

# Extended Oral Anticoagulant Therapy after a First Episode of Pulmonary Embolism

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**Background:** The optimal duration of oral anticoagulant treatment after a first episode of pulmonary embolism remains uncertain.

**Objective:** To evaluate the long-term clinical benefit of extending a 3-month course of oral anticoagulant therapy to 6 months (pulmonary embolism associated with temporary risk factors) or to 1 year (idiopathic pulmonary embolism) in patients with a first episode of pulmonary embolism.

**Design:** Multicenter randomized study with independent, blinded assessment of the outcome events.

**Setting:** 19 Italian hospitals.

**Patients:** 326 patients who had had 3 months of oral anticoagulant therapy without experiencing recurrence or bleeding.

**Measurements:** The primary study outcome was recurrence of symptomatic, objectively confirmed venous thromboembolism.

**Results:** Among 165 patients assigned to extended anticoagulant therapy, 15 patients (9.1%) had a recurrence of venous thromboembolism (3.1% per patient-year; average follow-up, 34.9

months), as compared with 18 of 161 patients (11.2%) assigned to discontinue treatment (4.1% per patient-year; average follow-up, 32.7 months); the rate ratio was 0.81 (95% CI, 0.42 to 1.56). All but one of the recurrences occurred after anticoagulant treatment was discontinued. Nineteen recurrences (57.6%) were episodes of pulmonary embolism, two of which were fatal. Three major bleeding episodes were observed during extended anticoagulation (1.8%). Among patients with idiopathic venous thromboembolism, 11 of 90 patients assigned to extended anticoagulation and 11 of 91 patients assigned to discontinue treatment experienced a recurrence (relative risk, 0.99 [CI, 0.45 to 2.16]).

**Conclusion:** Patients with pulmonary embolism have a substantial risk for recurrence after discontinuation of oral anticoagulation, regardless of treatment duration. Physicians should try to identify patients who are at high risk for recurrent venous thromboembolism and are therefore potential candidates for indefinite oral anticoagulant therapy.

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\*For a list of the Warfarin Optimal Duration Italian Trial Investigators, see Appendix, available at [www.annals.org](http://www.annals.org).

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Recent studies have shown that patients with a first episode of venous thromboembolism are protected from a recurrence while they are receiving anticoagulant treatment (1, 2). On the basis of differences in the risk for recurrence when anticoagulant treatment is discontinued, different durations of oral anticoagulation are currently recommended in different patient categories. A shorter period of anticoagulation is recommended for patients with venous thromboembolism associated with transient risk factors than for patients with idiopathic venous thromboembolism or venous thromboembolism associated with continuing risk factors (3–5).

Current recommendations on the duration of oral anticoagulant treatment for venous thromboembolism are based on studies that mostly included patients presenting with deep venous thrombosis (1, 2, 5–7). Only a limited proportion of patients included in these studies presented with pulmonary embolism. Deep venous thrombosis and pulmonary embolism are generally considered to be two clinical manifestations of the same disease. However, patients presenting with pulmonary embolism are reported to have a higher incidence of fatal recurrent venous thromboembolism than patients presenting with deep venous thrombosis (8, 9).

We performed a multicenter randomized trial to evaluate the long-term clinical benefit of extending a 3-month course of oral anticoagulant therapy to 6 months (pulmo-

nary embolism associated with temporary risk factors) or to 1 year (idiopathic pulmonary embolism) in patients with a first episode of pulmonary embolism. The primary outcome of the study was symptomatic, objectively confirmed recurrence of venous thromboembolism.

