromboembolism after a first episode, and several risk factors for recurrence have recently been identified. Some patients may complain of functional limitation or have persistent perfusion defects on lung scan, but chronic thromboembolic hypertension occurs in only a few patients after a single episode of acute pulmonary embolism.

## Overall long-term mortality of patients with pulmonary embolism

For the purpose of this review, we will consider studies reporting mortality after a minimum of 3 months of follow-up. Information regarding long-term outcome is available from different sources, mostly from randomized, controlled trials comparing different anticoagulant regimens for the secondary prevention of venous thromboembolism. Large randomized, controlled trials including patients with pulmonary embolism have recently been published, and this review is based largely on the results of these studies. Some data for follow-up at 3 months are also available from recent outcome studies

evaluating tests or strategies for the diagnosis of pulmonary embolism. In these studies, patients with suspected pulmonary embolism underwent diagnostic tests or a diagnostic work-up used to exclude pulmonary embolism. All patients in whom pulmonary embolism was ruled out with the diagnostic test under evaluation were followed for 3 months and received no anticoagulant treatment. Venous thromboembolic episodes occurring in these patients during follow-up are consistent with the presence of an initially unrecognized pulmonary embolism. However, all patients, including those having pulmonary embolism, were subjected to follow-up in most studies, providing another source of follow-up data for patients treated for pulmonary embolism. Long-term follow-up data for patients with pulmonary embolism are also available from several large registries. The information from these registries is probably less well controlled, but registries are much less subject to patient selection bias than randomized, controlled trials. We did not undertake a formal systematic search of the literature, but systematically reviewed all randomized, controlled trials on anticoagulant treatment for venous thromboembolism looking for specific data on the subgroup of patients with pulmonary embolism. We also reviewed all diagnostic outcome studies that have been published in English on patients with suspected pulmonary embolism, looking for the outcome of patients with confirmed pulmonary embolism.

**Keywords:** chronic thromboembolic pulmonary hypertension, deep venous thrombosis, mortality, pulmonary embolism, recurrence, venous thromboembolism

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medicine part of fsg

**Mortality at 3–6 months**

Randomized, controlled therapeutic trials

Most clinical trials evaluating new antithrombotic drugs include both patients with pulmonary embolism and patients with deep venous thrombosis, and the outcome of patients with pulmonary embolism is not given separately in most reports. However, data concerning the outcome of patients with pulmonary embolism are available from some such trials, and several large trials have recently been carried out in patients with pulmonary embolism. Most studies exclude patients with shock, patients with a life expectancy of less than 3 months and patients in whom anticoagulant treatment is contraindicated. However, all patients in such studies have objectively confirmed pulmonary embolism at inclusion and, in most trials, all clinical events, including death and recurrent thromboembolism, are assessed by a central adjudication committee whose members are unaware of the anticoagulant treatment given to the patient. The 3-month mortality rate for 5190 patients receiving different anticoagulant treatments for pulmonary embolism ranges from 0 to 4.7%, with a weighted average of 4.3% (Table 1) [1–5]. Mortality due to pulmonary embolism is much lower, ranging from 0 to 2.2%, with a weighted average of 0.8% (Table 1) [1–6]. The mortality data at 6 months are available from the recent van Gogh trial, in which 109 of the 2110 patients died during a 6-month course of anticoagulant treatment (5.2%) [1].

**Diagnostic outcome studies**

Diagnostic outcome studies provide another source of follow-up data for patients treated for pulmonary embolism. Hemodynamically unstable patients and patients with a life expectancy of less than 3 months are usually excluded from these trials. Among 1909 patients with objectively confirmed symptomatic pulmonary embolism

included in eight multicenter outcomes studies and followed up for 3 months whilst on anti-coagulant treatment, overall mortality rate ranges from 3.8 to 14.3%, with a weighted average 3-month mortality of 7.2% (Table 2) [7–14]. The mean pulmonary embolism-related mortality rate was 1.8% for the same studies.