## METHODS

### Study Patients

Consecutive patients ranging from 15 to 85 years of age with a first episode of symptomatic, objectively confirmed pulmonary embolism were included in the study if they had completed 3 uninterrupted months of oral anticoagulant therapy without having a recurrence or bleeding. The diagnosis of pulmonary embolism was confirmed by pulmonary angiography or spiral computed tomography or by a lung scan indicating a high probability of pulmonary embolism or a lung scan indicating an intermediate probability of pulmonary embolism in a patient with objectively diagnosed deep venous thrombosis. Study patients were categorized as having idiopathic pulmonary embolism or pulmonary embolism associated with transient risk factors. Idiopathic pulmonary embolism was defined as pulmonary embolism occurring in the absence of known cancer, known thrombophilia, or any transient risk factor for venous thromboembolism. Pulmonary embolism associated with transient risk factors was pulmonary embolism

**Context**

Optimal duration of anticoagulation after pulmonary embolism is uncertain, but physicians commonly prescribe 3 months of therapy for patients with transient risk factors for thrombosis and 6 months for patients with continuing or no known risk factors.

**Contribution**

After 3 months of successful anticoagulation, 326 patients were randomly assigned to stop therapy immediately or extend therapy to 6 months or 1 year. Regardless of duration of anticoagulation, 33 patients had recurrent thromboembolic events but only one event occurred in a patient still receiving therapy.

**Implications**

Extending the duration of anticoagulation does not seem to protect against recurrence once therapy has been discontinued. Patients at high risk for recurrence may require indefinite anticoagulation.

—The Editors

occurring after recent trauma with or without bone fracture, recent surgery or childbirth, or prolonged immobilization (that is, lasting >7 days), or occurring during the use of oral contraceptives or pregnancy. Patients with pulmonary embolism associated with permanent risk factors (known cancer or known thrombophilia) were excluded from the study. Systematic screening for occult cancer or thrombophilia was not performed before enrollment. Patients who required prolonged anticoagulant therapy for reasons other than venous thromboembolism were excluded from the study, as were patients with major psychiatric disorders, patients with a life expectancy shorter than 2 years, those who could not return for the follow-up visits, and those who declined to participate. The institutional review boards of the participating hospitals approved the study; all patients gave informed consent.

**Study Design and Interventions**

The Warfarin Optimal Duration Italian Trial in patients with pulmonary embolism (WODIT-PE) was a multicenter randomized, open trial with independent, blinded assessment of the outcome events. The study was designed to evaluate the clinical benefit of extending the 3-month course of oral anticoagulant therapy after a first episode of pulmonary embolism. Patients who had completed 3 months of warfarin or acenocumarol therapy were randomly assigned to discontinue anticoagulation or to continue it for 3 additional months (pulmonary embolism associated with transient risk factors) or 9 additional months (idiopathic pulmonary embolism). Randomization was performed centrally in permuted blocks of six.

The dose of warfarin or acenocumarol was adjusted to achieve a target international normalized ratio (INR) be-

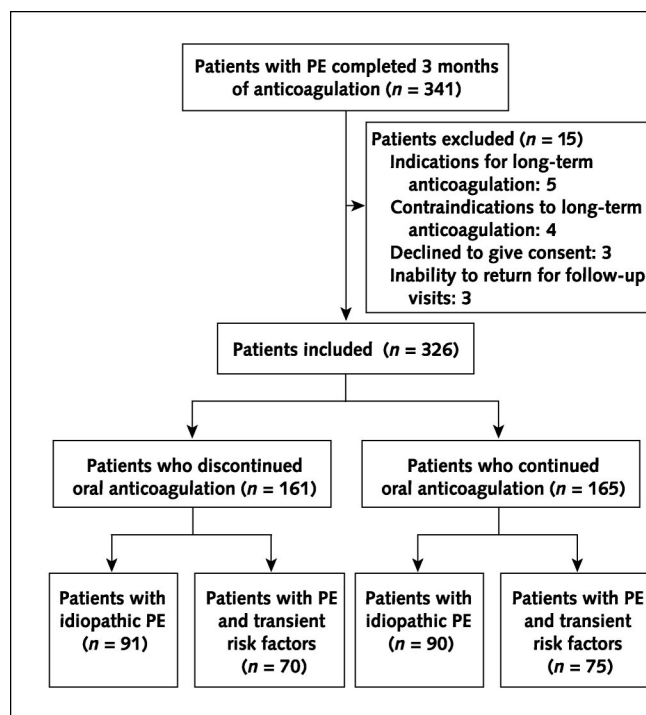
tween 2.0 and 3.0. The therapy was monitored in anticoagulant clinics associated with the study centers, all in Italy.

**Outcome Measures**

The primary outcome of the study was the recurrence of symptomatic, objectively confirmed venous thromboembolism after the initial 3 months of anticoagulation. The secondary outcome was the cumulative incidence of adverse outcome events (recurrence of venous thromboembolism, death, or major bleeding). The criteria for the diagnosis of recurrence of pulmonary embolism were a new filling defect revealed by pulmonary angiography or spiral computed tomography or a new high-probability perfusion defect revealed by ventilation–perfusion lung scan. Sudden, otherwise unexplained death was also considered a recurrence of pulmonary embolism. The criteria for the diagnosis of deep venous thrombosis as an outcome for recurrence of venous thromboembolism in patients without deep venous thrombosis at baseline were the presence of a noncompressible proximal vein on ultrasonography or an intraluminal filling defect on venography. In patients with deep venous thrombosis at baseline, the criteria for the diagnosis of recurrent deep venous thrombosis were abnormal results on compression ultrasonography (proximal veins) or venography in the contralateral leg or, in the ipsilateral leg, an extension of an intraluminal filling defect on venography; a newly noncompressible venous segment; or an increase of 4 mm or more in the diameter of the thrombus (proximal veins) on ultrasonography (10).

Bleeding was defined as major if it was clinically overt

Figure 1. Flow chart for inclusion of patients in the study.



PE = pulmonary embolism.

Table 1. Patient Characteristics at Enrollment

Characteristic	Treatment Group		Initial Event	
	Discontinuation of Oral Anticoagulant Therapy (n = 161)	Continuation of Oral Anticoagulant Therapy (n = 165)	Idiopathic Pulmonary Embolism (n = 181)	Transient Risk Factors for Pulmonary Embolism (n = 145)
Mean age $\pm$ SD, y	61.0 $\pm$ 15.5	62.9 $\pm$ 16.3	67.0 $\pm$ 12.4	56.2 $\pm$ 17.7
Men/women, n/n	67/94	65/100	78/103	54/91
Concomitant deep venous thrombosis, n (%)	89 (55.3)	91 (55.2)	101 (55.8)	79 (54.5)
Thrombolytic treatment, n (%)	15 (9.3)	16 (9.8)	21 (11.6)	10 (6.9)
Idiopathic pulmonary embolism, n (%)	91 (56.5)	90 (55.9)	—	—

and associated with either a decrease in the hemoglobin level of at least 20 g/L or the need to transfuse two or more units of red blood cells, if it was retroperitoneal or intracranial, if it warranted the permanent discontinuation of therapy with the study drug, or if it required rehospitalization. Deaths were classified as the result of pulmonary embolism, bleeding, or another identifiable cause or as unexplained.

All suspected outcome events (recurrent thromboembolism and bleeding episodes) and all deaths were reviewed centrally by an independent, external adjudication committee whose members were unaware of the treatment group assignments.

#### Follow-up

Patients were instructed to return for follow-up visits at 3, 6, and 12 months after randomization and every 6 months thereafter until the completion of the study. Patients were asked to return to the study center immediately if symptoms suggestive of recurrent venous thromboembolism or bleeding developed. For all patients who died during the follow-up period, the date and cause of death were documented. We attempted to gain permission for autopsies of all patients in whom pulmonary embolism could not be excluded as the cause of death.

#### Statistical Analysis

The primary analysis of efficacy was a comparison of the rates of symptomatic, objectively confirmed recurrence of venous thromboembolism in the two treatment groups. The analysis was performed on an intention-to-treat basis.