**Registries**

The mortality rates at 3 and 6 months for patients with pulmonary embolism are also reported in three large registries (Table 3). The cumulative mortality rate 3 months after diagnosis was 15.3% in 2393 patients with pulmonary embolism included in the International Cooperative Pulmonary Embolism Registry (ICOPER) alive at the time of diagnosis; death was attributed to pulmonary embolism in 6.9% of these patients [15]. Using the Californian patient discharge data set, Murin *et al.* reported on 21,625 patients hospitalized between January 1, 1991 and June 30, 1996 with a principal diagnosis of pulmonary embolism [16]. They found that 1528 patients (6.0%) died during index hospitalization, with an additional 1880 patients (8.7%) dying between discharge and 6 months of follow-up, giving a total 6-month mortality rate of 14.7%. Mortality rates were higher for patients with pulmonary embolism than for a similar cohort of patients hospitalized in the same hospitals for deep venous thrombosis, both during initial hospitalization (6.0 vs 1.1%; RR = 6.7; 95% CI: 6.1–7.4) and after 6 months of follow-up (14.7% for patients with pulmonary embolism vs 10.5% for patients with deep venous thrombosis,  $p < 0.001$ ) [16]. Mortality rates during 3 months of anticoagulant therapy have also been reported for 3391 patients with symptomatic pulmonary embolism included in the Registro Informatizado de Enfermedad Tromboembolica Española (RIETE) registry. Only patients without concurrent chronic heart

**Table 1. The 3-month outcomes in patients with pulmonary embolism (randomized controlled trials).**

Study	n	Overall mortality, n (%)	Mortality due to PE, n (%)	Recurrences, n (%)	Ref.
Meyer <i>et al.</i> (1995)	60	2 (3.3)	0	0	[3]
Columbus trial (1997)	271	–	6 (2.2)	16 (5.9)	[6]
Simonneau <i>et al.</i> (1997)	612	26 (4.2)	6 (1)	11 (1.8)	[4]
Matisse trial (2003)	2213	105 (4.7)	13 (0.6)	98 (4.4)	[2]
Wells <i>et al.</i> (2005)	90	3 (3.3)	0	2 (2.2)	[5]
van Gogh trial (2007)	2215	88 (3.9)	17 (0.8)	55 (2.5)	[1]
<b>Total</b>	<b>5461</b>	<b>224 (4.3)*</b>	<b>42 (0.8)</b>	<b>182 (3.3)</b>	

\*A total of 224 out of 5190 patients with data for 3-month mortality.

PE: Pulmonary embolism.

**Table 2. The 3-month outcomes in patients with pulmonary embolism (diagnostic outcome studies).**

Study	n	Overall mortality, n (%)	Mortality due to PE, n (%)	Recurrences, n (%)	Ref.
Hull <i>et al.</i> (1994)	150	11 (7.3)	1 (0.7)	8 (5.5)	[7]
Wells <i>et al.</i> (2001)	81	5 (6.2)	2 (2.5)	–	[14]
Perrier <i>et al.</i> (2001)	118	7 (5.9)	3 (2.5)	–	[10]
Musset <i>et al.</i> (2002)	345	13 (3.8)	3 (0.9)	8 (2.3)	[8]
van Strijen <i>et al.</i> (2003)	126	18 (14.3)	7 (5.5)	5 (3.9)	[13]
Perrier <i>et al.</i> (2004)	222	17 (7.7)	4 (1.8)	9 (4.1)	[11]
Perrier <i>et al.</i> (2005)	194	11 (5.7)	3 (1.5)	4 (2.1)	[12]
Nijkeuter <i>et al.</i> (2007)	673	55 (8.2)	11 (1.6)	20 (3.0)	[9]
<b>Total</b>	<b>1909</b>	<b>137 (7.2)</b>	<b>34 (1.8)</b>	<b>54 (3.2)</b>	

PE: Pulmonary embolism.

failure or chronic lung disease were considered for this analysis [17]. Mortality rates were 4.4% on day 15 and 9.5% on day 90. Pulmonary embolism was the cause of 56.4% of the deaths occurring during the initial 15-day period, but accounted for only 9.9% of the deaths observed between day 15 and day 90 [17].