It was assumed that the rate of recurrence of venous thromboembolism would be 12% in patients assigned to the discontinue oral anticoagulant therapy in the 2 years after discontinuation. We also assumed that the prolongation of oral anticoagulant therapy would produce a 50% reduction in the risk for recurrence. Given these assumptions, we needed 312 patients in each group to detect a difference of this magnitude between groups with a power of 80% and a type I error rate of 5%. To avoid the exposure of the study patients to an ineffective or dangerous therapeutic regimen, one prespecified interim analysis of efficacy and safety was planned after we randomly assigned 50% of planned patients. The following criteria for stopping the trial were defined a priori: an overall rate of re-

currence of thromboembolic events lower than 7.5%, an unequivocal reduction in the rate of recurrent venous thromboembolism in the patients assigned to continue therapy ( $P < 0.001$  by a one-sided test), a risk for recurrence in the continued therapy group that was less than 25% lower than that in the group assigned to discontinue therapy, or a rate of major bleeding higher than 5% in the continued therapy group.

The cumulative hazard of recurrent venous thromboembolism was calculated according to the Kaplan–Meier life-table method (11). Rates of recurrence in the two groups were compared with the use of the log-rank test (12).

## RESULTS

### Patients

Patients were recruited between January 1997 and December 2000 when, after 326 patients were included, the results of the interim analysis showed a difference of less than 25% in the risk for recurrent venous thromboembolism between the two treatment groups.

At the time of randomization, 341 consecutive patients met the inclusion criteria; 15 of these also met one of the exclusion criteria (Figure 1). The reasons for the exclusion of patients were other indications for long-term anticoagulant therapy (5 patients), contraindications to long-term anticoagulant therapy (4 patients), declining to give consent (3 patients), and inability to return for follow-up visits (3 patients). Therefore, 326 patients were enrolled in the study: 161 patients were assigned to discontinue oral anticoagulant therapy and 165 patients were assigned to continue therapy. The baseline characteristics of the patients are shown in Table 1.

Oral anticoagulant treatment was prematurely and permanently discontinued in 2 patients assigned to extend anticoagulation because of voluntary withdrawal. Anticoagulation continued beyond scheduled cessation because of newly diagnosed hereditary thrombophilia (2 patients in the extended group), newly identified lupus anticoagulant (1 patient in the extended group), or patient request (2 patients in the extended group and 2 patients in the discontinuation group). Anticoagulant treatment was resumed after scheduled cessation in 4 patients randomly assigned to discontinue anticoagulation because of atrial

**Table 2. Recurrences of Thromboembolic Events according to Treatment Group\***

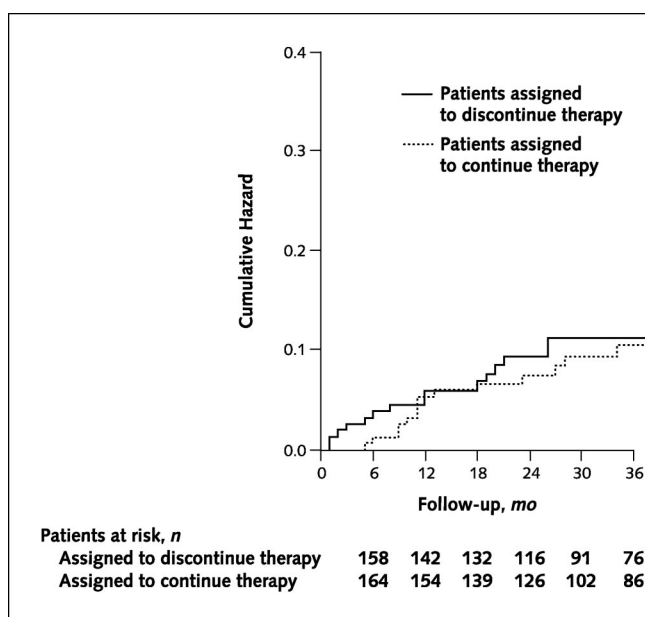
Event	Discontinuation of Oral Anticoagulant Therapy (n = 161)	Continuation of Oral Anticoagulant Therapy (n = 165)
	n (n)	
Deep venous thrombosis	7 (3)	7 (6)
Pulmonary embolism	7	5
Fatal	0	2 (1)
Nonfatal	7 (4)	3 (2)
Deep venous thrombosis and pulmonary embolism	4 (4)	3 (2)
Total	18 (11)	15 (11)
Idiopathic recurrences	15 (11)	13 (9)

\* Values in parentheses are thromboembolic recurrences in patients with idiopathic pulmonary embolism.

fibrillation (2 patients) or for voluntary decision (2 patients). On the basis of the linear interpolation of INR results between tests, we estimated that the INR was between 2.0 and 3.0 for an average of 83% of the time during the 9 months of extended anticoagulant treatment.

During the follow-up period, cancer was newly diagnosed in 19 patients (5.8%): 11 assigned to continue therapy and 8 assigned to discontinue therapy. Newly diagnosed types of cancer were breast cancer in 5 patients, urinary tract cancer in 5 patients, gastroenteric cancer in 4 patients, lung cancer in 2 patients, and lymphoma in 2 patients.

**Figure 2. Cumulative hazard of recurrence of venous thromboembolism in patients assigned to discontinue anticoagulation or to continue anticoagulation.**



The rows parallel to the time axis report the number of patients at risk in the two treatment groups.

**Recurrent Venous Thromboembolism**

Overall, 33 patients (10.1%; 3.6% per patient-year; average follow-up, 33.8 months) had recurrent venous thromboembolism. The features of the recurrences are shown in Table 2. Four episodes of recurrent venous thromboembolism occurred in association with transient risk factors, one in a patient with newly diagnosed cancer; all the other episodes were unprovoked. All but one of the recurrences occurred after anticoagulant treatment was discontinued. The recurrence during treatment was not associated with known risk factors. Nineteen recurrences (57.6%) were pulmonary embolism. Fatal recurrences occurred after treatment discontinuation in 2 patients randomly assigned to extend anticoagulation.

Of the 165 patients assigned to continue therapy, 15 patients (9.1%) had recurrent venous thromboembolism (3.1% per patient-year; average follow-up, 34.9 months) compared with 18 of the 161 patients (11.2%) assigned to discontinue therapy (4.1% per patient-year; average follow-up, 32.7 months), resulting in a rate ratio of 0.81 (95% CI, 0.42 to 1.56). In patients assigned to continue anticoagulation, the incidence of recurrence after treatment discontinuation was 3.8% per patient-year (average off-treatment period, 28.7 months). After treatment discontinuation, the incidence of recurrence was 5.6% in both treatment groups during the first year and 3.9% and 3.5% during the second year in patients randomly assigned to continue and discontinue treatment, respectively. The cumulative hazard of recurrent venous thromboembolism in the two groups is shown in Figure 2 (P > 0.2).

Among the patients with idiopathic pulmonary embolism, 11 recurrences occurred in 90 patients (12.2%) assigned to continue therapy (4.2% per patient-year; average follow-up, 34.8 months) and 11 recurrences occurred in 91 patients (12.1%) assigned to discontinue therapy (4.6% per patient-year; average follow-up, 31.7 months), resulting in a relative risk of 0.99 (CI, 0.45 to 2.16). In patients assigned to continue anticoagulation, the incidence of recurrence after treatment discontinuation was 5.1% per patient-year (average off-treatment period, 26.4 months).

Among the patients with pulmonary embolism associated with transient risk factors, 4 recurrences occurred in 75 patients (5.3%) assigned to continue therapy (1.8% per patient-year; average follow-up, 35.0 months) as compared with 7 recurrences in 70 patients (10.0%) assigned to discontinue therapy (3.5% per patient-year; average follow-up, 33.9 months), resulting in a rate ratio of 0.53 (CI, 0.16 to 1.74). In patients assigned to continue anticoagulation, the incidence of recurrence after treatment discontinuation was 2.0% per patient-year (average off-treatment period, 32.1 months).