#### Long-term mortality

Few studies have investigated the long-term mortality of patients with pulmonary embolism. Data are available for only one randomized, controlled therapeutic trial [18]. Several other trials have included large numbers of patients with venous thromboembolism for comparisons of different durations or intensities of anticoagulant treatment or evaluations of new drugs for the secondary prevention of venous thromboembolism. However, for most of these trials, outcomes were not reported separately for patients with pulmonary embolism. Some data can also be derived from single-center cohort studies and from one large population-based cohort.

Agnelli *et al.* carried out the only randomized clinical therapeutic trial evaluating two different durations of anticoagulant therapy in patients with a first episode of pulmonary embolism. The study included 326 patients who had received 3 months of anticoagulant treatment with no recurrence or bleeding. Patients were randomized to two groups:

anticoagulation therapy was stopped after 3 months in one group, and continued for a further 3–9 months in the other. A total of 19 patients (5.8%) died during the study period, after a mean follow-up of 33.8 months. Two deaths were attributed to pulmonary embolism (0.6%) [18]. Carson reported the 1-year outcome of 399 patients with objectively confirmed pulmonary embolism included in a prospective diagnostic study. The overall mortality rate after 1 year was 23.8%, whereas the pulmonary embolism-related mortality rate was 2.5% [19]. Several cohort studies have provided data on the long-term mortality of patients with pulmonary embolism [20–24]. Pengo *et al.* reported data for 223 patients recruited at a single center. In total, 41 patients (18.4%) died after a mean of 94.3 months of follow-up. A total of 18 patients (8.1%) died during hospitalization, as a result of the initial episode of pulmonary embolism, and only one subsequent death was related to pulmonary embolism. The cumulative mortality rate was 10.3% (95% CI: 6.3–14.4) at 3 months, 13.4% at 1 year, 20.1% at 5 years and 25.1% (95% CI: 14.2–36.0) at 10 years (Table 4) [23]. In another multicenter cohort study including 259 patients with a first episode of pulmonary embolism, 21 patients died during a mean follow-up period of 46 months (8.1%; 2.1 patient-years) [20]. Another cohort study reported the outcome of 301 patients who survived pulmonary embolism,

**Table 3. The 3–6-month outcomes in patients with pulmonary embolism (cohort studies).**

Study	n	Overall mortality, n (%)	Mortality due to PE, n (%)	Recurrences, n (%)	Ref.
Goldhaber <i>et al.</i> (1999)	2393	365 (15.3)	–	–	[15]
Murin <i>et al.</i> (2002)	21,625	3408 (15.7)	–	1243 (5.7)	[16]
Lobo <i>et al.</i> (2006)	3391	321 (9.5)	101 (2.9)	–	[17]
<b>Total</b>	<b>27,601</b>	<b>4127 (14.9)</b>			

PE: Pulmonary embolism.

**Table 4. Long-term outcomes in patients with pulmonary embolism (cohort studies).**

Study	n	1 year (%)	5 years (%)	8 years (%)	10 years (%)	Ref.
<b>Recurrent venous thromboembolism</b>						
Schulman <i>et al.</i> (2006)	107				34.6	[33]
Pengo <i>et al.</i> (2004)	223	8.0	22.1		29.1	[23]
<b>Cumulative death rate</b>						
Heit <i>et al.</i> (1999)	819	25.4	38.5	46.0		[25]
Pengo <i>et al.</i> (2004)	223	13.4	20.1		25.1	[23]