The incidence of recurrence was 12.2% in patients with idiopathic pulmonary embolism and 7.6% in patients with pulmonary embolism associated with transient risk factors (relative risk, 1.60 [CI, 0.80 to 3.19]). Figure 3 shows the cumulative hazards of recurrent venous throm-

boembolism in patients with idiopathic pulmonary embolism and in patients with pulmonary embolism associated with transient risk factors who received 3 months of anticoagulation or extended anticoagulation.

Twenty-five of 33 patients (75.8%) who experienced a recurrence had concomitant deep venous thrombosis at baseline as compared with 155 of 293 patients (52.9%) who did not have a recurrence, resulting in a relative risk of 1.43 (CI, 1.15 to 1.79;  $P = 0.012$ ).

**Bleeding Complications**

Eleven patients experienced a bleeding episode after randomization (3.4%): 7 episodes among patients assigned to continue treatment (4.2%) and 4 episodes among patients assigned to discontinue treatment (2.5%). Among patients randomly assigned to continue oral anticoagulant therapy, all bleeding episodes occurred during treatment. No bleeding event was fatal.

Three major bleeding events occurred during extended anticoagulant treatment (1.8%): 2 episodes in patients with INR in the target therapeutic range and 1 episode in a patient with INR above the therapeutic range (Table 3). One major bleeding episode occurred in a patient ran-

**Table 3. Adverse Outcomes according to Treatment Group\***

Outcome	Discontinuation of Oral Anticoagulant Therapy (n = 161)	Continuation of Oral Anticoagulant Therapy (n = 165)
	n (%)	
Recurrent venous thromboembolism	18 (11.2 [6–16])	15 (9.1 [5–13])
Death	7 (4.2 [1–7])	12 (7.5 [3–11])
Major bleeding	1	3
At least one adverse event	24 (14.9 [12–18])	27 (16.5 [13–19])

\* Values in square brackets are 95% CIs.

domly assigned to discontinue treatment. Major bleeding events were hematuria (2 patients), gastrointestinal bleeding (1 patient), and muscle hematoma (1 patient) requiring discontinuation of therapy with the study drug or rehospitalization.

**Deaths**

Nineteen patients (5.8%) died during the study period. Twelve patients assigned to continue therapy died: causes were heart failure (3 patients), recurrent pulmonary embolism (2 patients), myocardial infarction (2 patients), rupture of abdominal aortic aneurysm (2 patients), cancer (1 patient), pneumonia (1 patient), and respiratory failure (1 patient). Seven patients assigned to discontinue therapy died: causes were ischemic stroke (3 patients), cancer (2 patients), myocardial infarction (1 patient), and acute respiratory distress syndrome (1 patient). Fifteen of 181 patients with idiopathic pulmonary embolism (8.3%) died as compared with 4 of 145 patients with pulmonary embolism associated with transient risk factors (2.8%), resulting in a relative risk of 0.33 (CI, 0.11 to 0.98;  $P = 0.05$ ).

**Cumulative Adverse Outcomes**

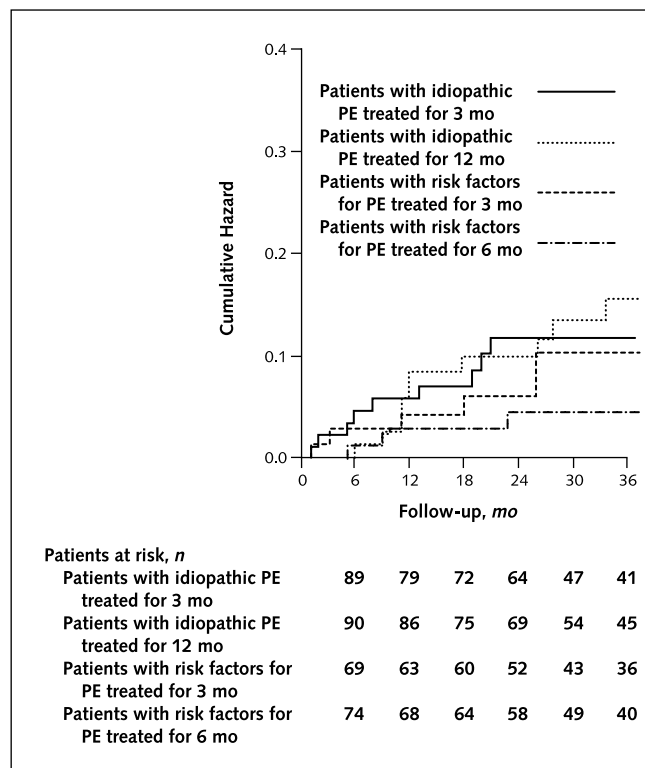
Twenty-seven and 24 patients randomly assigned to continue or discontinue therapy, respectively, experienced at least one adverse outcome event (recurrence of venous thromboembolism, death, or major bleeding) (Table 3). Thirty-six of 181 patients with idiopathic pulmonary embolism (19.9%) experienced at least one adverse clinical outcome event as compared with 15 of 145 patients with pulmonary embolism associated with transient risk factors (10.3%), resulting in a relative risk of 1.92 (CI, 1.10 to 3.37;  $P = 0.021$ ) (Table 4).

No adverse outcome events were observed in patients whose treatment was extended or resumed after its scheduled interruption or in patients who chose not to extend treatment.

**DISCUSSION**

We found that patients with a first episode of pulmonary embolism who received extended anticoagulation were protected from a recurrence of venous thromboembolism while they were receiving treatment. However, the clinical benefit during the additional months of anticoag-

**Figure 3. Cumulative hazard of recurrence of venous thromboembolism in patients with idiopathic pulmonary embolism and in patients with pulmonary embolism (PE) associated with transient risk factors according to treatment duration.**



The rows parallel to the time axis report the number of patients at risk in each treatment group.

Table 4. Adverse Outcomes according to Initial Event and Treatment Group\*

Outcome	Idiopathic Pulmonary Embolism			Transient Risk Factors for Pulmonary Embolism		
	Anticoagulant Withdrawal (n = 91)	Extended Treatment (n = 90)	Total (n = 181)	Anticoagulant Withdrawal (n = 70)	Extended Treatment (n = 75)	Total (n = 145)
	n		n (%)	n		n (%)
Venous thromboembolism	11	11	22 (12.1 [7–17])	7	4	11 (7.6 [3–12])
Death	7	8	15 (8.3 [6–10])	0	4	4 (2.8 [1–5])
Major bleeding	1	2	3	0	1	1
At least one adverse event	17	19	36 (19.9 [14–26])	7	8	15 (10.3 [5–15])

\* Values in square brackets are 95% CIs.

ulation was not maintained after treatment was discontinued. The CIs of the relative risk for recurrent venous thromboembolism do not rule out substantive differences between the two treatment groups. However, our results in patients with pulmonary embolism are consistent with those previously observed in patients with deep venous thrombosis, a disease whose pathophysiology is similar to that of pulmonary embolism (2). The similarity in the results between the two studies, concerning both the incidence of the events and their time patterns, bolsters the conclusion that in patients with venous thromboembolism, prolonging anticoagulant therapy beyond 3 months simply delays recurrence until anticoagulant therapy is stopped.

Prospective interventional trials (1, 2, 6, 7) and cohort studies (13, 14) evaluated the long-term clinical course of patients with deep venous thrombosis, while limited data are available on the long-term clinical course of patients with pulmonary embolism (15, 16). Our study provides information of potential interest concerning the long-term clinical course of pulmonary embolism. Patients with idiopathic pulmonary embolism have a worse long-term clinical outcome than patients with a first episode of pulmonary embolism associated with transient risk factors. Actually, 19.9% of patients with idiopathic pulmonary embolism experienced at least one adverse clinical outcome compared with 10.3% of patients with pulmonary embolism associated with transient risk factors. We observed that patients with concomitant deep venous thrombosis at baseline were at high risk for adverse clinical outcome. Indeed, 13.9% of patients with concomitant deep venous thrombosis at baseline experienced recurrent venous thromboembolism compared with 5.8% of patients without concomitant deep venous thrombosis at baseline. In this study, in patients presenting with pulmonary embolism, about 60% of the recurrences were a second episode of pulmonary embolism. In contrast, in a study with a similar experimental design, only 18% of the recurrences were pulmonary embolism in patients presenting with deep venous thrombosis (2).