after their admission to hospital. A total of 45 patients (14.9%) died after a mean of 3.1 years (4.8 per hundred patient-year death rate). The pulmonary embolism related-mortality rate was 2.7% [21]. Another study reported a much higher mortality rate of 43.4% in 320 patients followed for a mean period of 2.1 years after an episode of pulmonary embolism. Death was related to pulmonary embolism in 9.7% of the patients [22]. Most of the patients in this study suffered pulmonary embolism during hospitalization for another disease, and the mean age of these patients was 71–74 years. Ribeiro *et al.* reported data for 78 patients admitted for pulmonary embolism. Five of these patients (6.4%) died during the first month of follow-up and a total of 17 (21.8%) died during the whole 5-year period of follow-up; none of the 12 late deaths was due to pulmonary embolism [24]. In a large population-based cohort study, 819 patients with pulmonary embolism identified during their lifetime were followed for a mean of 6.1 years [25]. The cumulative mortality rate was 7.7% at day 7, 13.1% at day 30 and 25.4% at 1 year. Thus, long-term mortality rates differ considerably according to the type of study; some of these differences may be related to the duration of follow-up and patient selection. In general, most deaths during long-term follow-up seem to be related to associated disease rather than to recurrent pulmonary embolism or to the initial episode.

Douketis *et al.* reported the outcome of 602 patients with symptomatic pulmonary embolism, with or without associated deep-vein thrombosis, who were enrolled in one clinical trial and in one cohort study. Patients in both cohorts were followed after the resumption of oral anticoagulant treatment, and the rate of subsequent fatal recurrences of pulmonary embolism was assessed. The 602 patients were followed for a total of 2437 person-years; the frequency of any fatal pulmonary embolism was 0.57 per 100 person-years of follow-up and the frequency of definite or probable fatal pulmonary embolism was 0.20 per 100 person-years of follow-up. The case fatality rate of

recurrent venous thromboembolism in patients with an initial pulmonary embolism was 3.9% for definite or probable pulmonary embolism [26].

Published risk factors for death in patients with pulmonary embolism include age, malignancy [15,19,21,22,25], chronic heart disease, chronic lung disease [15,19,22,25], hypotension, right ventricular dysfunction [15], immobilization, initial pulmonary vascular obstruction [22], idiopathic venous thromboembolism [18,26], confinement to a hospital or nursing home at the onset of venous thromboembolism and neurologic disease [25].

#### Recurrent venous thromboembolism Recurrent disease during the initial 3–6 months of treatment

In randomized, controlled trials evaluating different anticoagulant regimens for the treatment of pulmonary embolism, the rate of objectively confirmed recurrent venous thromboembolism during the initial 3-month treatment period ranges from 0 (in one small trial) to 5.9% [3,6]. Combining the results of six randomized, controlled trials including 5461 patients with pulmonary embolism, the weighted rate of recurrent venous thromboembolism was 3.3% (Table 1) [1–6]. The rate of objectively documented recurrent venous thromboembolism during a 3-month course of anticoagulant therapy was also recorded in six large diagnostic outcome studies, in which 1710 patients with confirmed pulmonary embolism were followed for 3 months of anticoagulant treatment. In these studies, the rate of recurrent venous thromboembolism ranged from 2.1 to 5.5%, with a weighted mean value of 3.2% (Table 2) [7–9,11–13]. In the Californian registry, the rate of recurrent venous thromboembolism during the first 3 months of follow-up was 7.9% [15,16,27,28].

#### Recurrent disease during long-term follow-up

Long-term recurrent disease has been evaluated in several cohort studies and ranges from 1.8 per 100 patient-years to 8.3 per 100 patient-years [19–23].

However, the duration of anticoagulant treatment was not controlled in these studies. In most randomized, controlled trials comparing different durations or intensities of anticoagulant treatment or new anticoagulant drugs for the secondary prevention of venous thromboembolism, the outcome of patients with deep venous thrombosis and that for patients with pulmonary embolism are not given separately. The risk of long-term recurrent venous thromboembolism in patients with pulmonary embolism has been assessed in five studies [18,29–32]. In the study by Agnelli *et al.*, recurrent venous thromboembolism occurred in 3.1 and 3.8% per patient-year after the cessation of anticoagulant treatment [18]. Kearon *et al.* compared prolonged warfarin treatment with placebo in 162 patients with venous thromboembolism who had completed 3 months of anticoagulant therapy. A total of 22 patients administered placebo had symptomatic pulmonary embolism at presentation and five (22.7%) had recurrent venous thromboembolism during a mean follow-up period of 9 months (corresponding to a 30% per patient-year recurrence rate) [30]. In another study, 897 patients with venous thromboembolism were allocated to receive 6 weeks or 6 months of anticoagulant therapy and were followed for 2 years [32]. Pulmonary embolism was present at inclusion in 107 of these patients, and 22 patients (20.5%) had recurrent venous thromboembolism during the follow-up period (corresponding to a 10.2% per patient-year recurrence rate), with most recurrences occurring after anticoagulant therapy had been stopped [32]. In the van Gogh extension study, 1215 patients with venous thromboembolism who had completed 6 months of anticoagulant treatment were allocated to receive either idraparinix or placebo for a further period of 6 months [29]. Among the 587 patients with an initial pulmonary embolism, 283 received idraparinix, three of whom had a recurrent event (1.1%). By contrast, 13 of the 304 patients with pulmonary embolism given placebo presented recurrent venous thromboembolism during the 6-month treatment period (4.3% for a corresponding 8.6% per patient-year recurrence rate). In another study reporting on the long-term recurrence rate after pulmonary embolism, 738 patients who had completed 3 or more months of warfarin for unprovoked venous thromboembolism were randomly assigned to continue warfarin therapy, with a target International Normalized Ratio (INR) of 2.0–3.0 or a target INR of 1.5–1.9, and were followed for an average of 2.4 years [31]. A total of 259 patients

had had pulmonary embolism: 142 were allocated to the conventional-intensity therapy group and two of these patients suffered recurrent venous thromboembolism (0.6% per patient-year); 117 were allocated to the low-intensity therapy group and seven of these patients had a recurrent event (2.6% per patient-year) [31]. In most studies, similar recurrence rates were reported for patients with pulmonary embolism and patients with deep venous thrombosis. However, patients who had initially had a pulmonary embolism tended to have recurrences in the form of another pulmonary embolism, and patients who had initially had deep venous thrombosis tended to have recurrences in the form of deep venous thrombosis. Among 259 patients with pulmonary embolism included in several randomized, controlled trials who had a recurrent thromboembolic event during or after the end of anticoagulant treatment, the recurrence took the form of a new pulmonary embolism in 175 patients (67.6%) and deep venous thrombosis in 84 patients (32.4%). By contrast, among the 372 recurrences occurring in patients with an initial deep venous thrombosis, the recurrence took the form of a new deep-vein thrombosis in 261 patients (70.2%) and pulmonary embolism in 111 patients (29.8%) [2,4–6,18,29,30,33]. The 10-year incidence of recurrent venous thromboembolism in patients with an initial pulmonary embolism is known from two long-term studies. In the report by Pengo *et al.*, the cumulative incidence of recurrent venous thromboembolism was 4.9% after 3 months, 8.0% after 1 year, 22.1% after 5 years and 29.1% (95% CI: 16.9–41.3) after 10 years of follow-up [23]. In the study by Schulman *et al.*, the cumulative 10-year recurrence rate after 6 weeks or 6 months of anticoagulant therapy for a first episode of venous thromboembolism was 34.5% for the 107 patients who had pulmonary embolism at inclusion (Table 4) [33].

Among patients with recurrent pulmonary embolism, the case fatality rate varies from 10 to 45% [2,18]. However, this rate may be overestimated, as autopsy was rarely performed when pulmonary embolism was clinically suspected as the cause of death, and some patients with sudden unexplained death were considered to have had a new pulmonary embolism in the absence of a clear alternative cause of death.