Current guidelines recommend 3 months of oral anticoagulant therapy for patients with venous thromboembolism associated with temporary risk factors. In patients with pulmonary embolism associated with temporary risk

factors, we observed a potential reduction in the risk for recurrence in patients receiving 6 months of oral anticoagulant treatment compared with patients receiving 3-month treatment. This observation has some biological plausibility. Risk for recurrence in patients with venous thromboembolism associated with temporary risk factors is essentially linked to the index episode, and thus prolonging anticoagulation could prevent recurrence by making the causative determinants of the index episode more remote.

The bleeding rate was lower in our study than in other studies with oral anticoagulant therapy. This is probably due to the experimental design of the study, which included only patients who did not experience a bleeding episode in the first 3 months of anticoagulant treatment (the period of higher risk for bleeding).

Our study, like other studies with oral anticoagulant therapy, was not a placebo-controlled, double-blind trial. However, our findings are probably valid since we took many measures to avoid bias: inclusion of consecutive patients, central randomization, follow-up of all randomly assigned patients, central adjudication of all outcome events by a committee unaware of the treatment assigned and INR results, assessment of recurrences of venous thromboembolism and bleeding on the basis of predetermined objective criteria, and inclusion in the study analysis of all randomly assigned patients. The open-label nature of the study could have caused a suspicion bias in the attending physician concerning whether to order confirmatory tests for recurrent venous thromboembolism. However, this potential for bias was reduced by the fact that almost all recurrences occurred after treatment withdrawal.

The results of this study in patients with pulmonary embolism, together with the results of previous studies in patients with deep venous thrombosis (2, 7), indicate that the optimal long-term management of patients with venous thromboembolism is unlikely to be defined by further studies comparing different durations of anticoagulant treatment. Rather, these results indicate that strategies for risk stratification should be implemented to identify patients at high risk for recurrent venous thromboembolism after anticoagulant treatment is discontinued. These patients are potential candidates for indefinite oral anticoagulant therapy because the continuation of anticoagulation

might result in more benefit than harm. The low bleeding rate during extended anticoagulant treatment and the high proportion of recurrences presenting as pulmonary embolism might support indefinite treatment in high-risk patients. The development of oral antithrombotic agents that have an improved safety profile and, as a consequence, do not require laboratory monitoring could pave the way toward extending anticoagulant therapy indefinitely.

The optimal method to assess the risk for recurrence of venous thromboembolism is currently undefined. Patients with idiopathic pulmonary embolism are at higher risk for recurrence than patients with pulmonary embolism associated with transient risk factors. Clinical risk factors for recurrence in patients with idiopathic or unprovoked pulmonary embolism could be identified by pooled analysis of data from recent intervention trials (1, 2, 6, 7) and prospective registries. Other approaches for risk stratification might include screening for genetic thrombophilia, assay of D-dimer at the end of the treatment period (17), and assessment of residual pulmonary hypertension. Our finding that patients with concomitant deep venous thrombosis at the time of the initial pulmonary embolism are at high risk for recurrence of venous thromboembolism could contribute to identify candidates to indefinite anticoagulation.

In conclusion, patients with a first episode of pulmonary embolism have a substantial risk for recurrence, particularly a second pulmonary embolism, after oral anticoagulant therapy is discontinued, no matter how long they are treated. Physicians should identify patients with idiopathic pulmonary embolism who are at high risk for recurrent venous thromboembolism and therefore are potential candidates for indefinite oral anticoagulant therapy.

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## APPENDIX: OTHER WARFARIN OPTIMAL DURATION ITALIAN TRIAL INVESTIGATORS

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