### Chronic thromboembolic pulmonary hypertension

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare but devastating disease

with a high mortality rate, even with prolonged anticoagulant treatment. When feasible, pulmonary endarterectomy can increase survival rates, and operative mortality is now below 10% in experienced hands. Most patients with CTEPH complain of dyspnea on exercise. Although CTEPH is usually considered a long-term consequence of acute pulmonary embolism, no single episode of acute pulmonary embolism is generally diagnosed before CTEPH. The frequency of CTEPH after an episode of acute pulmonary embolism has recently been estimated in a few cohort studies. In the study by Pengo *et al.*, the cumulative rate of symptomatic CTEPH was 3.8% (95% CI: 1.1–6.5) 2 years after a first episode of acute pulmonary embolism [23]. No additional diagnosis of symptomatic CTEPH occurred more than 2 years after the initial episode of pulmonary embolism. Risk factors for CTEPH among patients with acute pulmonary embolism include age (OR: 1.8; 95% CI: 1.2–2.6), previous pulmonary embolism (OR: 19; 95% CI: 4.5–79.8), idiopathic pulmonary embolism (OR: 5.7; 95% CI: 1.4–23.0) and initial large perfusion defects (OR: 2.2; 95% CI: 1.5–3.3) [23]. In other recent studies, the rate of symptomatic CTEPH after an acute episode of pulmonary embolism varied from 0.8 to 3.8% after a follow-up period of 12 to 46 months [20,22,34]. As echocardiography was not carried out on a regular basis at inclusion in these studies, some of these patients may have had CTEPH at the time of the initial diagnosis of pulmonary embolism. More data are required to clarify the true occurrence of CTEPH after acute pulmonary embolism.

#### Persistent lung-scan defects

A few studies have investigated persistent lung scan defects at the end of anticoagulant treatment for pulmonary embolism. Wartski and Collignon included 157 patients from the THESEE study, a multicenter randomized comparison of unfractionated heparin and low-molecular-weight heparin followed by oral anticoagulants for 3 months in patients with pulmonary embolism. Pulmonary vascular obstruction was calculated on routine follow-up perfusion lung scans carried out in all patients after 8 days, and then again after 3 months. On day 8, 13% of the patients had normalized perfusion lung scans and 34% of patients had normalized perfusion lung scans 3 months after diagnosis. Thus, 66% of patients had residual defects at the end of the 3-month treatment period and no resolution of perfusion defects was observed in 10% of patients [35]. Other studies

have shown that more than 50% of patients with pulmonary embolism still have perfusion defects 6 months after diagnosis. In a recent cohort study including 226 patients with symptomatic pulmonary embolism who underwent perfusion lung scanning 12 months after diagnosis, residual perfusion defects were observed in 31.4% of the patients [34]. In patients with persistent perfusion defects, the delay between first symptoms of pulmonary embolism and diagnosis was longer and vascular obstruction on initial computed tomography was more proximal. Patients with persistent lung-scan defects were older than those who had a normal or near-normal perfusion lung scans 12 months after diagnosis. Patients with persistent lung-scan defects were also more likely to report dyspnea on exercise, and had a higher pulmonary artery pressure at follow-up [34]. The long-term clinical significance of these findings remains unknown.

#### Conclusion

The mortality rates at 3–6 months in patients with pulmonary embolism are below 5% in most therapeutic clinical trials including selected clinically stable patients without major comorbidity. In diagnostic outcome studies, mortality rates after 3–6 months of follow-up are in the range of 5–10%, but in both types of study, pulmonary embolism-related mortality remains lower than 2%. Patients included in these types of study receive anticoagulant treatment throughout the study period, and all have an expected survival of more than 3 months at inclusion. At 3 months after diagnosis, mortality rates seem to be higher in cohorts or registries, ranging from 10 to 15% in most cases. The patients included in these studies are generally unselected, and most of the observed deaths occur during the initial hospitalization. The higher mortality rates observed in registries or cohort studies are probably related to underlying disease, but may also be due to pulmonary embolism itself, as hemodynamically unstable patients are included in most of these studies. The risk of recurrent venous thromboembolism during 3 months of anticoagulant treatment is below 5% in both randomized clinical trials and diagnostic outcome studies. In registries, the rate of recurrence is marginally higher, but not all recurrent venous thromboembolic events are objectively confirmed in such studies. The risk of recurrent venous thromboembolism after anticoagulant treatment varies by a large extent across studies, and the risk of fatal recurrent pulmonary embolism has recently been estimated at 0.20 per 100

patient-years. Patients with an initial pulmonary embolism do not seem to have a higher risk of recurrence than patients with an initial deep venous thrombosis, but recurrent events are more likely to take the form of a pulmonary embolism if the initial event was a pulmonary embolism, and are more likely to take the form of a deep venous thrombosis if the first event was a deep venous thrombosis. Chronic thromboembolic pulmonary hypertension is a rare long-term complication of acute pulmonary embolism, with most patients developing the disease during the first 2 years after the diagnosis of pulmonary embolism. A significant proportion of patients have persistent perfusion defects several months after the diagnosis of pulmonary embolism, but the clinical significance of this finding is unknown.

### Future perspective

The aim of current and future studies in the field of pulmonary embolism is to define patients at risk of recurrent venous thromboembolism or of developing chronic thromboembolic pulmonary hypertension. The role of residual perfusion defects should be considered in this context. Recently published long-term results suggest that the prolongation of anticoagulant treatment delays recurrence but does not reduce the long-

term risk of recurrent disease. If confirmed, these findings may change current views concerning the optimal duration of anticoagulant treatment. The nature of recurrences seems to be strongly influenced by the initial event (the recurrence tends to take the same form as the initial event: pulmonary embolism in patients with a history of pulmonary embolism and deep venous thrombosis in patients with a history of deep venous thrombosis). However, these findings require confirmation and the molecular basis of this difference in behavior is currently unknown. The growing body of information regarding the risk of recurrence after an initial course of 3–6 months of anticoagulant treatment may make it possible to adapt the duration of anticoagulant treatment to the risk of recurrent disease and to select appropriate candidates for lifelong anticoagulant treatment.

### Financial & competing interests disclosure

*The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.*

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## Executive summary

### **Long-term mortality of patients with pulmonary embolism**

- The long-term mortality of patients with pulmonary embolism varies widely according to the source of the information. The death rate after 3 months of anticoagulant treatment is below 5% in randomized clinical trials, between 5 and 10% in diagnostic outcome studies and in the range of 15% in most registries and cohort studies.

### **Recurrent venous thromboembolism during anticoagulant treatment**

- The rate of recurrent venous thromboembolism during anticoagulant treatment is below 5% in randomized clinical trials and in diagnostic outcome studies, and lies between 5 and 10% in registries.

### **Recurrent venous thromboembolism after anticoagulant treatment**

- The rate of recurrent venous thromboembolism is higher during the first years after the end of treatment, declining after 5 years. At 10 years after diagnosis, the cumulative rate of recurrent venous thromboembolism is in the range of 30 to 35%.

### **The nature of the recurrent event depends on the initial event**

- Recurrences tend to take the form of the initial event: pulmonary embolism in patients with previous pulmonary embolism and deep venous thrombosis in patients with previous deep venous thrombosis. The reasons for this remain unknown.

### **Chronic thromboembolic pulmonary hypertension is a rare complication of acute pulmonary embolism**

- Chronic thromboembolic pulmonary hypertension occurs in less than 5% of patients admitted for acute pulmonary embolism.

### **Persistent perfusion defects are observed in more than 50% of patients during follow-up**

- Less than 50% of patients have a normal perfusion lung scan 6–12 months after an initial episode of pulmonary embolism. Risk factors for persistent perfusion defects include older age, delay between first symptoms and diagnosis, and proximal pulmonary embolism. The long-term significance of these findings is unknown.

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